Ivermectin reduces COVID-19 risk: real-time meta-analysis of 106 studies (c19ivm ivmmeta)

@CovidAnalysis, Oct 20, 2026, Version 258 (V1 2020), c19early.org/imeta.html

Abstract

Significantly lower risk is seen for mortality, ventilation, ICU admission, hospitalization, recovery, cases, and viral clearance. All remain significant for higher quality studies. 66 studies from 60 independent teams in 28 different countries show significant improvements.

Meta-analysis using the most serious outcome shows 62% [52-70%] and 84% [75-89%] lower risk for early treatment and prophylaxis, with similar results for higher quality studies, primary outcomes, peer-reviewed studies, and for RCTs.

Results are very robust—in worst case exclusion sensitivity analysis 65 of 106 studies must be excluded before statistical significance is lost. Emergent results matching biological mechanisms confirm efficacy: meta-regression of efficacy vs. treatment delay ($p = 0.0038$), efficacy gradient across stages ($p < 0.0000001$), and fed vs. fasting administration ($p = 0.03$).

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Pharmacokinetics show significant inter-individual variability [1]. Efficacy varies depending on the manufacturer [2]. Administration with a high-fat meal increases the bioavailability of ivermectin, and may aid distribution to target tissues.

Over 20 countries 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 and sources to reproduce this analysis are in the appendix. Multiple other meta-analyses show efficacy [3-7].

Ivermectin for COVID-19 HIGHLIGHTS

- Ivermectin **reduces risk** with very high confidence for mortality, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and in pooled analysis.
- Emergent results matching biological mechanisms **confirm efficacy**: meta-regression of efficacy vs. treatment delay ($p = 0.0038$), efficacy gradient across stages ($p < 0.0000001$), and fed vs. fasting administration ($p = 0.03$).
- 4th treatment shown **effective** in August 2020, now with $p < 0.0000000001$ from 106 studies, recognized in 24 countries.
- Real-time updates and corrections with a consistent protocol for 227 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

Introduction

Immediate treatment recommended

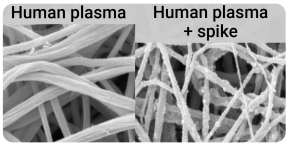
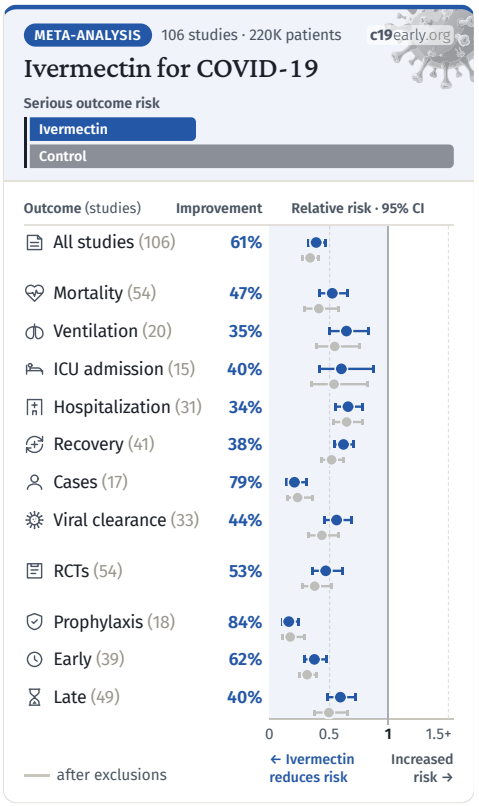
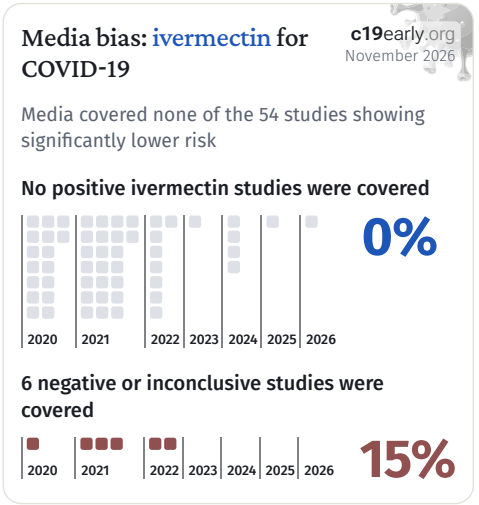
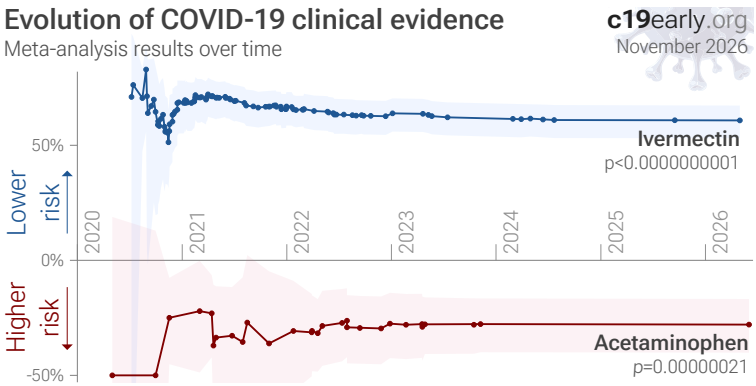


Fig. 1. SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from [8].

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury [9-25] and cognitive deficits [12,17], cardiovascular complications [26-32], DNA damage [33-36], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits [37]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.







Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 500+ host and viral proteins and other factors [A,38-45], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 12,000 compounds may reduce COVID-19 risk [46], either by directly minimizing infection or

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replication, by supporting immune system function, or by minimizing secondary complications.

Extensive supporting research

Ivermectin, better known for antiparasitic activity, is a broad spectrum antiviral with activity against many viruses including H7N7[47], Dengue[48-50], HIV-1[49], Simian virus 40[51], Zika[50,52,53], West Nile[53], Yellow Fever[54,55], Japanese encephalitis[54], Chikungunya[55], Semliki Forest virus[55], Human papillomavirus[56], Epstein-Barr[56], BK Polyomavirus[57], and Sindbis virus[55].

Ivermectin inhibits importin-α/β-dependent nuclear import of viral proteins[47,49,51,58], shows spike-ACE2 disruption at 1nM with microfluidic diffusional sizing[59], binds to glycan sites on the SARS-CoV-2 spike protein preventing interaction with blood and epithelial cells and inhibiting hemagglutination[60,61], shows dose-dependent inhibition of wildtype and omicron variants[62], exhibits dose-dependent inhibition of lung injury[63,64], may inhibit SARS-CoV-2 via IMPase inhibition[50], may inhibit SARS-CoV-2 induced formation of fibrin clots resistant to degradation[65], inhibits SARS-CoV-2 3CL^{pro}[66], may inhibit SARS-CoV-2 RdRp activity[67,68], may minimize viral myocarditis by inhibiting NF-κB/p65-mediated inflammation in macrophages[69], may be beneficial for COVID-19 ARDS by blocking GSDMD and NET formation[70], may interfere with SARS-CoV-2's immune evasion via ORF8 binding[71], may inhibit SARS-CoV-2 by disrupting CD147 interaction[72-75], may inhibit SARS-CoV-2 attachment to lipid rafts via spike NTD binding[76], shows protection against inflammation, cytokine storm, and mortality in an LPS mouse model sharing key pathological features of severe COVID-19[77,78], may be beneficial in severe COVID-19 by binding IGF1 to inhibit the promotion of inflammation, fibrosis, and cell proliferation that leads to lung damage[79], significantly mitigates bleomycin-induced pulmonary fibrosis by reducing collagen accumulation and inflammatory cell infiltration[80], improves oxidative stress markers while suppressing myofibroblast proliferation[80], may minimize SARS-CoV-2 induced cardiac damage[81,82], may counter immune evasion by inhibiting NSP15-TBK1/KPNA1 interaction and restoring IRF3 activation[83], may disrupt SARS-CoV-2 N and ORF6 protein nuclear transport and their suppression of host interferon responses[84], reduces TAZ/YAP nuclear import, relieving SARS-CoV-2-driven suppression of IRF3 and NF-κB antiviral pathways[85], increases Bifidobacteria which play a key role in the immune system[86], has immunomodulatory[87] and anti-inflammatory[88,89] properties, and has an extensive and very positive safety profile[90].

Analysis

We analyze all significant controlled studies 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, studies within each treatment stage, mortality, ventilation, ICU admission, hospitalization, recovery, cases, viral clearance, peer-reviewed studies, Randomized Controlled Trials (RCTs), and after exclusion of lower quality studies.

Treatment timing

Fig. 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.

Preclinical Research

Ivermectin, better known for antiparasitic activity, is a broad spectrum antiviral with activity against many viruses including H7N7[47], Dengue[48-50], HIV-1[49], Simian virus 40[51], Zika[50,52,53], West Nile[53], Yellow Fever[54,55], Japanese encephalitis[54], Chikungunya[55], Semliki Forest virus[55], Human papillomavirus[56], Epstein-Barr[56], BK Polyomavirus[57], and Sindbis virus[55].

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35 *in silico* studies support the efficacy of ivermectin[65,67,68,71,76,79,84,91-118].

28 *in vitro* studies support the efficacy of ivermectin[50,56,59,60,62,66,76,77,81,82,85,87,119-134].

15 *in vivo* animal studies support the efficacy of ivermectin[63,64,69,77,80,89,126,130,135-141].

Studies show synergistic antiviral effects for ivermectin in combination with favipiravir[129], niclosamide[124], paxlovid[119], and remdesivir[120,122,132,142], which may allow increased efficacy and/or similar efficacy at lower doses, potentially reducing dose-dependent side effects.

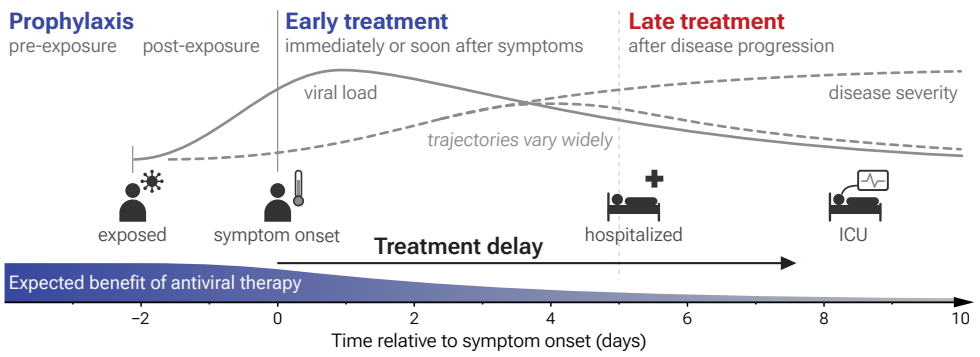

Fig. 2. Treatment stages.

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Table 1. **Random-effects meta-analysis results for ivermectin.** Results show the relative risk and 95% confidence interval.

Studies show complementary effects for ivermectin in combination with hydroxychloroquine [124] and doxycycline [103].

8 studies investigate novel formulations of ivermectin that may be more effective for COVID-19 [123,136,137,141,143-146].

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 1 summarizes the results of random-effects meta-analysis for all studies, for Randomized Controlled Trials, for peer-reviewed studies, with different exclusions, for specific outcomes, and by treatment stage. Fig. 3 shows a timeline of the results in ivermectin studies. Fig. 4 plots individual results by treatment stage. Fig. 5, 6, 7, 8, 9, 10, 11, and 12 show forest plots for random-effects meta-analysis of all studies with pooled effects, and for specific outcomes: mortality, ICU admission, mechanical ventilation, hospitalization, recovery, cases, and viral clearance. Fig. 13 shows results for peer reviewed trials only, and the supplementary data contains peer reviewed and individual outcome results after exclusions.

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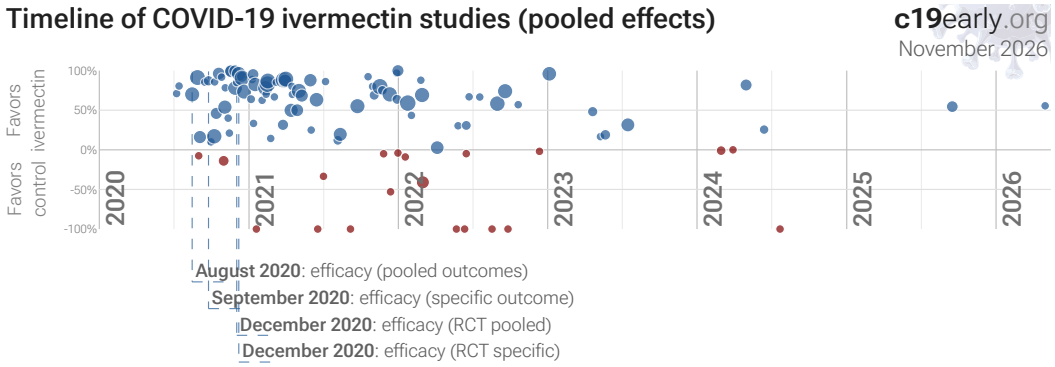

Fig. 3. **Timeline of results in ivermectin studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, pooled outcomes in RCTs, and one or more specific outcome in RCTs. Efficacy based on RCTs only was delayed by 3.6 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 1.3 months, compared to using pooled outcomes.

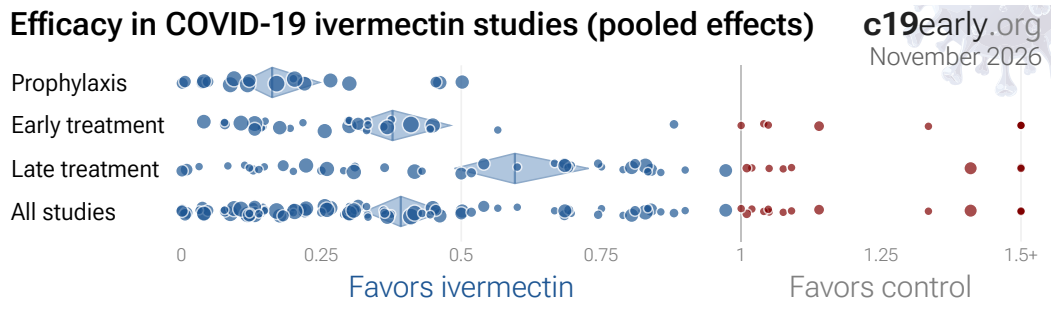

Fig. 4. Results by treatment stage.

Ivermectin COVID-19 studies

c19early.org
November 2026

Study	Improvement	RR · 95% CI	Outcome	Treatment	Control	Dose (4d)	Relative Risk
Chowdhury (RCT)	81%	0.19 · 0.01–3.96	hosp.	0/60	2/56	14mg	OT[1] CT[2]
Espitia-Hernandez	70%	0.30 · 0.16–0.55	recov. time	28 (n)	7 (n)	12mg	CT[2]
Carvallo	85%	0.15 · 0.02–1.28	death	1/32	3/14	36mg	CT[2]
Mahmud (DB RCT)	86%	0.14 · 0.01–2.75	death	0/183	3/183	12mg	CT[2]
Szente Fonseca	−14%	1.14 · 0.75–1.66	hosp.	340 (n)	377 (n)	24mg	
Cadegiani	78%	0.22 · 0.01–4.48	death	0/110	2/137	42mg	CT[2]
Ahmed (DB RCT)	85%	0.15 · 0.01–2.70	symptoms	0/17	3/19	48mg	
Chaccour (DB RCT)	96%	0.04 · 0.00–1.01	symptoms	12 (n)	12 (n)	28mg	SAINT
Ghauri	92%	0.08 · 0.01–0.88	no recov.	0/37	7/53	48mg	
Babalola (DB RCT)	64%	0.36 · 0.10–1.27	viral+	40 (n)	20 (n)	24mg	OT[1]
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	RIVET-COV
Biber (DB RCT)	70%	0.30 · 0.03–2.76	hosp.	1/47	3/42	36mg	
Elalfy	87%	0.13 · 0.06–0.27	viral+	7/62	44/51	36mg	CT[2]
López-Me.. (DB RCT)	67%	0.33 · 0.01–8.11	death	0/200	1/198	84mg	
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.	77,381 (all patients)		24mg	censored, see notes CS[5]
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 · 0.11–58.11	ventilation	1/27	0/14	168mg	
Vallejos (DB RCT)	−33%	1.33 · 0.30–5.72	death	4/250	3/251	24mg	
Reis (DB RCT)	12%	0.88 · 0.49–1.55	death	21/679	24/679	84mg	TOGETHER
Buonfrate (DB RCT)	−211%	3.11 · 0.13–73.31	hosp.	1/28	0/31	336mg	COVER
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	MD[3] CT[2] SC[4]
Abbas (DB RCT)	−4%	1.04 · 0.07–16.41	death	1/99	1/103	84mg	
de Jesús Ascenci..	59%	0.41 · 0.36–0.47	death/hosp.	7,898 (n)	20,150 (n)	12mg	CT[2]
Manomai.. (DB RCT)	43%	0.57 · 0.20–1.46	no recov.	3/36	6/36	48mg	
de la Ro.. (DB RCT)	−187%	2.87 · 0.12–67.49	misc.	1/30	0/26	36mg	
Rezai (DB RCT)	−5%	1.05 · 0.07–16.68	death	1/268	1/281	84mg	
Mirahma.. (DB RCT)	67%	0.33 · 0.03–3.14	ventilation	1/131	3/130	24mg	
Schilling (RCT)	67%	0.33 · 0.01–7.97	hosp.	0/45	1/45	168mg	PLATCOV
Bramante (DB RCT)	−197%	2.97 · 0.12–72.71	death	1/408	0/396	90mg	COVID-OUT OT[1]
Mikamo (DB RCT)	−205%	3.05 · 0.12–74.69	progression	1/502	0/527	63mg	IVERMILCO
Siripongbo.. (RCT)	0%	1.00 · 0.07–15.26	progression	1/30	1/30	168mg	FINCOV CT[2]
Wijewic.. (DB RCT)	−196%	2.96 · 0.12–71.99	death	1/127	0/122	96mg	
Mouawia (RCT)	56%	0.44 · 0.14–1.37	hosp.	4/63	9/63	12mg	
Early treatment	**62%**	0.38 · 0.30–0.48		71/16,013	245/43,025		62% lower risk

Tau² = 0.15, I² = 46.9%, p < 0.0001

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	CT[2]
Camprubí	40%	0.60 · 0.18–2.01	ventilation	3/13	5/13	14mg	

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Study	Improvement	RR · 95% CI	Outcome	Treatment	Control	Dose (4d)	Relative Risk
Spoorthi	21%	0.79 · 0.64–0.98	recov. time	50 (n)	50 (n)	n/a	CT[2]
Budhiraja	99%	0.01 · 0.00–0.15	death	0/34	103/942	n/a	
Ravikirti (DB RCT)	89%	0.11 · 0.01–2.05	death	0/55	4/57	24mg	
Okumuş (DB RCT)	33%	0.67 · 0.27–1.64	death	6/30	9/30	56mg	
Shahbazn.. (DB RCT)	−197%	2.97 · 0.13–70.51	death	1/35	0/34	14mg	
Lima-Morales	78%	0.22 · 0.12–0.41	death	15/481	52/287	12mg	CT[2]
Beltran .. (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	censored, see notes
Huvemek (DB RCT)	32%	0.68 · 0.38–1.23	no improv.	13/50	19/50	84mg	
Ahsan	50%	0.50 · 0.28–0.90	death	17/110	17/55	21mg	CT[2]
Abd-Elsalam (RCT)	25%	0.75 · 0.17–3.06	death	3/82	4/82	36mg	
Hazan	86%	0.14 · 0.01–2.15	death	0/24	synthetic	24mg	see notes CT[2] SC[4]
Elavarasi	20%	0.80 · 0.61–1.06	death	48/283	311/1,475	n/a	
Rezk	80%	0.20 · 0.01–4.13	death	0/160	2/160	72mg	
Lim (RCT)	69%	0.31 · 0.09–1.11	death	3/241	10/249	112mg	I-TECH
Ozer	75%	0.25 · 0.06–1.13	death	2/60	8/60	28mg	
Ferreira	−5%	1.05 · 0.32–3.43	death	3/21	11/81	n/a	
Jamir (ICU)	−53%	1.53 · 0.88–2.67	death	32/76	69/190	n/a	ICU patients
Mustafa	64%	0.36 · 0.12–1.14	death	3/73	42/371	varies	
Zubair	−9%	1.09 · 0.33–3.64	death	5/90	5/98	12mg	
Thairu (PSM)	88%	0.12 · 0.01–2.14	death	0/21	4/26	56mg	
Efimenko (PSM)	69%	0.31 · 0.20–0.48	death	1,072 (n)	40,536 (n)	n/a	self-censored, see notes OT[1]
Soto	−41%	1.41 · 1.16–1.76	death	280/484	374/934	n/a	
Ravikirti	3%	0.97 · 0.74–1.24	death	53/171	254/794	varies	
George (RCT)	30%	0.70 · 0.25–1.93	death	5/35	8/39	24mg	
Naggie (DB RCT)	−202%	3.02 · 0.12–74.08	death	1/708	0/724	168mg	ACTIV-6
Rezai (DB RCT)	31%	0.69 · 0.35–1.39	death	13/311	18/298	84mg	
Qadeer	58%	0.42 · 0.31–0.56	viral+	35/105	84/105	48mg	
Aref (RCT)	74%	0.26 · 0.12–0.55	recov. time	49 (n)	47 (n)	n/a	LONG COVID
Ochoa-Ja.. (DB RCT)	57%	0.43 · 0.07–2.50	death	2/37	4/38	28mg	
Sarojvisut (RCT)	−2%	1.02 · 0.06–16.15	death	1/157	1/160	112mg	
Munir	48%	0.52 · 0.22–1.21	death	92 (n)	908 (n)	n/a	
Llenas-García	17%	0.83 · 0.38–1.84	death	10/96	12/96	14mg	
Wada (DB RCT)	19%	0.81 · 0.44–1.38	progression	19/106	23/106	14mg	
Osati	32%	0.68 · 0.45–0.92	death	448 (n)	849 (n)	n/a	
Hayward (RCT)	−1%	1.01 · 0.61–1.68	death/hosp.	34/2,157	27/1,806	73mg	PRINCIPLE
Varnaseri (DB RCT)	82%	0.18 · 0.04–0.78	ventilation	2/55	11/55	84mg	
Hashmi (RCT)	26%	0.74 · 0.38–1.47	death	81 (n)	69 (n)	56mg	REMAP-CAP ICU patients
Late treatment	**40%**	0.60 · 0.49–0.73		741/8,783	2,994/54,985		**40% lower risk**
Tau² = 0.24, I² = 79.5%, p < 0.0001							
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	see notes CT[2]
Behera	54%	0.46 · 0.29–0.71	cases	41/117	145/255	42mg	
Carvallo	100%	0.00 · 0.00–0.02	cases	0/788	237/407	48mg	see notes CT[2]
Hellwig (ECO.)	78%	0.22 · 0.06–0.76	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	
IVERCOR PREP	73%	0.27 · 0.15–0.48	cases	13/389	61/486	48mg	MD[3]
Chahla (RCT)	95%	0.05 · 0.00–0.80	m/s case	0/117	10/117	48mg	CT[2]

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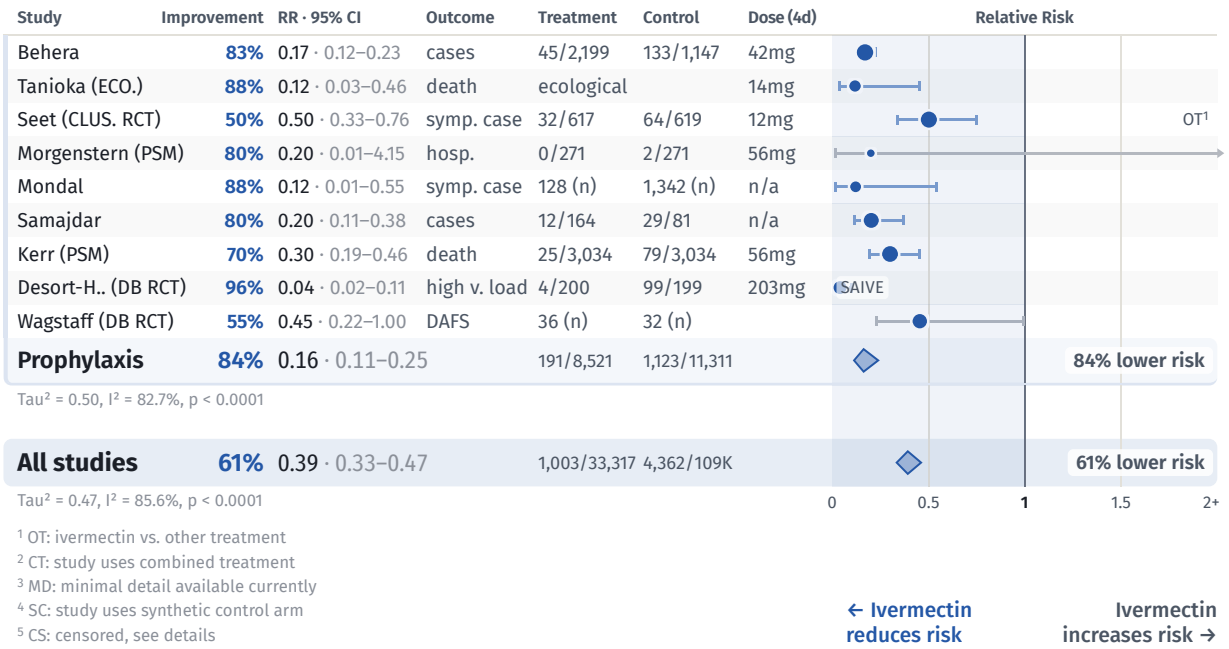

Fig. 5. **Random-effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. Simplified dosages are shown for comparison, these are the total dose in the first four days for treatment, or the monthly dose for prophylaxis, for a 70kg person. For details of effect extraction and full dosage information see the appendix.

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Ivermectin COVID-19 mortality results

c19early.org
November 2026

Study	Improvement	RR · 95% CI	Treatment	Control	Dose (4d)	Relative Risk
Carvallo	85%	0.15 · 0.02–1.28	1/32	3/14	36mg	CT[2]
Mahmud (DB RCT)	86%	0.14 · 0.01–2.75	0/183	3/183	12mg	CT[2]
Cadegiani	78%	0.22 · 0.01–4.48	0/110	2/137	42mg	CT[2]
López-Me.. (DB RCT)	67%	0.33 · 0.01–8.11	0/200	1/198	84mg	
Loue (QR)	70%	0.30 · 0.04–2.20	1/10	5/15	14mg	
Vallejos (DB RCT)	-33%	1.33 · 0.30–5.72	4/250	3/251	24mg	
Reis (DB RCT)	12%	0.88 · 0.49–1.55	21/679	24/679	84mg	TOGETHER; impossible data, see notes
Mayer	55%	0.45 · 0.32–0.63	3,266 (n)	17,966 (n)	151mg	
Borody	92%	0.08 · 0.01–0.79	0/600	6/600	96mg	MD[3] CT[2] SC[4]
Abbas (DB RCT)	-4%	1.04 · 0.07–16.41	1/99	1/103	84mg	
de Jesús Ascenci..	15%	0.85 · 0.68–1.06	101/7,898	303/20,150	12mg	CT[2]
Rezai (DB RCT)	-5%	1.05 · 0.07–16.68	1/268	1/281	84mg	
Bramante (DB RCT)	-197%	2.97 · 0.12–72.71	1/408	0/396	90mg	COVID-OUT; OT[1]
Wijewic.. (DB RCT)	-196%	2.96 · 0.12–71.99	1/127	0/122	96mg	
Early treatment	**37%**	0.63 · 0.43–0.92	132/14,130	352/41,095		**37% lower risk**
Tau² = 0.11, I² = 38.2%, p = 0.015						
Gorial	71%	0.29 · 0.01–5.76	0/16	2/71	14mg	
Khan	87%	0.13 · 0.02–1.00	1/115	9/133	12mg	
Soto-Becerra	17%	0.83 · 0.71–0.97	92/203	1,438/2,630	14mg	
Rajter (PSM)	46%	0.54 · 0.27–0.99	13/98	24/98	14mg	
Hashim (SB RCT)	92%	0.08 · 0.00–1.44	0/59	6/70	28mg	CT[2]
Budhiraja	99%	0.01 · 0.00–0.15	0/34	103/942	n/a	
Ravikirti (DB RCT)	89%	0.11 · 0.01–2.05	0/55	4/57	24mg	
Okumuş (DB RCT)	33%	0.67 · 0.27–1.64	6/30	9/30	56mg	
Shahbazn.. (DB RCT)	-197%	2.97 · 0.13–70.51	1/35	0/34	14mg	
Lima-Morales	78%	0.22 · 0.12–0.41	15/481	52/287	12mg	CT[2]
Beltran .. (DB RCT)	14%	0.86 · 0.29–2.56	5/36	6/37	12mg	
Ahsan	50%	0.50 · 0.28–0.90	17/110	17/55	21mg	CT[2]
Abd-Elsalam (RCT)	25%	0.75 · 0.17–3.06	3/82	4/82	36mg	
Hazan	86%	0.14 · 0.01–2.15	0/24	synthetic	24mg	see notes CT[2] SC[4]
Elavarasi	20%	0.80 · 0.61–1.06	48/283	311/1,475	n/a	
Rezk	80%	0.20 · 0.01–4.13	0/160	2/160	72mg	
Lim (RCT)	69%	0.31 · 0.09–1.11	3/241	10/249	112mg	I-TECH
Ozer	75%	0.25 · 0.06–1.13	2/60	8/60	28mg	
Ferreira	-5%	1.05 · 0.32–3.43	3/21	11/81	n/a	
Jamir (ICU)	-53%	1.53 · 0.88–2.67	32/76	69/190	n/a	ICU patients
Mustafa	64%	0.36 · 0.12–1.14	3/73	42/371	varies	
Zubair	-9%	1.09 · 0.33–3.64	5/90	5/98	12mg	
Thairu (PSM)	88%	0.12 · 0.01–2.14	0/21	4/26	56mg	
Efimenko (PSM)	69%	0.31 · 0.20–0.48	1,072 (n)	40,536 (n)	n/a	self-censored, see notes OT[1]
Soto	-41%	1.41 · 1.16–1.76	280/484	374/934	n/a	
Ravikirti	3%	0.97 · 0.74–1.24	53/171	254/794	varies	
George (RCT)	30%	0.70 · 0.25–1.93	5/35	8/39	24mg	
Naggie (DB RCT)	-202%	3.02 · 0.12–74.08	1/708	0/724	168mg	ACTIV-6
Rezai (DB RCT)	31%	0.69 · 0.35–1.39	13/311	18/298	84mg	
Ochoa-Ja.. (DB RCT)	57%	0.43 · 0.07–2.50	2/37	4/38	28mg	
Sarojvisut (RCT)	-2%	1.02 · 0.06–16.15	1/157	1/160	112mg	
Munir	48%	0.52 · 0.22–1.21	92 (n)	908 (n)	n/a	
Llenas-García	17%	0.83 · 0.38–1.84	10/96	12/96	14mg	
Osati	32%	0.68 · 0.45–0.92	448 (n)	849 (n)	n/a	

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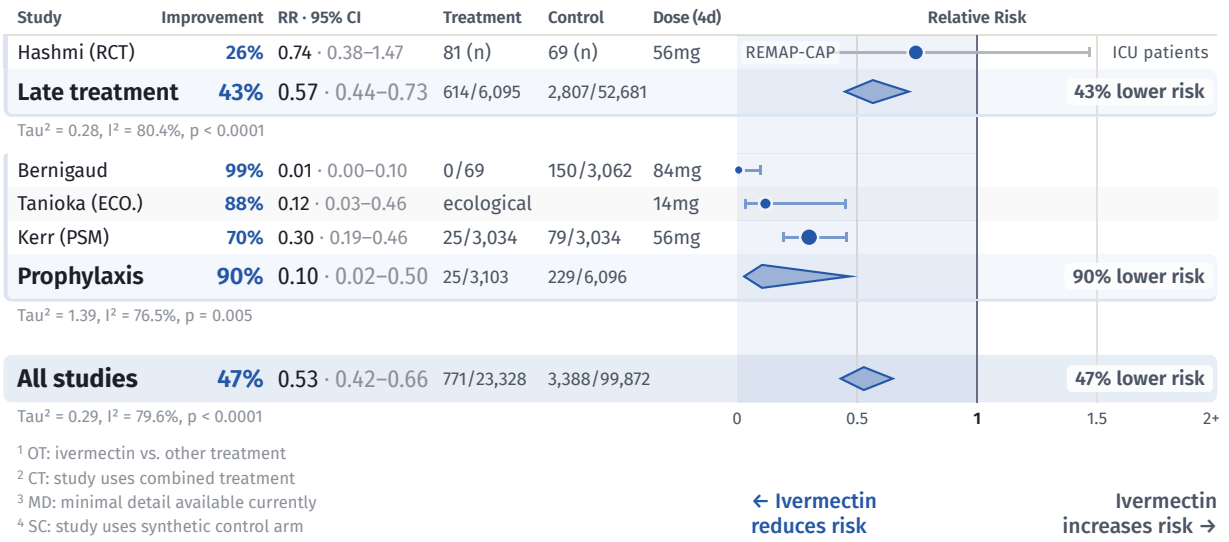

Fig. 6. Random-effects meta-analysis for mortality results.

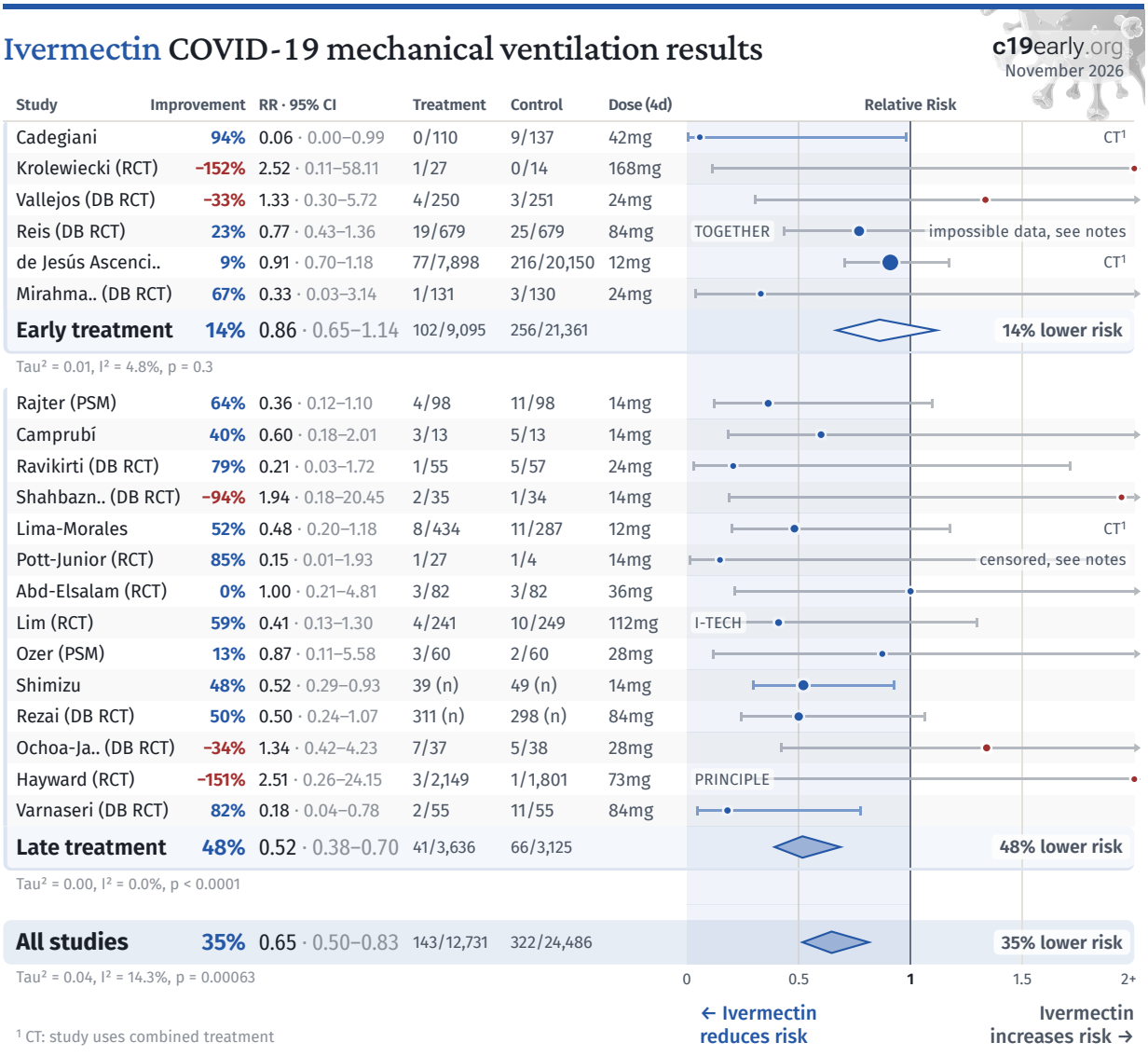

Fig. 7. Random-effects meta-analysis for mechanical ventilation.

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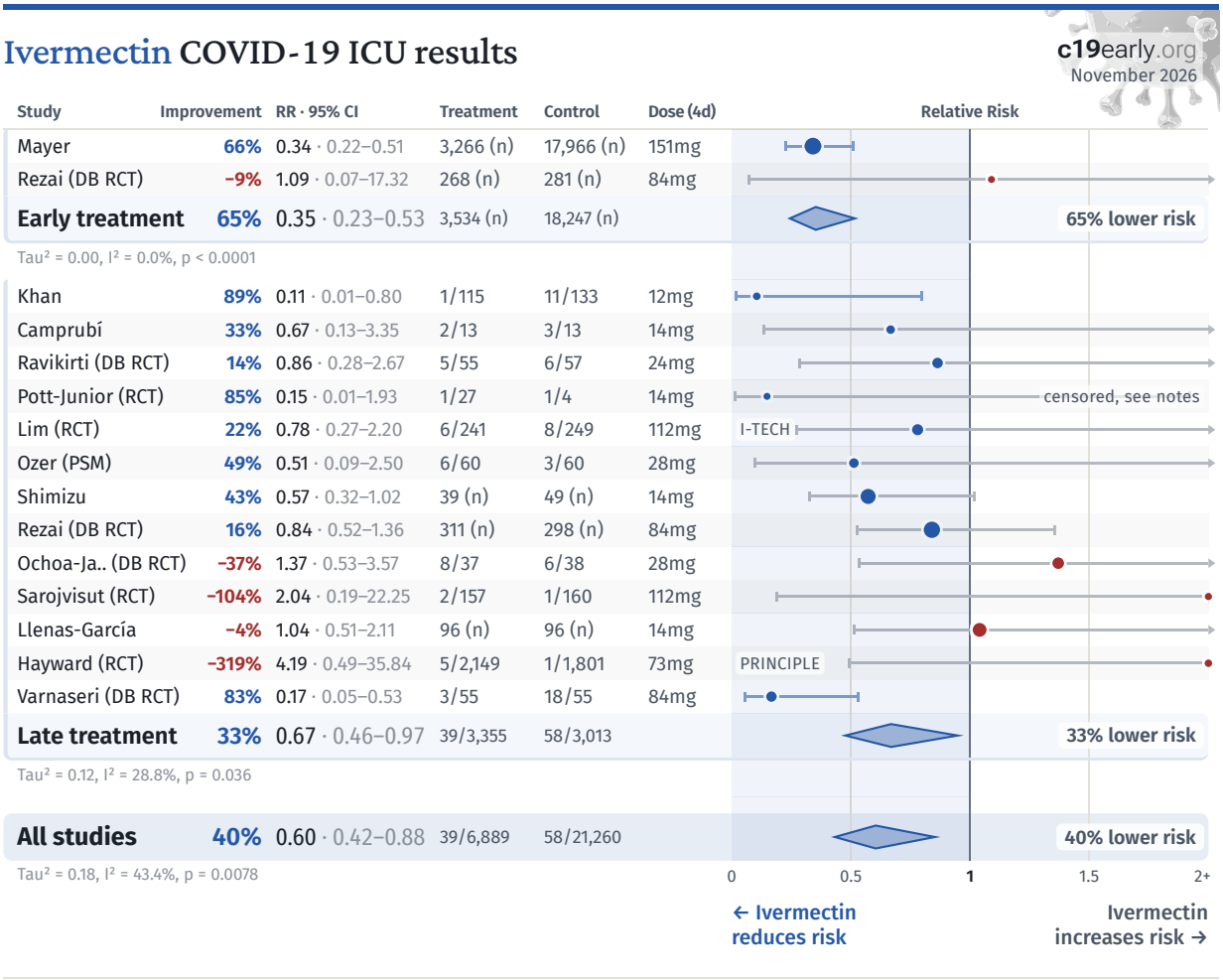

Fig. 8. Random-effects meta-analysis for ICU admission.

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Fig. 9. Random-effects meta-analysis for hospitalization.

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Ivermectin COVID-19 recovery results

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November 2026

Study	Improvement	RR · 95% CI	Outcome	Treatment	Control	Dose (4d)	Relative Risk
Chowdhury (RCT)	46%	0.54 · 0.40–0.73	no recov.	27/60	47/56	14mg	OT[1] CT[2]
Espitia-Hernandez	70%	0.30 · 0.16–0.55	recov. time	28 (n)	7 (n)	12mg	CT[2]
Mahmud (DB RCT)	94%	0.06 · 0.04–0.09	no recov.	72/183	100/180	12mg	CT[2]
Ghauri	92%	0.08 · 0.01–0.88	no recov.	0/37	7/53	48mg	
Babalola (DB RCT)	41%	0.59 · 0.33–1.05	ΔSpo2	38 (n)	18 (n)	24mg	OT[1]
Mohan (DB RCT)	62%	0.38 · 0.08–1.75	no recov.	2/40	6/45	28mg	RIVET-COV
López-Me.. (DB RCT)	15%	0.85 · 0.56–1.25	no recov.	36/200	42/198	84mg	
Chahla (CLUS. RCT)	87%	0.13 · 0.03–0.54	no disch.	2/110	20/144	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	
Reis (DB RCT)	5%	0.95 · 0.81–1.14	no recov.	679 (n)	679 (n)	84mg	TOGETHER impossible data, see notes
Abbas (DB RCT)	36%	0.64 · 0.43–0.96	no recov.	26/99	42/103	84mg	
Manomai.. (DB RCT)	43%	0.57 · 0.20–1.46	no recov.	3/36	6/36	48mg	
Rezai (DB RCT)	-2%	1.02 · 0.96–1.08	no recov.	268 (n)	281 (n)	84mg	
Mirahma.. (DB RCT)	39%	0.61 · 0.26–1.42	no recov.	8/131	13/130	24mg	
Mikamo (DB RCT)	4%	0.96 · 0.78–1.20	no recov.	502 (n)	527 (n)	63mg	IVERMILCO
Siripongbo.. (RCT)	39%	0.61 · 0.28–1.29	symp. score	30 (n)	30 (n)	168mg	FINCOV CT[2]
Mouawia (RCT)	31%	0.69 · 0.53–0.90	no recov.	63 (n)	63 (n)	12mg	
Early treatment	**51%**	0.49 · 0.36–0.67		182/2,611	302/2,657		**51% lower risk**
Tau² = 0.32, I² = 93.4%, p < 0.0001							
Gorial	71%	0.29 · 0.01–5.76	no recov.	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	no recov.	1/115	9/133	12mg	
Chachar (RCT)	10%	0.90 · 0.44–1.83	no recov.	9/25	10/25	36mg	
Hashim (SB RCT)	41%	0.59 · 0.46–0.77	recov. time	70 (n)	70 (n)	28mg	CT[2]
Spoorthi	21%	0.79 · 0.64–0.98	recov. time	50 (n)	50 (n)	n/a	CT[2]
Ravikirti (DB RCT)	89%	0.11 · 0.01–2.05	no disch.	0/55	4/57	24mg	
Shahbazn.. (DB RCT)	32%	0.68 · 0.47–1.00	recov. time	35 (n)	34 (n)	14mg	
Lima-Morales	59%	0.41 · 0.30–0.55	no recov.	75/481	118/287	12mg	CT[2]
Beltran .. (DB RCT)	-37%	1.37 · 0.33–5.70	no disch.	4/36	3/37	12mg	
Rezk	33%	0.67 · 0.35–1.27	no recov.	14/145	20/138	72mg	
Lim (RCT)	-2%	1.02 · 0.85–1.23	no recov.	116/241	116/247	112mg	I-TECH
Thairu (PSM)	55%	0.45 · 0.31–0.67	no disch.	61 (n)	26 (n)	56mg	
George (RCT)	19%	0.81 · 0.52–1.27	recov. time	35 (n)	39 (n)	24mg	
Naggie (DB RCT)	2%	0.98 · 0.89–1.09	recovery	708 (n)	724 (n)	168mg	ACTIV-6
Rezai (DB RCT)	24%	0.76 · 0.60–0.96	no recov.	311 (n)	298 (n)	84mg	
Aref (RCT)	74%	0.26 · 0.12–0.55	recov. time	49 (n)	47 (n)	n/a	LONG COVID
Sarojvisut (RCT)	4%	0.96 · 0.82–1.12	recov. time	157 (n)	160 (n)	112mg	
Wada (DB RCT)	60%	0.40 · 0.13–1.24	no recov.	4/107	10/107	14mg	
Hayward (RCT)	16%	0.84 · 0.78–0.92	no recov.	2,157 (n)	1,806 (n)	73mg	PRINCIPLE
Varnaseri (DB RCT)	28%	0.72 · 0.66–0.78	recov. time	55 (n)	55 (n)	84mg	
Late treatment	**27%**	0.73 · 0.64–0.82		234/4,960	299/4,454		**27% lower risk**
Tau² = 0.04, I² = 76.8%, p < 0.0001							
Wagstaff (DB RCT)	55%	0.45 · 0.22–1.00	DAFS	36 (n)	32 (n)		
Prophylaxis	**55%**	0.45 · 0.22–0.95		36 (n)	32 (n)		**55% lower risk**
Tau² = 0.00, I² = 0.0%, p = 0.036							

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Study	Improvement	RR · 95% CI	Outcome	Treatment	Control	Dose (4d)	Relative Risk
All studies	**38%**	0.62 · 0.55–0.71		416/7,607	601/7,143		38% lower risk

Tau² = 0.10, I² = 89.1%, p < 0.0001

0 0.5 1 1.5 2+

[1] OT: ivermectin vs. other treatment
[2] CT: study uses combined treatment

← Ivermectin reduces risk

Ivermectin increases risk →

Fig. 10. Random-effects meta-analysis for recovery.

Ivermectin COVID-19 case results

c19early.org
November 2026

Study	Improvement	RR · 95% CI	Outcome	Treatment	Control	Dose (1m)	Relative Risk
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	see notes CT[2]
Behera	54%	0.46 · 0.29–0.71	cases	41/117	145/255	42mg	
Carvallo	100%	0.00 · 0.00–0.02	cases	0/788	237/407	48mg	see notes CT[2]
Hellwig (ECO.)	78%	0.22 · 0.06–0.76	cases	ecological		14mg	
Bernigaud	55%	0.45 · 0.22–0.91	cases	7/69	692/3,062	84mg	
Alam	91%	0.09 · 0.04–0.25	cases	4/58	44/60	12mg	
IVERCOR PREP	73%	0.27 · 0.15–0.48	cases	13/389	61/486	48mg	MD[3]
Chahla (RCT)	84%	0.16 · 0.04–0.46	cases	4/117	25/117	48mg	CT[2]
Behera	83%	0.17 · 0.12–0.23	cases	45/2,199	133/1,147	42mg	
Seet (CLUS. RCT)	50%	0.50 · 0.33–0.76	symp. case	32/617	64/619	12mg	OT[1]
Morgenstern (PSM)	74%	0.26 · 0.10–0.71	cases	5/271	18/271	56mg	
Mondal	88%	0.12 · 0.01–0.55	symp. case	128 (n)	1,342 (n)	n/a	
Samajdar	80%	0.20 · 0.11–0.38	cases	12/164	29/81	n/a	
Kerr (PSM)	44%	0.56 · 0.53–0.58	cases	population-based cohort		56mg	
Desort-H.. (DB RCT)	96%	0.04 · 0.02–0.11	high v. load	4/200	99/199	203mg	SAIVE
Wagstaff (DB RCT)	47%	0.53 · 0.29–0.91	viral+ time	36 (n)	32 (n)		
Prophylaxis	**79%**	0.21 · 0.14–0.31		182/5,487	1,617/8,277		79% lower risk

Tau² = 0.48, I² = 91.3%, p < 0.0001

All studies	**79%**	0.21 · 0.14–0.31		182/5,487	1,617/8,277		79% lower risk

Tau² = 0.48, I² = 91.3%, p < 0.0001

0 0.5 1 1.5 2+

[1] OT: ivermectin vs. other treatment
[2] CT: study uses combined treatment
[3] MD: minimal detail available currently

← Ivermectin reduces risk

Ivermectin increases risk →

Fig. 11. Random-effects meta-analysis for cases.

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Fig. 12. Random-effects meta-analysis for viral clearance.

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Ivermectin COVID-19 peer reviewed studies

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November 2026

Study	Improvement	RR · 95% CI	Outcome	Treatment	Control	Dose (4d)	Relative Risk
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	SAINT
Ghauri	92%	0.08 · 0.01–0.88	no recov.	0/37	7/53	48mg	
Babalola (DB RCT)	64%	0.36 · 0.10–1.27	viral+	40 (n)	20 (n)	24mg	OT¹
Mohan (DB RCT)	62%	0.38 · 0.08–1.75	no recov.	2/40	6/45	28mg	RIVET-COV
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	
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	
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 · 0.11–58.11	ventilation	1/27	0/14	168mg	
Vallejos (DB RCT)	−33%	1.33 · 0.30–5.72	death	4/250	3/251	24mg	
Reis (DB RCT)	12%	0.88 · 0.49–1.55	death	21/679	24/679	84mg	TOGETHER impossible data, see notes
Buonfrate (DB RCT)	−211%	3.11 · 0.13–73.31	hosp.	1/28	0/31	336mg	COVER
Mayer	55%	0.45 · 0.32–0.63	death	3,266 (n)	17,966 (n)	151mg	
Abbas (DB RCT)	−4%	1.04 · 0.07–16.41	death	1/99	1/103	84mg	
de Jesús Ascenci..	59%	0.41 · 0.36–0.47	death/hosp.	7,898 (n)	20,150 (n)	12mg	CT²
Manomai.. (DB RCT)	43%	0.57 · 0.20–1.46	no recov.	3/36	6/36	48mg	
de la Ro.. (DB RCT)	−187%	2.87 · 0.12–67.49	misc.	1/30	0/26	36mg	
Rezai (DB RCT)	−5%	1.05 · 0.07–16.68	death	1/268	1/281	84mg	
Mirahma.. (DB RCT)	67%	0.33 · 0.03–3.14	ventilation	1/131	3/130	24mg	
Schilling (RCT)	67%	0.33 · 0.01–7.97	hosp.	0/45	1/45	168mg	PLATCOV
Bramante (DB RCT)	−197%	2.97 · 0.12–72.71	death	1/408	0/396	90mg	COVID-OUT OT¹
Mikamo (DB RCT)	−205%	3.05 · 0.12–74.69	progression	1/502	0/527	63mg	IVERMILCO
Siripongbo.. (RCT)	0%	1.00 · 0.07–15.26	progression	1/30	1/30	168mg	FINCOV CT²
Wijewic.. (DB RCT)	−196%	2.96 · 0.12–71.99	death	1/127	0/122	96mg	
Mouawia (RCT)	56%	0.44 · 0.14–1.37	hosp.	4/63	9/63	12mg	
Early treatment	**60%**	0.40 · 0.31–0.52		67/15,372	214/42,380		60% lower risk
Tau² = 0.15, I² = 46.3%, p < 0.0001							
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	
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	CT²
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	CT²
Ravikirti (DB RCT)	89%	0.11 · 0.01–2.05	death	0/55	4/57	24mg	
Okumuş (DB RCT)	33%	0.67 · 0.27–1.64	death	6/30	9/30	56mg	
Shahbazn.. (DB RCT)	−197%	2.97 · 0.13–70.51	death	1/35	0/34	14mg	
Lima-Morales	78%	0.22 · 0.12–0.41	death	15/481	52/287	12mg	CT²

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Study	Improvement	RR · 95% CI	Outcome	Treatment	Control	Dose (4d)	Relative Risk
Beltran .. (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	censored, see notes
Ahsan	50%	0.50 · 0.28–0.90	death	17/110	17/55	21mg	CT[2]
Abd-Elsalam (RCT)	25%	0.75 · 0.17–3.06	death	3/82	4/82	36mg	
Elavarasi	20%	0.80 · 0.61–1.06	death	48/283	311/1,475	n/a	
Rezk	80%	0.20 · 0.01–4.13	death	0/160	2/160	72mg	
Lim (RCT)	69%	0.31 · 0.09–1.11	death	3/241	10/249	112mg	I-TECH
Ozer	75%	0.25 · 0.06–1.13	death	2/60	8/60	28mg	
Ferreira	-5%	1.05 · 0.32–3.43	death	3/21	11/81	n/a	
Jamir (ICU)	-53%	1.53 · 0.88–2.67	death	32/76	69/190	n/a	ICU patients
Mustafa	64%	0.36 · 0.12–1.14	death	3/73	42/371	varies	
Zubair	-9%	1.09 · 0.33–3.64	death	5/90	5/98	12mg	
Thairu (PSM)	88%	0.12 · 0.01–2.14	death	0/21	4/26	56mg	
Efimenko (PSM)	69%	0.31 · 0.20–0.48	death	1,072 (n)	40,536 (n)	n/a	self-censored, see notes OT[1]
Soto	-41%	1.41 · 1.16–1.76	death	280/484	374/934	n/a	
George (RCT)	30%	0.70 · 0.25–1.93	death	5/35	8/39	24mg	
Naggie (DB RCT)	-202%	3.02 · 0.12–74.08	death	1/708	0/724	168mg	ACTIV-6
Rezai (DB RCT)	31%	0.69 · 0.35–1.39	death	13/311	18/298	84mg	
Qadeer	58%	0.42 · 0.31–0.56	viral+	35/105	84/105	48mg	
Aref (RCT)	74%	0.26 · 0.12–0.55	recov. time	49 (n)	47 (n)	n/a	LONG COVID
Ochoa-Ja.. (DB RCT)	57%	0.43 · 0.07–2.50	death	2/37	4/38	28mg	
Sarojvisut (RCT)	-2%	1.02 · 0.06–16.15	death	1/157	1/160	112mg	
Munir	48%	0.52 · 0.22–1.21	death	92 (n)	908 (n)	n/a	
Llenas-García	17%	0.83 · 0.38–1.84	death	10/96	12/96	14mg	
Wada (DB RCT)	19%	0.81 · 0.44–1.38	progression	19/106	23/106	14mg	
Hayward (RCT)	-1%	1.01 · 0.61–1.68	death/hosp.	34/2,157	27/1,806	73mg	PRINCIPLE
Varnaseri (DB RCT)	82%	0.18 · 0.04–0.78	ventilation	2/55	11/55	84mg	
Hashmi (RCT)	26%	0.74 · 0.38–1.47	death	81 (n)	69 (n)	56mg	REMAP-CAP ICU patients
Late treatment	**42%**	0.58 · 0.45–0.73		583/7,837	1,178/49,649		**42% lower risk**
Tau² = 0.33, I² = 81.5%, p < 0.0001							
Shouman (RCT)	91%	0.09 · 0.03–0.23	symp. case	15/203	59/101	36mg	
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	see notes CT[2]
Hellwig (ECO.)	78%	0.22 · 0.06–0.76	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	
Chahla (RCT)	95%	0.05 · 0.00–0.80	m/s case	0/117	10/117	48mg	CT[2]
Behera	83%	0.17 · 0.12–0.23	cases	45/2,199	133/1,147	42mg	
Seet (CLUS. RCT)	50%	0.50 · 0.33–0.76	symp. case	32/617	64/619	12mg	OT[1]
Morgenstern (PSM)	80%	0.20 · 0.01–4.15	hosp.	0/271	2/271	56mg	
Mondal	88%	0.12 · 0.01–0.55	symp. case	128 (n)	1,342 (n)	n/a	
Samajdar	80%	0.20 · 0.11–0.38	cases	12/164	29/81	n/a	
Kerr (PSM)	70%	0.30 · 0.19–0.46	death	25/3,034	79/3,034	56mg	
Wagstaff (DB RCT)	55%	0.45 · 0.22–1.00	DAFS	36 (n)	32 (n)		
Prophylaxis	**82%**	0.18 · 0.11–0.29		174/7,801	952/10,528		**82% lower risk**
Tau² = 0.48, I² = 84.0%, p < 0.0001							

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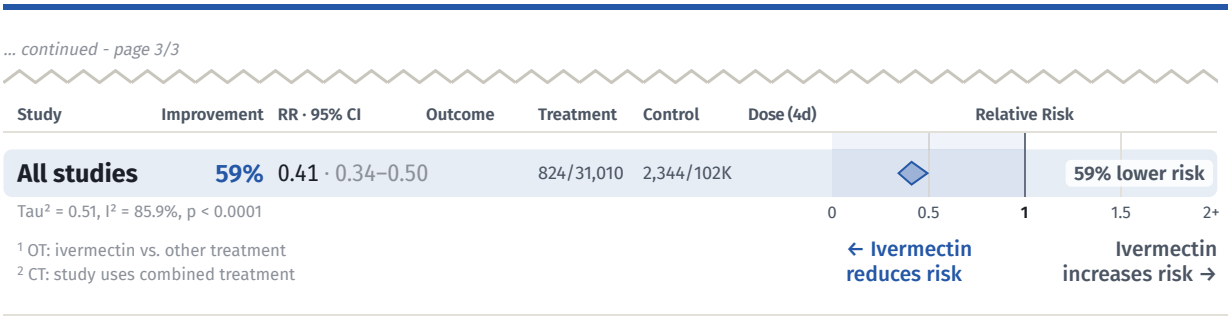

Fig. 13. **Random-effects meta-analysis for peer-reviewed studies.** *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta-analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta-analyses including 114 trials. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Randomized Controlled Trials (RCTs)

Results restricted to Randomized Controlled Trials (RCTs) are shown in Fig. 14, 15, 16, and 17, Table 1, and Table 2. The supplementary data contains RCT results after exclusions.

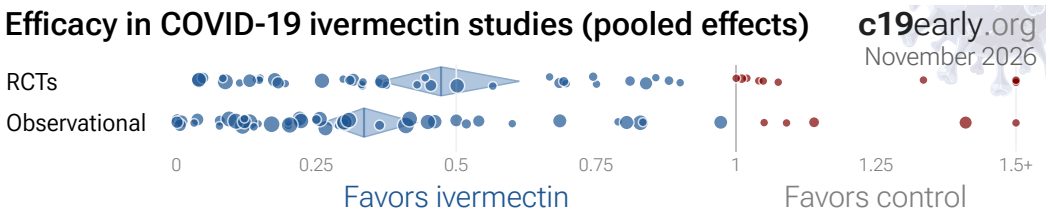

Fig. 14. **Randomized Controlled Trials.** The distribution of results for RCTs is similar to the distribution for observational studies.

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Ivermectin COVID-19 Randomized Controlled Trials

c19early.org
November 2026

Study	Improvement	RR · 95% CI	Outcome	Treatment	Control	Dose (4d)	Relative Risk
Chowdhury (RCT)	81%	0.19 · 0.01–3.96	hosp.	0/60	2/56	14mg	OT¹ CT²
Mahmud (DB RCT)	86%	0.14 · 0.01–2.75	death	0/183	3/183	12mg	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	SAINT
Babalola (DB RCT)	64%	0.36 · 0.10–1.27	viral+	40 (n)	20 (n)	24mg	OT¹
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	RIVET-COV
Biber (DB RCT)	70%	0.30 · 0.03–2.76	hosp.	1/47	3/42	36mg	
López-Me.. (DB RCT)	67%	0.33 · 0.01–8.11	death	0/200	1/198	84mg	
Chahla (CLUS. RCT)	87%	0.13 · 0.03–0.54	no disch.	2/110	20/144	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 · 0.11–58.11	ventilation	1/27	0/14	168mg	
Vallejos (DB RCT)	−33%	1.33 · 0.30–5.72	death	4/250	3/251	24mg	
Reis (DB RCT)	12%	0.88 · 0.49–1.55	death	21/679	24/679	84mg	TOGETHER impossible data, see notes
Buonfrate (DB RCT)	−211%	3.11 · 0.13–73.31	hosp.	1/28	0/31	336mg	COVER
Abbas (DB RCT)	−4%	1.04 · 0.07–16.41	death	1/99	1/103	84mg	
Manomai.. (DB RCT)	43%	0.57 · 0.20–1.46	no recov.	3/36	6/36	48mg	
de la Ro.. (DB RCT)	−187%	2.87 · 0.12–67.49	misc.	1/30	0/26	36mg	
Rezai (DB RCT)	−5%	1.05 · 0.07–16.68	death	1/268	1/281	84mg	
Mirahma.. (DB RCT)	67%	0.33 · 0.03–3.14	ventilation	1/131	3/130	24mg	
Schilling (RCT)	67%	0.33 · 0.01–7.97	hosp.	0/45	1/45	168mg	PLATCOV
Bramante (DB RCT)	−197%	2.97 · 0.12–72.71	death	1/408	0/396	90mg	COVID-OUT OT¹
Mikamo (DB RCT)	−205%	3.05 · 0.12–74.69	progression	1/502	0/527	63mg	IVERMILCO
Siripongbo.. (RCT)	0%	1.00 · 0.07–15.26	progression	1/30	1/30	168mg	FINCOV CT²
Wijewic.. (DB RCT)	−196%	2.96 · 0.12–71.99	death	1/127	0/122	96mg	
Mouawia (RCT)	56%	0.44 · 0.14–1.37	hosp.	4/63	9/63	12mg	
Early treatment	**55%**	0.45 · 0.34–0.61		57/3,580	131/3,605		**55% lower risk**
Tau² = 0.05, I² = 8.9%, p < 0.0001							
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	
Chachar (RCT)	10%	0.90 · 0.44–1.83	no recov.	9/25	10/25	36mg	
Hashim (SB RCT)	92%	0.08 · 0.00–1.44	death	0/59	6/70	28mg	CT²
Ravikirti (DB RCT)	89%	0.11 · 0.01–2.05	death	0/55	4/57	24mg	
Okumuş (DB RCT)	33%	0.67 · 0.27–1.64	death	6/30	9/30	56mg	
Shahbazn.. (DB RCT)	−197%	2.97 · 0.13–70.51	death	1/35	0/34	14mg	
Beltran .. (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	censored, see notes
Huvemek (DB RCT)	32%	0.68 · 0.38–1.23	no improv.	13/50	19/50	84mg	
Abd-Elsalam (RCT)	25%	0.75 · 0.17–3.06	death	3/82	4/82	36mg	
Lim (RCT)	69%	0.31 · 0.09–1.11	death	3/241	10/249	112mg	I-TECH
George (RCT)	30%	0.70 · 0.25–1.93	death	5/35	8/39	24mg	
Naggie (DB RCT)	−202%	3.02 · 0.12–74.08	death	1/708	0/724	168mg	ACTIV-6
Rezai (DB RCT)	31%	0.69 · 0.35–1.39	death	13/311	18/298	84mg	
Aref (RCT)	74%	0.26 · 0.12–0.55	recov. time	49 (n)	47 (n)	n/a	LONG COVID
Ochoa-Ja.. (DB RCT)	57%	0.43 · 0.07–2.50	death	2/37	4/38	28mg	
Sarojvisut (RCT)	−2%	1.02 · 0.06–16.15	death	1/157	1/160	112mg	
Wada (DB RCT)	19%	0.81 · 0.44–1.38	progression	19/106	23/106	14mg	
Hayward (RCT)	−1%	1.01 · 0.61–1.68	death/hosp.	34/2,157	27/1,806	73mg	PRINCIPLE
Varnaseri (DB RCT)	82%	0.18 · 0.04–0.78	ventilation	2/55	11/55	84mg	

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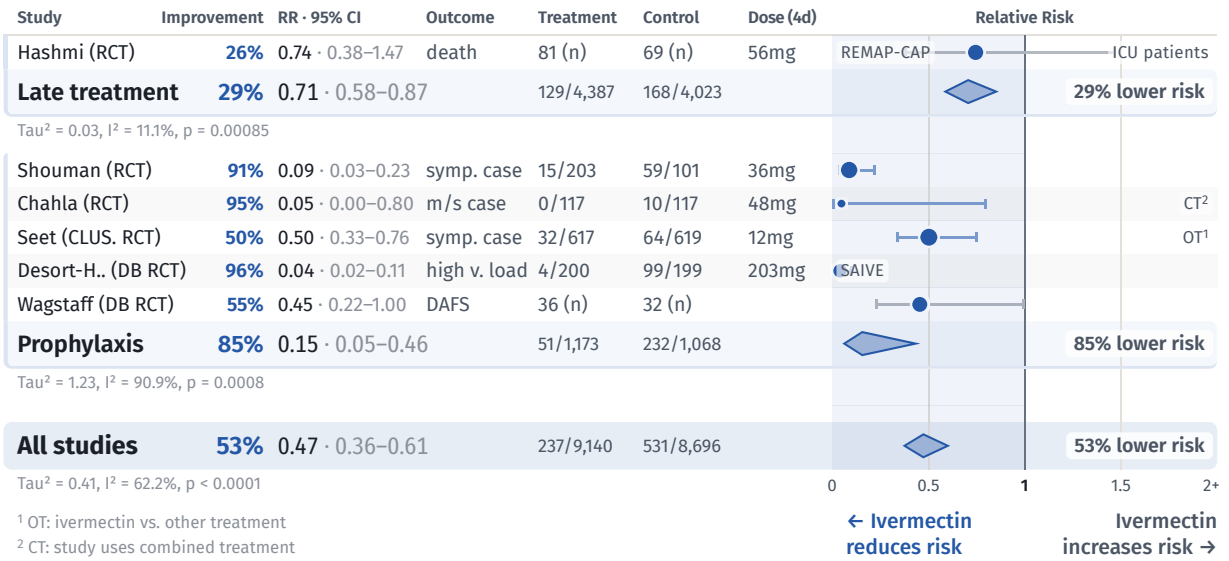

Fig. 15. **Random-effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. Simplified dosages are shown for comparison, these are the total dose in the first four days for treatment, or the monthly dose for prophylaxis, for a 70kg person. For details of effect extraction and full dosage information see the appendix.

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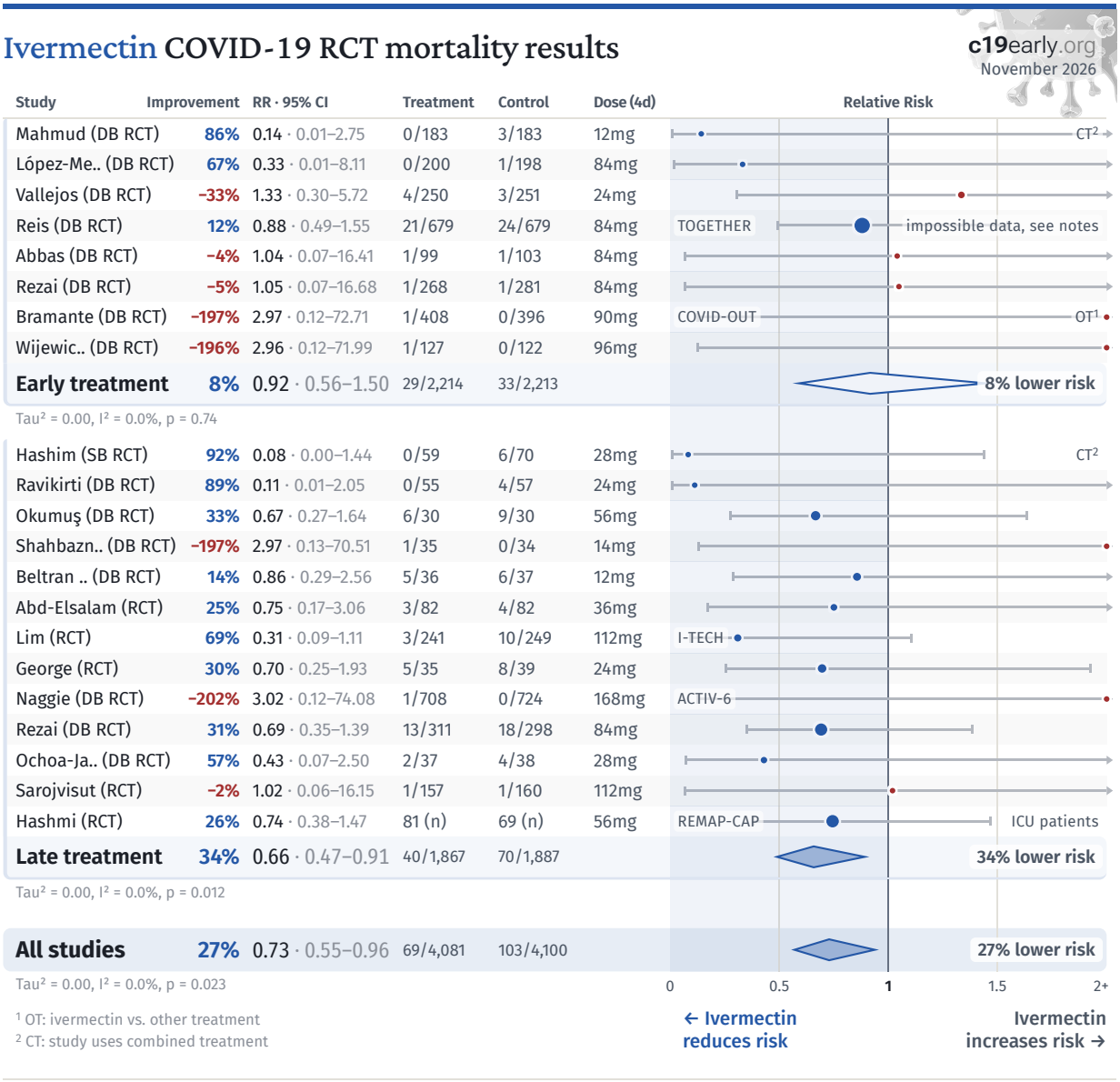

Fig. 16. Random-effects meta-analysis for RCT mortality results.

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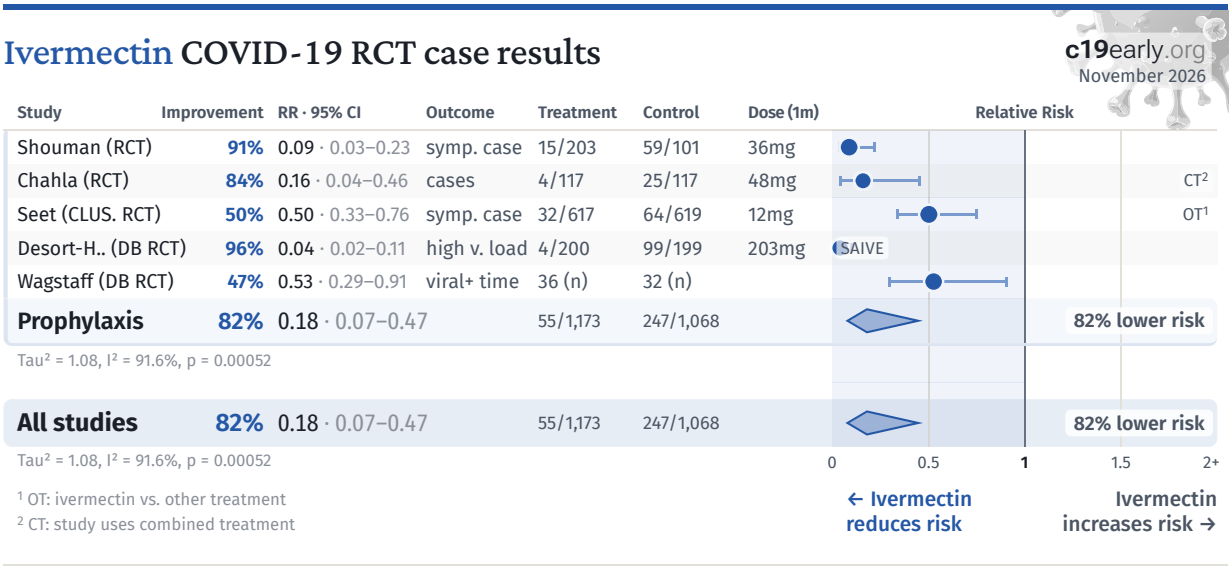

Fig. 18. Random-effects meta-analysis for RCT case results.

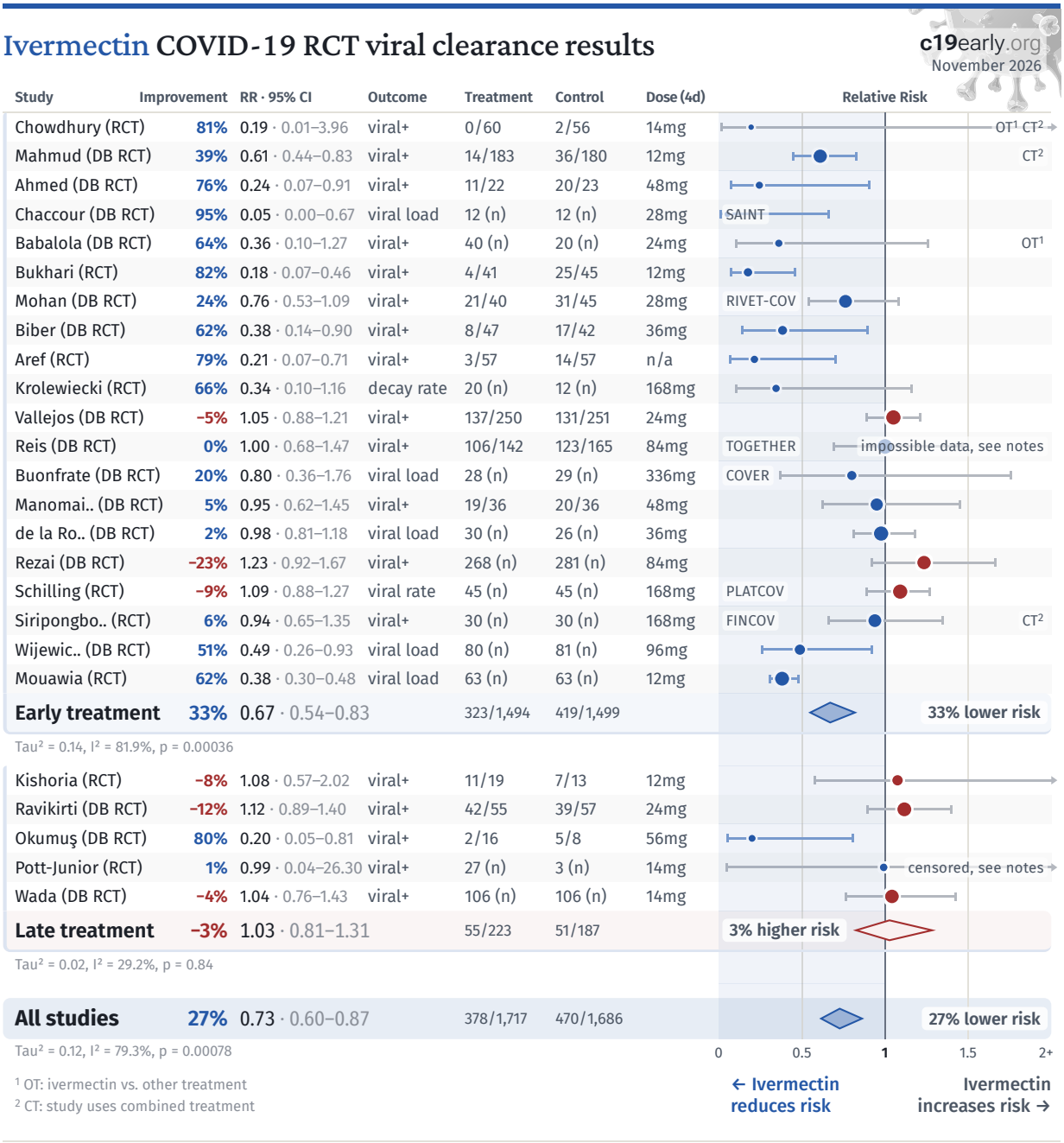

Fig. 17. Random-effects meta-analysis for RCT viral clearance results.

RCTs have many potential biases

RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases [149], and analysis of double-blind RCTs has identified extreme levels of bias [150]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs

RCTs are expensive and many RCTs are funded by pharmaceutical companies or other organizations with conflicts of interest, for example governments that previously denied treatment with the study drug. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. *Bekelman et al.* and *Lundh et al.* show that industry-sponsored studies are more likely to be favorable. For COVID-19, some ma-

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jor philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment

High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 227 treatments we have analyzed, 67% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

RCT bias for widely available treatments

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. 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, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

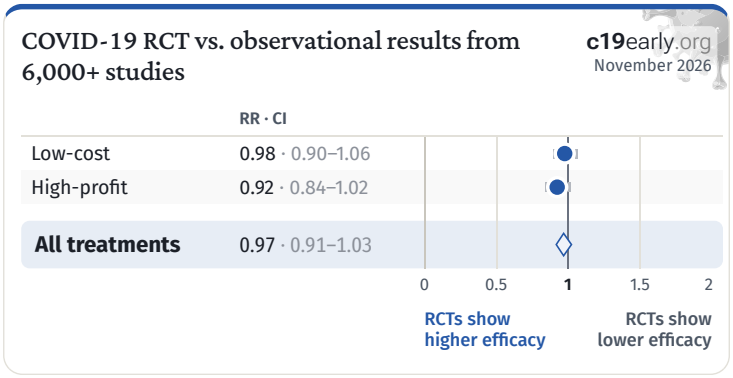

Fig. 19. For COVID-19, observational study results do not systematically differ from RCTs, RR 0.97 [0.91-1.03] across 227 treatments [154].

Observational studies have been shown to be reliable

Evidence shows that observational studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* analyzed reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates.

We performed a similar analysis across the 227 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.97 [0.91-1.03] [157]. Similar results are found for all low-cost treatments, RR 0.98 [0.90-1.06]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.84-1.02]. Details can be found in the supplementary data.

Lee et al. showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or remote survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see [159,160].

RCTs may be less reliable

Concato et al. report a paradoxical finding—RCT results had higher variability, and only RCTs were found to sometimes report significant results the opposite of the overall result. The same trend is seen for the most popular (most politicized) COVID-19 treatments including ivermectin—considering all statistically significant results reported in studies, RCTs are slightly more likely to report a result in the opposite direction. In other words, for these COVID-19 treatments and for the topics covered by *Concato et al.*, assuming causality from a single study is more likely to result in an incorrect conclusion for RCTs.

Increased risk of inconsistent results for RCTs suggests higher prevalence of bias, which may arise due to many issues including design bias, conflicts of interest, treatment differences by physicians aware of allocation, attrition bias, ascertainment bias, randomization failures, errors, or fraud.

Using all studies identifies efficacy 8+ months faster (9+ months for low-cost treatments)

Currently, 59 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of these, 54% have been confirmed in RCTs, with a mean delay of 7.8 months (62% with 8.7 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

All studies must be carefully analyzed

Neither observational studies nor RCTs prove causation—any study can be flawed or fraudulent. We need much more, for example a combination of results from many independent teams, detailed understanding of each study, knowledge of conflicts/team reliability, dose-response relationships, delay-response relationships, logical results across outcomes, or details consistent with preclinical expectations.

All studies must be evaluated individually. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta-analyses.

Exclusions

To avoid bias in the selection of studies, we analyze all non-retracted studies. 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 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, 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), or be subject to bias. However, they can also be very high quality [5].

A team of researchers has analyzed the data in ivermectin studies and identified several studies with concerns. Retracted studies are not in this analysis. All other studies that the team has identified are excluded here. For more details see the response section.

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Detailed description of issues with *Reis, Naggie, Bramante, Hayward, López-Medina, Vallejos, Beltran Gonzalez* can be found in the study notes section.

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 [169]. 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. *IVERCOR PREP* reports prophylaxis results, however only very minimal details are currently available in a news report and an online presentation. *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. *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. *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 et al.*, 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. *Angkasekwinai* does not make sense as reported, for details see [178].

Summarizing, the studies excluded are as follows, and the resulting forest plot is shown in Fig. 20. The supplementary data shows results after restrictions and exclusions.

Abbas, very minimal patient information, three different results for the recovery outcome, selective omission of the statistically significant recovery p-value, and other inconsistencies.

Ahsan, unadjusted results with no group details.

Beltran Gonzalez, major inconsistencies reported and the data is no longer available [181], although the authors state that it is available, and have shared it with an anti-treatment group.

Borody, preliminary report with minimal details.

Buonfrate, significant unadjusted group differences, with 3 times as many patients in the ivermectin arms having the baseline visit in a hospital setting, and arm C having large differences in baseline gender, weight, cough, pyrexia, and anosmia, excessive dose for arm C.

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.

Chachar, multiple significant issues pending author response, see discussion.

de Jesús Ascencio-Montiel, unadjusted results with alternate outcome adjusted results showing significant changes with adjustments. Excluded results: death, mechanical ventilation, hospitalization, progression.

de la Rocha, data mismatch, no response from authors.

Elavarasi, unadjusted results with no group details.

Ferreira, unadjusted results with no group details; substantial unadjusted confounding by indication likely.

Hashmi, baseline severity favors control, post-hoc outcome and SAP changes, see discussion.

Hazan (B), 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.

IVERCOR PREP, minimal details provided.

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.

Mikamo, very low risk group with almost no progression leaves little room for improvement, unbalanced baseline dyspnea and high symptom scores, design and post-hoc changes favor null result.

Mustafa, unadjusted results with no group details.

Qadeer, minimal baseline details provided.

Ravikirti, exclusion of patients in less severe condition, data/analysis concerns.

Reis, multiple anomalies as per detailed analysis.

Rezai, multiple critical issues, see study page.

Rezai (B), multiple critical issues, see study page.

Samajdar, minimal details provided; unadjusted results with no group details; results may be significantly affected by survey bias.

Sarojvisut, many critical issues including missing primary outcome results, non-reproducible values, and protocol violations.

Schilling, post-hoc change to exclude patients treated before high viral load, population very low risk, recovering quickly without treatment, high baseline immunity, 2.2x greater baseline antibody negative for the treatment arm.

Siripongboonsitti, data consistency issues, very low risk patients/variants with almost no progression, all patients received known effective antiviral, baseline differences.

Soto, substantial unadjusted confounding by indication likely; substantial confounding by time possible due to significant changes in SOC and treatment propensity near the start of the pandemic.

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.

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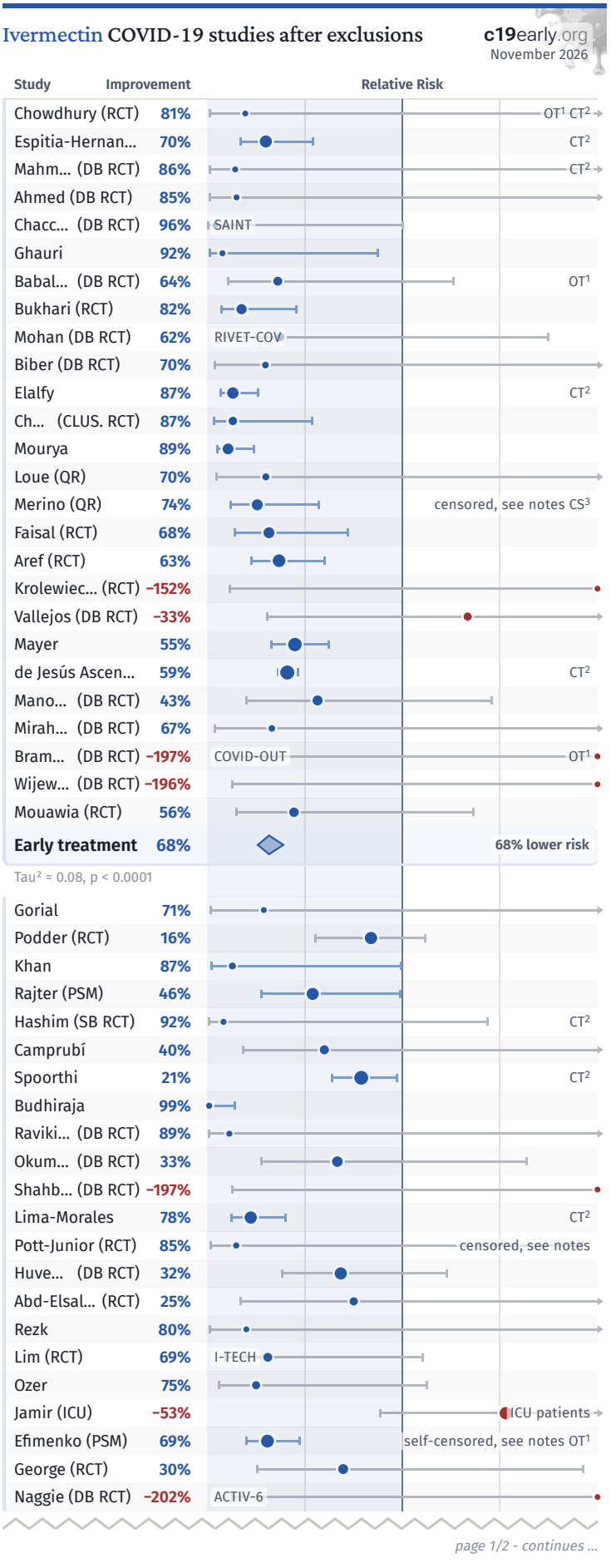
Tanioka, not a typical trial, analysis of African countries that used or did not use ivermectin prophylaxis for parasitic infections.

Thairu, significant confounding by time possible due to separation of groups in different time periods.

Zubair, substantial unadjusted confounding by indication likely; unadjusted results with no group details.



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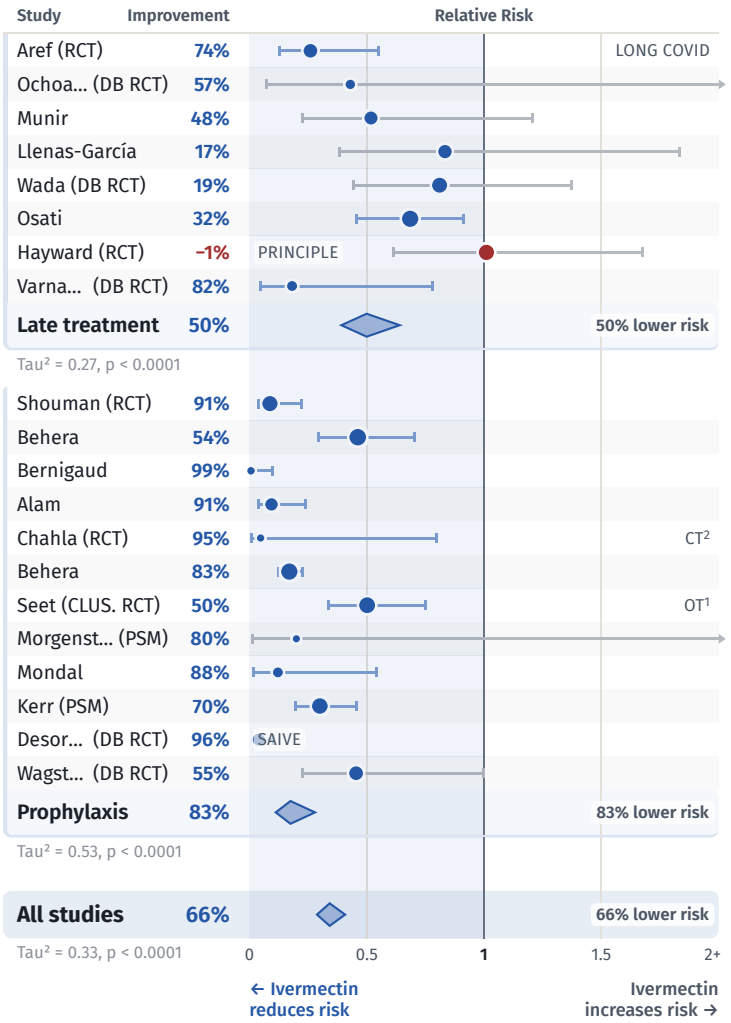

Fig. 20. **Random-effects meta-analysis excluding studies with significant issues.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Fed vs. Fasting Administration

Ivermectin is highly lipophilic and should be administered with a high-fat meal to maximize absorption. *Guzzo et al.* show that the plasma concentration of ivermectin is much higher when administered with food, with a geometric mean AUC 2.6 times higher (Fig. 21). Many ivermectin studies specify fasting, and other studies do not specify administration. Fasting administration is expected to significantly reduce efficacy for COVID-19 due to lower plasma and tissue concentrations. Fasting administration may result in insufficient distribution to specific tissues such as the lung, resulting in no efficacy. Note that COVID-19 use is very different to anthelmintic use in the gastrointestinal tract where fasting is recommended and distribution to other tissues is not required.

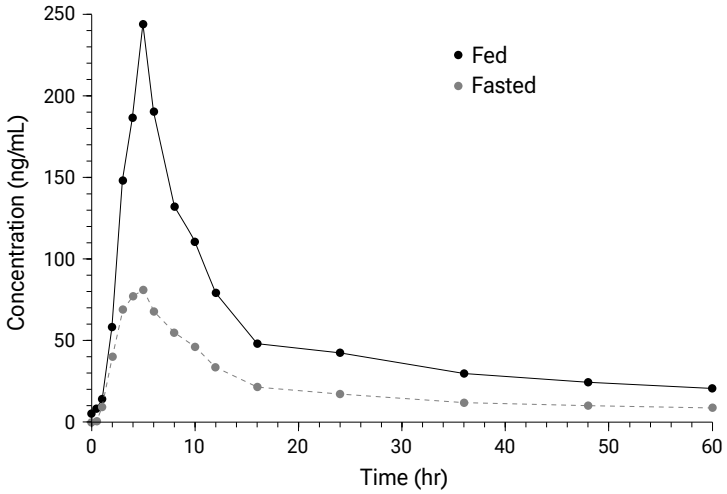

Fig. 21. Ivermectin plasma concentration is significantly higher when administered with a meal. The graph shows mean plasma concentration profiles following single 30mg oral doses for fed and fasted administration, from *Guzzo et al.*

Fig. 22 shows random-effects meta-analysis for studies that specify fed vs. fasting administration. Studies specifying fed administration show 3.1 times higher efficacy, p = 0.03. Ideally, we could further compare high-fat vs. low-fat meals, however most studies do not specify or provide details of the fat content of the meals.

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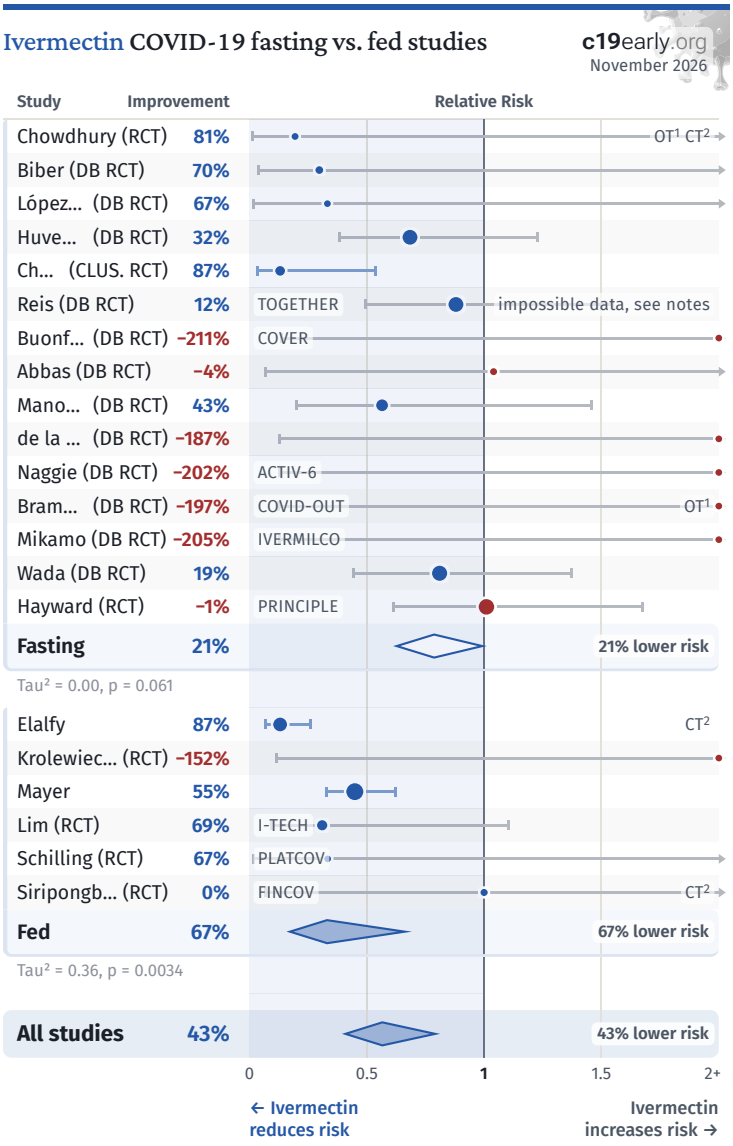

Fig. 22. Random-effects meta-analysis for studies that specify fed vs. fasting administration. Studies specifying fed administration show 3.1 times higher efficacy, $p = 0.03$.

Many studies do not specify administration, however we can classify these into outpatient vs. hospitalized administration. When unspecified, many hospital systems will default to the labeled instructions for anthelmintic use, which is fasting; however lower-resource hospitals globally may not have the same systems and processes, patients on enteral nutrition may not have feeding suspended, and some trials may use fed administration without reporting it. In contrast, for unspecified outpatient use, patients are more likely to take their medication near meals, while some medication may be delivered with standard fasting instructions which some patients will diligently follow. Therefore, we can group trials into four categories with an increasing percentage of fed administration: a) trials specifying fasting administration, b) unspecified hospitalized administration, c) unspecified outpatient administration, and d) trials specifying fed administration. Assigning these ordinal numbers 1 to 4, random-effects meta-regression shows a significant trend with increasing efficacy for higher percentages of fed administration. For every step between the groups, meta-regression shows that the Risk Ratio decreases by a factor of 1.35 (slope $\beta = -0.30$ [-0.49 to -0.10]; $p = 0.0026$).

These results reinforce the reliability of the overall finding that ivermectin reduces risk for COVID-19. If the observed efficacy was due to a systematic bias increasing efficacy in results, we would not expect to find a significant trend across administration that matches the biological mechanisms.

There is strong rationale for administration with a high-fat meal to have greater benefits than what is indicated by the higher plasma concentration seen in studies. Consider the following comparison:

- *Empty stomach*: the smaller amount of absorbed drug enters the portal vein, binding primarily to albumin. This blood flows directly to the liver, subjecting the drug to hepatic first-pass metabolism before it reaches the rest of the body or lungs.
- *With a high-fat meal*: dietary fat triggers the intestine to package absorbed lipids, and the lipophilic ivermectin dissolved within them, into chylomicrons (large lipoprotein particles). Because chylomicrons are too large for the portal vein capillaries, they go into the lymphatic system: intestinal lymphatics → thoracic duct → left subclavian vein. The subclavian vein empties into the heart, which pumps the blood immediately to the lungs. This physical bypass of the liver allows the drug to hit the lung tissue first.

This is simplified and studies showing the degree different routes are used have not been done. Some additional notes supporting this route:

- *Solubility*: while solubilization aids initial entry into the intestinal cell, the presence of long-chain triglycerides biologically requires the cell to repackage that fat into chylomicrons. Ivermectin's high logP (~5.8) suggests partitioning into this chylomicron core, and use of the lymphatic route regardless of solubility alone.
- *Lipoprotein affinity*: rabbit studies showing correlations between lipid levels and drug concentration (even via IV) confirm ivermectin's strong affinity for lipoproteins. This supports the mechanism: if the drug avidly binds lipoproteins in the blood (IV), it will also bind the nascent lipoproteins (chylomicrons) formed during digestion, which are the specific vehicles that travel the lymphatic pathway.
- *Flow vs. density*: while adipose tissue has a higher density of Lipoprotein Lipase (LPL), the lungs receive 100% of the cardiac output. Every chylomicron passes through the pulmonary capillary bed first. This exposure creates a sieve-like effect, allowing pulmonary LPL to act on the drug payload before it reaches peripheral fat.
- *Mechanism of release (supersaturation)*: as pulmonary LPL hydrolyzes the chylomicron to extract fuel, the particle's core shrinks. This creates a state of supersaturation for the drug cargo. Thermodynamic principles suggest that the drug must leave the shrinking oil droplet and partition into the nearest lipophilic membrane, in this case the lung endothelium, resulting in high local tissue concentration.

Efficacy by Treatment Delay

Fig. 23 shows a mixed-effects meta-regression of efficacy as a function of treatment delay in COVID-19 ivermectin studies, showing that efficacy declines significantly with treatment delay ($p = 0.0038$). Early treatment is critical. This significant efficacy gradient reinforces the reliability of the overall finding that ivermectin reduces risk for COVID-19. If the observed efficacy was due to a systematic bias increasing efficacy in results, we would not expect to find a significant gradient in efficacy as a function of treatment delay that matches the biological mechanisms.

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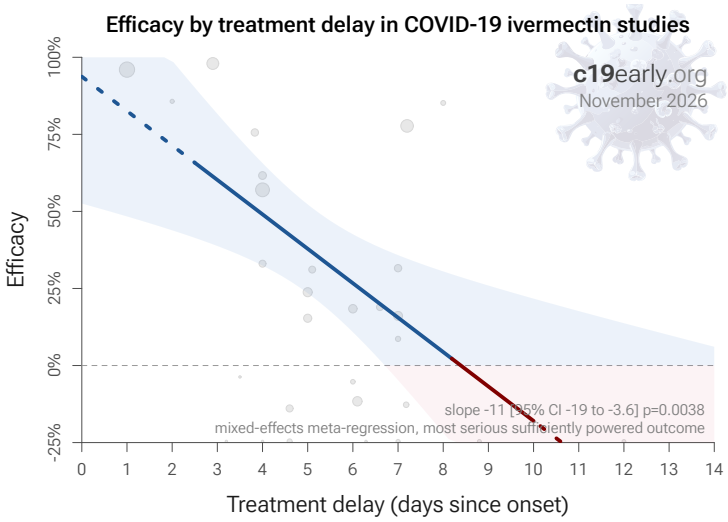

Fig. 23. Early treatment is more effective (p = 0.0038). Meta-regression showing efficacy as a function of treatment delay in COVID-19 ivermectin studies.

For comparison, Fig. 24 shows a meta-regression for all studies providing specific values across 227 treatments. Efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

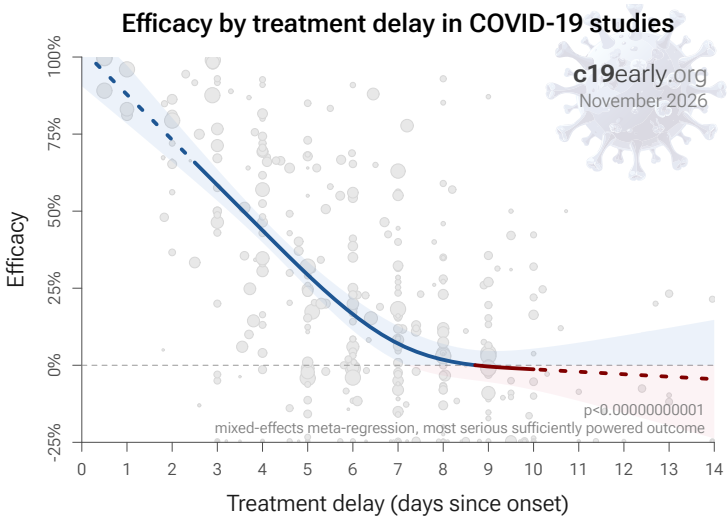

Fig. 24. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 227 treatments.

Efficacy Gradient By Stage

Preclinical studies show mechanisms relevant to all stages: blocking initial infection, minimizing viral replication, and mitigating secondary complications. Specifically, for blocking initial infection: spike-ACE2 disruption[59], lipid raft attachment inhibition[76], glycan binding[60,209], and CD147 inhibition[72-75]; for minimizing viral replication: importin-α/β nuclear transport blockade[47,49,51,58], 3CLpro inhibition[66], and RdRp interference[67]; and for mitigating secondary complications: inhibiting fibrin clots[65], reducing lung fibrosis[63,79,80], protecting against myocarditis[69,81], and dampening cytokine storm[77,78].

If there are beneficial mechanisms relevant to all stages, we would expect to see benefits combine and increase for earlier treatment, and again for prophylactic treatment—as treatment is delayed the benefit of specific mechanisms is reduced or lost. Random-effects meta-regression shows a significant association with increasing efficacy for early treatment and prophylaxis. For every step towards earlier intervention (late treatment → early treatment → prophylaxis), meta-regression shows that the Risk Ratio decreases by a factor of 1.79 (slope β = -0.58 [-0.78 to -0.38]; $p < 0.0000001$). In other words, the protective effect becomes stronger as intervention is done earlier.

This gradient reinforces the reliability of the overall finding that ivermectin reduces risk for COVID-19. If the observed efficacy was due to a systematic bias increasing efficacy in results, we would not expect to find a trend across stages that matches the biological mechanisms.

Interactions Matching Biological Mechanisms

With 106 studies for ivermectin, we can analyze interactions and trends across studies and groups. Significant interactions that match the biological mechanisms provide further confirmation of efficacy. We find significant interactions for: meta-regression of efficacy vs. treatment delay (p = 0.0038), efficacy gradient across stages ($p < 0.0000001$), and fed vs. fasting administration (p = 0.03).

This reinforces the reliability of the overall finding that ivermectin reduces risk for COVID-19. If the observed efficacy was due to a systematic bias increasing efficacy in results, we would not expect analysis across studies to find these significant interactions that match the biological mechanisms. These results would not happen without a real treatment effect - it would require an unrealistic conspiracy where many well-respected and independent teams in many countries conspire to harm humanity and coordinate fraudulent results.

Results vary as expected across studies—only possible with a real treatment effect

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While meta-analysis shows very strong confidence in efficacy, emergent results across studies that match biological mechanisms provides additional confirmation.

Treatment delay	Meta-regression of efficacy as a function of treatment delay matches expectations (p = 0.0038).
Gradient across stages	Preclinical studies show mechanisms relevant to all stages: blocking initial infection, minimizing viral replication, and mitigating secondary complications; therefore we expect benefits to combine and increase for earlier treatment, and again for prophylaxis—as intervention is delayed the benefit of specific mechanisms is reduced or lost. Meta-regression confirms this relationship with $p < 0.0000001$. (Specifically, for blocking initial infection: spike-ACE2 disruption[59], lipid raft attachment inhibition[76], glycan binding[60,209], and CD147 inhibition[72-75]; for minimizing viral replication: importin-α/β nuclear transport blockade[47,49,51,58], 3CLpro inhibition[66], and RdRp interference[67]; and for mitigating secondary complications: inhibiting fibrin clots[65], reducing lung fibrosis[63,79,80], protecting against myocarditis[69,81], and dampening cytokine storm[77,78]).
Fed vs. fasting	Administration with a high-fat meal is expected to significantly increase bioavailability, but also support distribution to the lung, bypassing hepatic first-pass metabolism. Studies specifying fed vs. fasting administration show 3.1 times greater efficacy, interaction p = 0.03).

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Media Bias

Low-cost treatments were subject to bias and censorship during the pandemic. Scientific bias is seen in the design, analysis, presentation, and selective reporting of studies, which often favored negative results. A similar bias is seen in the media coverage for low-cost treatments. While broadly seen, bias was particularly notable for ivermectin and hydroxychloroquine, e.g., Scott Alexander noted that *"if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele."*[210].

We analyze media coverage for the 227 treatments we cover using Altmetric[211] and PlumX Metrics[212]. Altmetric covers ~14,000 news outlets[213] and PlumX covers ~55,000 news sources[214]. The two services are complementary with coverage of different news sources and different methods for identifying articles not containing a DOI. We consider studies to have received significant media coverage if they were covered by at least 100 articles in either Altmetric of PlumX[214,215]. The most widespread study was covered by 1,047 outlets. Studies covered by major syndicated sources shows hundreds of news articles, while studies covered by few outlets typically appear in niche medical news sources or press releases.

Fig. 25 shows that the mainstream media did not cover any of the positive studies for ivermectin, however they did cover 6 negative or inconclusive studies. Fig. 26 and 27 analyze coverage for all low-cost treatments and all high-profit treatments, showing significant bias. For low-cost treatments media coverage favored negative results 5.4× more than positive results, whereas for high-profit treatments coverage favored positive results 3.8× more than negative results.

The media bias may result in widespread incorrect perceptions on the relative efficacy of high-profit and low-cost treatments. The impact is significant—increased cost limits the use of high-profit treatments and treatment equity. High-profit treatments were also more difficult to access, especially for earlier treatment which improves efficacy and minimizes community transmission.

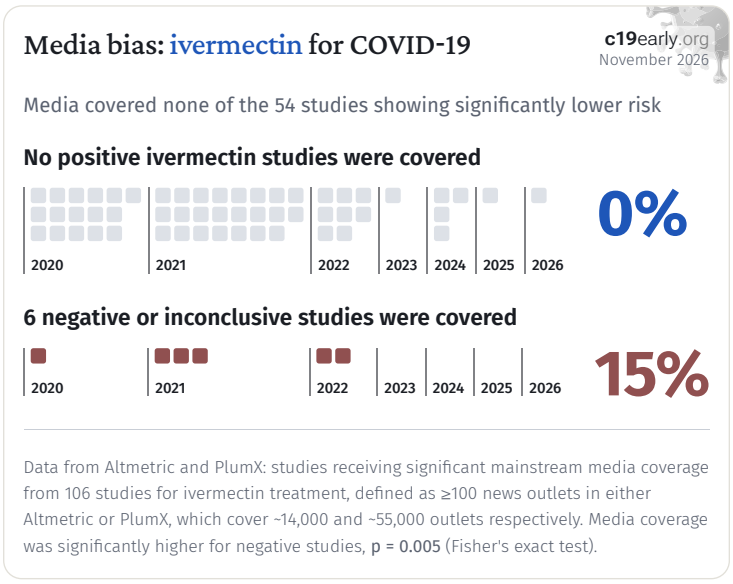

Fig. 25. Mainstream media did not cover any of the positive studies for ivermectin.

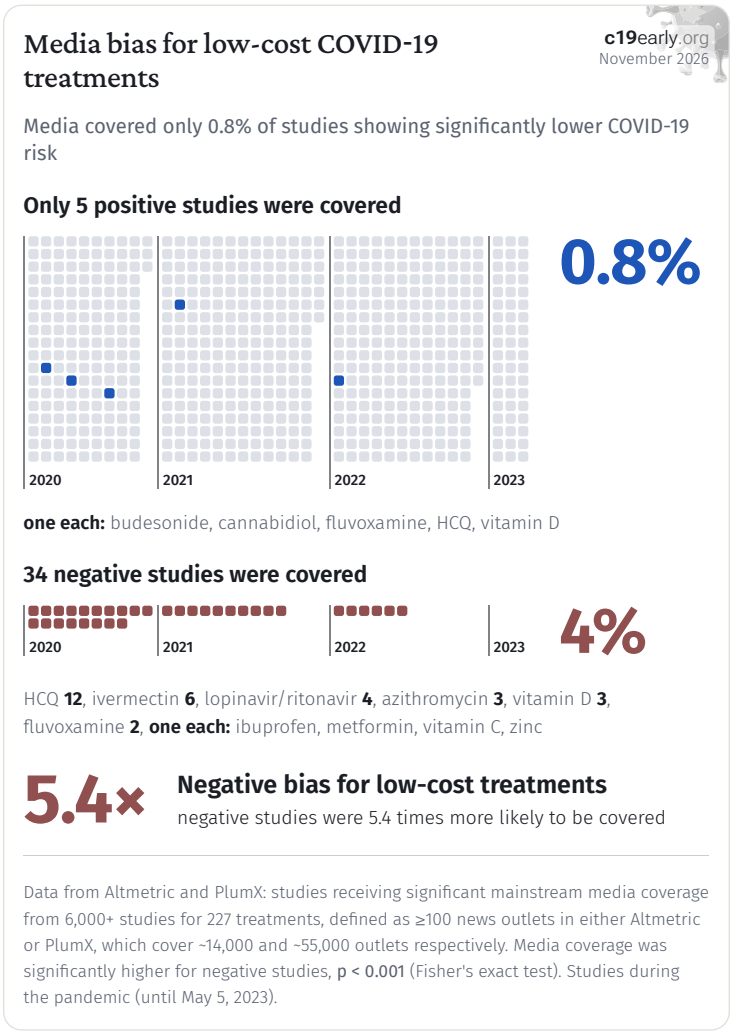

Fig. 26. Mainstream media coverage was biased against positive results for low-cost treatments. When restricting to RCTs, the bias was even larger, with negative RCTs 6.9× more likely to be covered.

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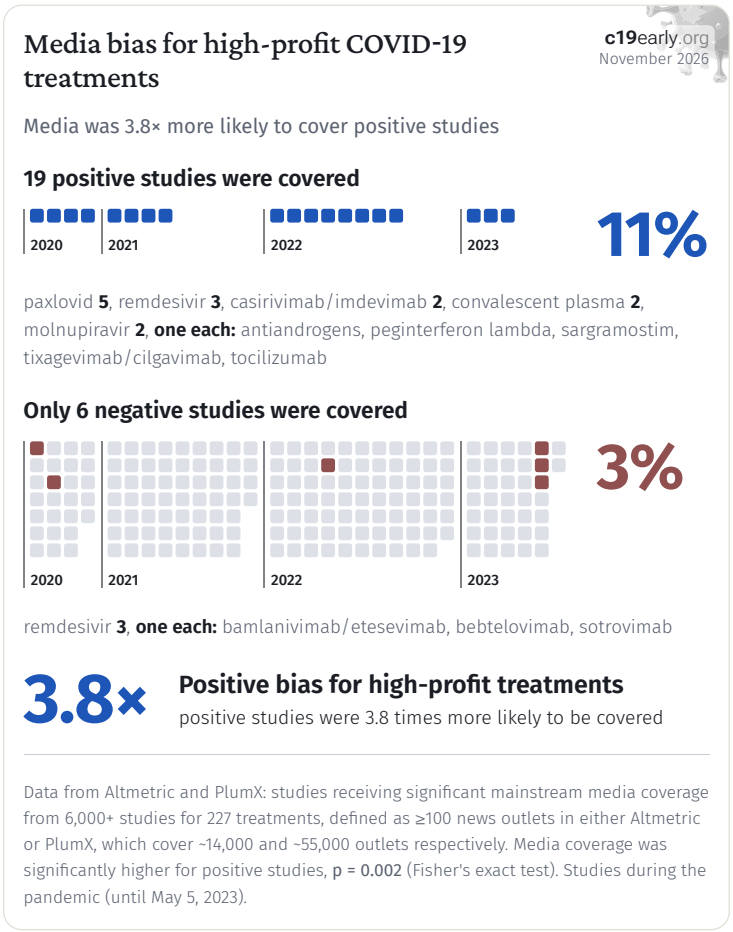

Fig. 27. **For high-profit treatments, mainstream media coverage was biased towards positive results. When restricting to RCTs, the bias was even larger, with positive RCTs 12.0× more likely to be covered.**

A combination of factors may have led to the very low media coverage of low-cost treatments:

- Politicization led to a media environment where coverage was often framed to support a political narrative rather than to provide objective scientific information. As Scott Alexander said: *"if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele*." There was strong social pressure to discredit low-cost treatments.
- Censorship of information conflicting with selected authorities. For example, individuals and organizations presenting conflicting science were often shadowbanned or completely banned on Twitter and YouTube if the science they were reporting conflicted with the opinions of specific authorities selected by those companies, including when the authorities had not even reviewed the scientific results in question.
- FDA requires "*no adequate, approved, and available alternatives*" in order to grant an EUA for novel high-profit interventions, creating an incentive for authorities to ignore or downplay existing low-cost treatments.
- Regulatory capture biases authorities towards high-profit interventions.
- Authorities ignored most evidence for low-cost treatments, for example the NIH references only 2% of studies in delayed, rarely-updated, biased commentaries with no quantitive analysis.
- Media coverage of science is often not very accurate, e.g., misunderstanding confounding issues. For example the media widely considered the RECOVERY HCQ RCT to be conclusive on efficacy, but very late treatment of late-stage patients (mostly on oxygen already) with an excessive toxic dose (shown dangerous in a dose comparison RCT) provides no information on the recommended early/prophylactic treatment. With difficulting in understanding basic confounders like treatment delay and dose, the media may favor deferring to authorities. Many studies for low-cost treatments require greater expertise to analyze.
- Substantial funding from pharmaceutical advertising biases editorial decisions towards high-profit interventions.
- PR power - companies/teams with strong PR presence are favored in the media, which correlates with high-profit and high conflict of interest studies.
- The media was very negative in general, inflating risk, and elevating fear and anxiety. A negative bias may improve ratings and revenue, increasing motivation to continue watching coverage.

Erasing Efficacy

For HCQ, meta-analysis including late stage / excessive dose trials—where results are poor and trials were large—hides positive results for early treatment and prophylaxis[217].

For ivermectin overdosing is more difficult and late treatment shows efficacy. How did Cochrane generate a null result? Their meta-analysis[218,219] required unprecedented measures for a politically acceptable outcome, and has extreme COI—many authors also did the paxlovid analysis.

- Authors created a retrospective analysis excluding most studies, splitting results across multiple analyses, and disregarding efficacy if independent evidence is combined[218].
- Authors pledged to update the analysis but only did so once in >5 years. The second version required voiding the protocol and using novel mechanisms to exclude even more studies, for example specific registration requirements (applied selectively)[219].
- Are authors restricting to high quality trials? No, their quality evaluation is highly inaccurate, e.g., including (violating their own protocol[220]) and claiming low risk of bias for the Together trial, however the trial has very high actual known bias—reporting multiple impossible numbers, refusing to release data despite pledging to, breaking blinding (even externally), and having randomization failure, extreme COI, many protocol violations, and other issues[161].
- Three pre-exposure prophylaxis RCTs, all showing significant efficacy, were ignored by specifying post-exposure only. In contrast, many of the same authors include pre-exposure studies for paxlovid. In 2023, an ivermectin post-exposure RCT showed efficacy with *p<0.00000000001*—no update has been made since 2022.
- Authors claimed updates would be made as new results were available, however they have only released two versions, both retrospective with separate protocols specified after all included results were known.

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For more details see the analysis of each version [218,219].

Authority Delay

26 low-cost treatments were approved in one or more countries, yet many countries approved no low-cost treatments. The countries that did adopt low-cost treatments analyzed the evidence early and made timely approvals. With few exceptions, authorities did not change their initial views, regardless of how much evidence accumulated showing either efficacy or harm. Why?

The harms of smoking here hidden for 25 years [B]. Authorities did not analyze the data in real-time, failing to act when harm was known. Widespread acknowledgement of harm came only after attempts by two new surgeon generals, along with pressure from health advocates and a new president, and a review of 7,000 studies.

Similarly for COVID-19, most authorities and experts did not proactively analyze data in real-time. This guarantees delayed recognition of efficacy or harm, by which time moral, legal, career, and reputational liabilities strongly disincentivize any admission of error. Claims of no efficacy (for effective treatments) or safety (for harmful treatments) were often made prior to strong data being available. Correction would require admitting to errors that increased mortality, which is unlikely with the same generation of officials.

Analysis of potential treatments was rarely done, and when done these were typically minimal efforts. For example, NIH reviews were highly delayed, cover only a tiny fraction of treatments, reference only 2% of studies for the treatments covered, and include no quantitative analysis. They appear as rarely updated side projects from external panels implicitly tasked with justifying prior failures. As with smoking, the thousands of studies could (and should) have been analyzed and acted on in real-time.

A key structural improvement, applicable to all current and future diseases, is for authorities to implement real-time proactive analysis of clinical evidence. This does not remove all bias, but does make it possible to act on evidence, whereas delayed action may be unlikely due to moral, legal, career, and reputational liabilities.

The US FDA recommended against ivermectin in an article stating that *"The FDA has not reviewed data to support use of ivermectin in COVID-19 patients to treat or to prevent COVID-19"* [221]. This confirms that the FDA had not reviewed the evidence at all, let alone in real-time.

Heterogeneity

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

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours [222,223]. Baloxavir marboxil studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

Early treatment is more effective: baloxavir marboxil

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Treatment delay	Result
Post-exposure prophylaxis	86% fewer cases [224]
<24 hours	-33 hours symptoms [225]
24-48 hours	-13 hours symptoms [225]
Inpatients	-2.5 hours to improvement [226]

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

As shown in the treatment delay section, the efficacy of COVID-19 treatment declines as a function of the treatment delay. Early treatment is critical for COVID-19.

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, for example as in *López-Medina et al.*

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [227], for example the Gamma variant shows significantly different characteristics [228-231]. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants [232,233].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen. Higher dosage has shown increased efficacy [234]. The method of administration is critical. Administration with a high-fat meal shows significantly higher concentrations, and may mean the difference between efficacy and no efficacy within specific tissues, as detailed in the administration section.

Medication quality

The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams et al.* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu et al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic [103,119,120,122,124,129,132,142,207,236-251], therefore efficacy may depend strongly on combined treatments.

Effect measured

Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treat-

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Delayed public health acknowledgments

Official acknowledgment of efficacy or harm is often delayed—legal, career, and status risks disincentivize admission of error.

	EVIDENCE	OFFICIAL ACKNOWLEDGMENT	APPROX. DELAY
Citrus Fruit (vitamin C) for Scurvy (effectiveness)	1747: James Lind conducted one of the first-ever controlled clinical trials, proving that oranges and lemons cured scurvy in sailors.	1795: The British Royal Navy finally made a daily ration of lemon juice a standard issue for all its sailors, effectively eliminating the disease.	48 years
Handwashing (lower mortality)	1847: Dr. Ignaz Semmelweis provided conclusive proof that having doctors wash their hands with a chlorine solution before delivering babies reduced maternal mortality rates from over 18% to around 1%.	~1870s: Semmelweis's findings were rejected and he was ridiculed. His work was only validated decades later (after his death).	~20+ years
Helicobacter pylori (bacteria causes ulcers)	1982-1984: Marshall and Warren discovered that Helicobacter pylori bacteria causes ulcers, confirmed via direct exposure. Officials maintained that ulcers were caused by stress and spicy food.	1994: The US NIH released a consensus statement officially recommending antibiotics as the standard treatment for peptic ulcers, overturning decades of acid-suppression therapy.	~12 years
Asbestos (causes asbestosis & cancer)	1924: The *British Medical Journal* published the first case study of a death from "asbestosis." By 1918, U.S. insurance companies had stopped selling life insurance to asbestos workers.	1971 (US): The Occupational Safety and Health Administration (OSHA) was formed and began regulating asbestos as a carcinogen, setting the first federal workplace safety standards for it.	~47 years
Leaded Gasoline (neurotoxicity)	~1924: Dangers of low-level lead exposure were known. Experts like Alice Hamilton warned the U.S. Surgeon General that adding lead to gasoline would cause widespread public poisoning.	1973 (US): The Environmental Protection Agency (EPA) ordered the first phasedown of lead in gasoline, following the Clean Air Act of 1970. A full ban for on-road vehicles took effect in 1996.	~49 years
Harms of Smoking (causes lung cancer)	1939: Franz Müller (Germany) published the first case-control epidemiological study strongly linking tobacco smoking to lung cancer. This was followed by major U.S. & U.K. studies in the 1950s.	1964 (US): The U.S. Surgeon General's report, "Smoking and Health," was released. It was the first U.S. government report to definitively link smoking to lung cancer and heart disease.	25 years

ment may be more effective against secondary complications and have minimal effect on viral clearance.

Meta-analysis

The distribution of studies will alter the outcome of a meta-analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta-analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta-analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Ivermectin

Ivermectin studies vary widely in all the factors above, which makes the consistently positive results 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. Note that trial with a design favoring null results have become common, and are likely to dominate future trials. For example, the Together Trial tested ivermectin in locations known to have a high degree of self-medication, up to 7 days from onset (while claiming to be an early treatment trial), and using low doses compared to clinical recommendations for the dominant variant. The ACTIV-6 trial had a median treatment delay of 6 days and very low risk patients.

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Pooled Effects

Pooled effects are no longer required to show efficacy as of September 2020

This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however pooled effects are no longer required for ivermectin as of September 2020. Efficacy is now known based on specific outcomes for all studies and when restricted to RCTs. Efficacy based on specific outcomes was delayed by 1.3 months compared to using pooled outcomes.

Combining studies is required

For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. "*The studies reported different outcomes*" is not a good reason for disregarding results. Pooling the results of studies reporting different outcomes allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Specific outcome and pooled analyses

We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Ethical and practical issues limit high-risk trials

Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster and safer collection of evidence.

Validating pooled outcome analysis for COVID-19

For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

Analysis of the the association between different outcomes across studies from all 227 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Fig. 28 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.0000000001$). Similarly, Fig. 29 shows that improved recovery is very strongly associated with lower mortality ($p < 0.0000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Fig. 30 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.0000000074$ to $p = 0.00000000015$.

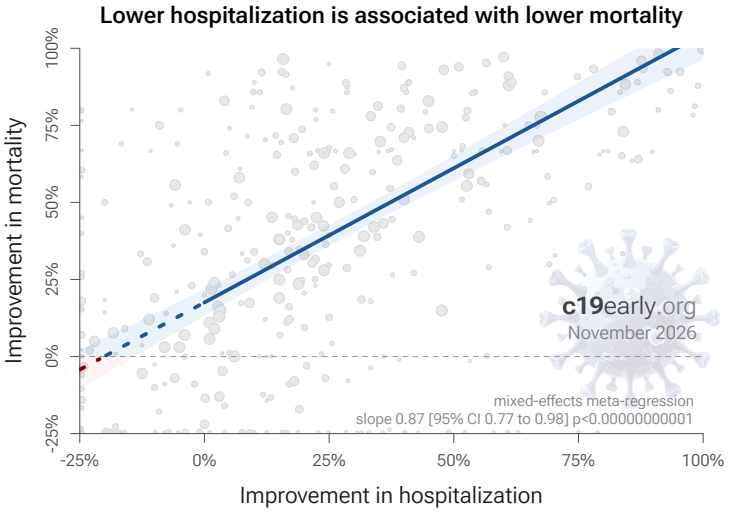

Fig. 28. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

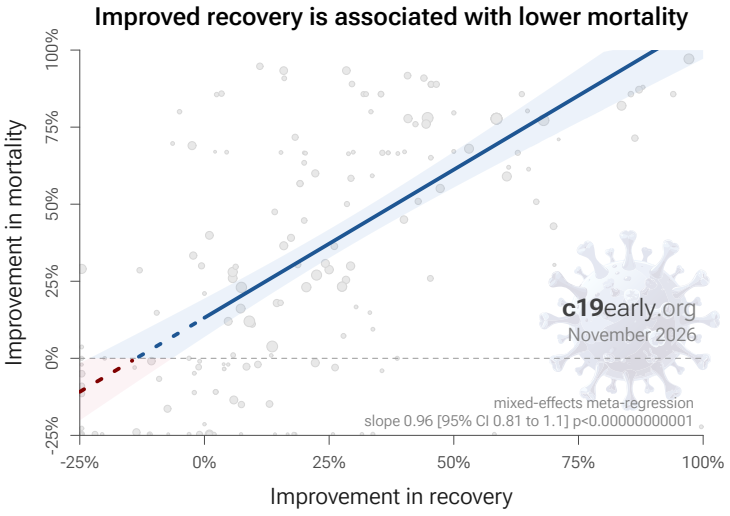

Fig. 29. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

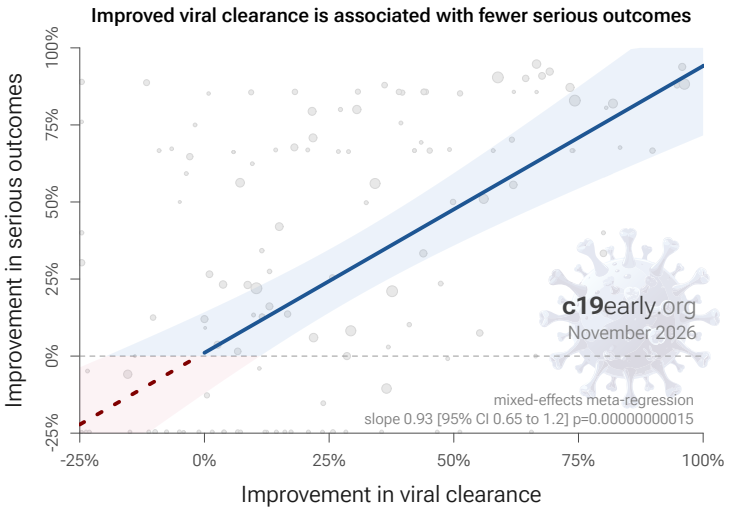

Fig. 28. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

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Pooled outcomes identify efficacy 5 months faster (7 months for RCTs)

Currently, 59 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 85% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.6 months. When restricting to RCTs only, 53% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.5 months. Fig. 31 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

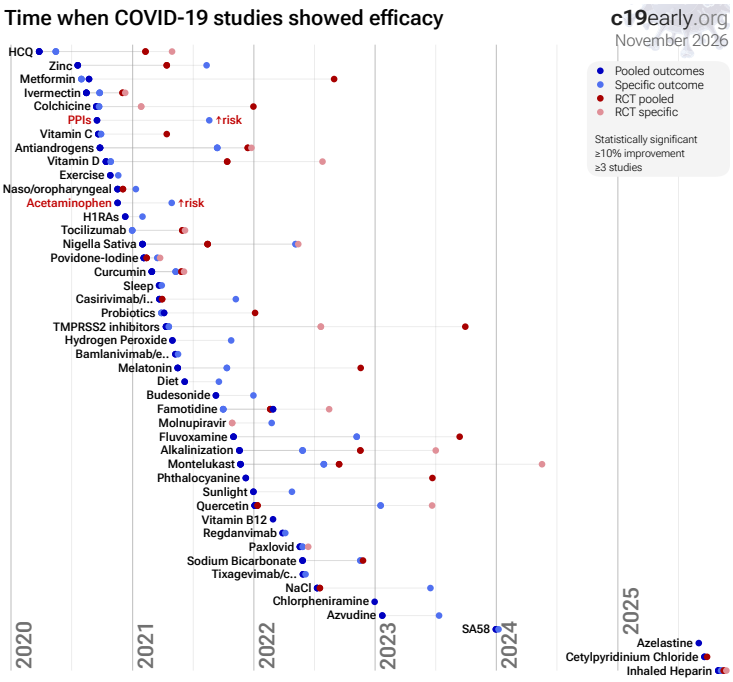


Fig. 31. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations

Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as differences in treatment delay are more likely to hide efficacy.

Summary

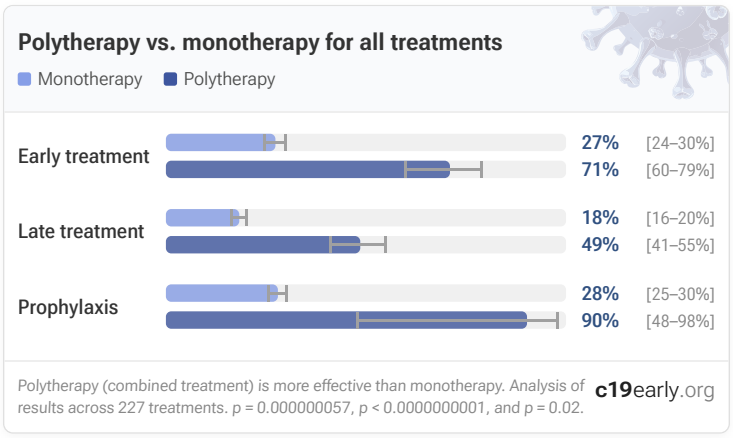
Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta-analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Polytherapy

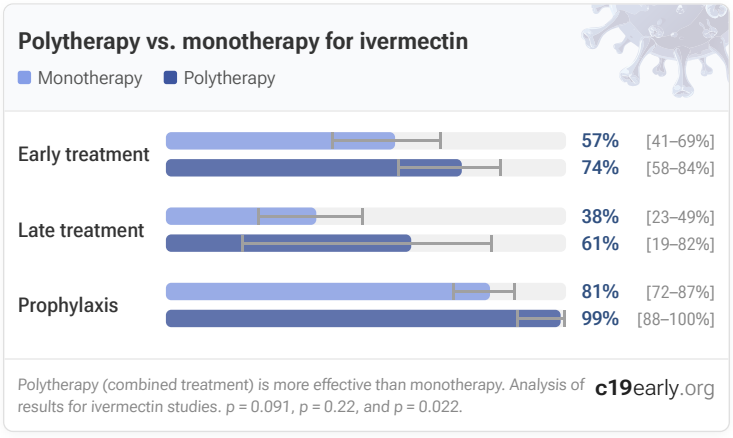
There are many complementary mechanisms of action for COVID-19 treatments, with over 500 therapeutic targets [253]. Studies show complementary and synergistic effects with polytherapy [103,119,120,122,124,129,132,142,207,236-251]. For example, Jitobaom et al. [124] shows >10x reduction in IC_{50} with ivermectin and niclosamide, an RCT by Said et al. [240] showed the combination of nigella sativa and vitamin D was more effective than either alone, and an RCT by Wannigama et al. [254] showed improved results with fluvoxamine combined with additional treatments, compared to fluvoxamine alone.

SARS-CoV-2 can rapidly acquire mutations altering infectivity, disease severity, and drug resistance even without selective pressure [255-262]. Antigenic drift can undermine more variant-specific treatments like monoclonal antibodies and more specific antivirals. Treatment with targeted antivirals may select for escape mutations [263]. The efficacy of treatments varies depending on cell type [264] due to differences in viral receptor expression, drug distribution and metabolism, and cell-specific mechanisms. Efficacy may also vary based on genetic variants [265-275].

Variable efficacy across variants, cell types, tissues, and host genetics, along with the complementary and synergistic actions of different treatments, all point to greater efficacy with polytherapy. In many studies, the standard of care given to all patients includes other treatments—efficacy seen in these trials may rely in part on synergistic effects. Less variant specific treatments and polytherapy targeting multiple viral and host proteins may be more effective. Meta-analysis of all early treatment trials shows 71% [60-79%] lower risk for studies using combined treatments, compared to 27% [24-30%] for single treatments.



While not reaching statistical significance for all stages, ivermectin studies using polytherapy also show greater efficacy than monotherapy studies.



Combined treatment is more effective

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SARS-CoV-2 involves the complex interplay of 500+ host and viral proteins and factors, providing many therapeutic targets. Many compounds have antiviral activity for SARS-CoV-2, with many different mechanisms including blocking attachment, entry, and replication. Combinations of treatments, with careful attention to potential side effects, allows improved efficacy via complementary and synergistic mechanisms.

Tissue and cell coverage	Different compounds have different tissue penetration profiles and efficacy across cell types
Variant coverage	Compounds with different viral resistance profiles
Intra/extracellular	Disabling and removing intracellular and extracellular viral particles
Resistance	Minimizing persistence and emergence of resistant variants
Genetics	Robustness against individual variations in efficacy based on genetics
Lower doses	Potentially lower doses of individual agents, reducing toxicity
Viral and host-directed	Antivirals targeting viral and host proteins
Immune system function	Supporting or enhancing natural immune system function
Disease phases	Addressing multiple disease phases (viral replication, inflammation, secondary complications)

Discussion

WHO

WHO updated their treatment recommendations on 3/30/2021[276]. 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 days.

Despite this extremely positive result, they recommended only using ivermectin in clinical trials. The analysis contains many flaws[277]:

- Of the 106 studies (54 RCTs), they only included 16.
- They excluded all 18 prophylaxis studies (5 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[5].
- 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[234].
- 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[278], even prompting an open letter from over 170 physicians concluding that the study is fatally flawed[279]. *Beltran 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"[280]. 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"[281]. The clinical team lead refers to their analysis of ivermectin as "fighting this overuse of unproven therapies ... without evidence of efficacy"[281], despite the extensive evidence of efficacy from the 106 studies by 1,299 scientists with 220,588 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[282].

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[283].

Merck

Merck has recommended against ivermectin[284], however this recommendation has not been updated for days.

They stated that there is *"no scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies"*. This is contradicted numerous studies, including *Jitobaom, Li, Fauquet, Boschi, Shahin, Abd-Elmawla, Ma, Vottero, Mody, Parvez, Li (B), Gao, Bagheri-Far, Lefebvre, Zhang, DiNicolantonio, Zhao, Zaher, Liu (B), Liu (C), Gayozo, Kofler, Munson, Yan, Haque, de Oliveira Só, Agamah, Oranu, Chellasamy, Umar, Alvarado, Aminpour, Parvez (B), Francés-Monerris, González-Paz, González-Paz (B), Rana, Muthusamy, Qureshi, Schöning, Bello, Udofia, Choudhury, Kern, Saha (B), Eweas, Francés-Monerris (B), Kalhor, Swargiary, Maurya, Lehrer, Suravajhala, How, Lew, García-Aguilar, De Forni, Saha (C), Jitobaom (B), Croci, Zheng, Delandre, Segatori, Jitobaom (C), Mountain Valley MD, Yesilbag, Jeffreys, Surnar, Caly, Uematsu, Albariqi, Errecalde, Madrid, de Melo, Arévalo, Chaccour, Zatloukal, Zaidi, Wehbe, Kalfas, Jans, Heidary*.

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 *de Jesús Ascencio-Montiel, Babalola, Chowdhury, Espitia-Hernandez, Mahmud, Chaccour (B), Ghauri, Bukhari, Mohan, Elalfy, Chahla, Mourya, Loue, Merino, Faisal, Aref, Mayer, Manomaipiboon, Khan, Hashim, Budhiraja, Ravikirti (B), Okumuş, Lima-Morales, Huvemek, Baguma, Shimizu, Aref (B), Varnaseri, Behera, Bernigaud, Alam, Chahla (B), Behera (B), Seet, Morgenstern, Mondal, Kerr*.

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

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 [338], to help eliminate river blindness.
- Merck has their own new COVID-19 treatments MK-7110 (formerly CD24Fc) [339] and Molnupiravir (MK-4482) [340,341]. Merck has a ~$US1.2B agreement to supply molnupiravir to the US government, if it receives EUA or approval [342]. Over $US10B in near-term orders are expected if approved [343].
- 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 [283].

For other concerns regarding Merck's statement and prior actions related to Vioxx, see *Scheim (E)*.

FDA

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 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 [345]. For comparison, acetaminophen overdose results in ~33,000 yearly hospitalizations in the USA (~12,000 unintentional) [346]. 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 *Caly, Buonfrate, Qadeer, Thairu, Babalola, Chowdhury, Espitia-Hernandez, Mahmud, Bukhari, Mohan, Elalfy, Mourya, Aref, Khan, Okumuş, Ahmed, Biber, Wijewickrema, Mouawia, Rezk*, including 12 RCTs.

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

NIH

Update: NIH has updated the recommendation, based heavily on the Together Trial, while making no mention of the impossible data, blinding, randomization, and protocol failures, or that the co-principal investigator privately reported that "There is a clear signal that IVM works in COVID patients".

NIH has reported that there is insufficient evidence to recommended for or against ivermectin [352]. A table with summaries of 11 studies is provided, dated Dec 20, 2023, and they reference another 21 studies without analysis, however there are 106 studies to date. No quantitative analysis is provided. The NIH recommendation is "insufficient evidence", indicating that new evidence must be reviewed immediately, however most evidence has not been reviewed to date.

The likely members of the panel have been revealed by FOIA requests [353]. In the first request, all but two member names were redacted [354], however all are visible in a second request [355]. Many panel members appear to have major conflicts of interest [353,356] as shown in the following table.

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Conflicts of interest - NIH COVID-19 treatment guidelines

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9 of 9 authors have conflicts: **43** relationships with **13** entities.

● Board or advisory role ● Payments ● Research funding ● Stock or equity ● Affiliation

Author	Conflicts
Prof. Adaora Adimora	● **Merck** · advisory board [1] ● **Merck** · consultant [1] ● **Merck** · research support [2] ● **Gilead** · consultant; institution received research funding. "Aadimora AA has received consulting fees from Viiv, and Gilead and her institution has received funding from Gilead for her research." [3] ● **Gilead** · research support [4] ● **Merck** · Open Payments, $62,000 [5] ● **Gilead** · Open Payments, $88,000 [5]
Prof. Roger Bedimo	● **Merck** · advisory board [1] ● **Gilead** · honoraria [4] ● **Merck** · Open Payments, $149,000 [6] ● **Sanofi** · Open Payments, $76,000 [6] ● **Gilead** · Open Payments, $23,000 [6]
Prof. Rajesh Gandhi	● **Gilead** · grants. "Dr. Gandhi reports grants and personal fees from Gilead, personal fees from Merck, grants and personal fees from Theratechnologies, grants from ViiV, grants from Janssen." [7] ● **Gilead** · advisory board and personal fees [8] ● **Merck** · advisory board and personal fees [4] ● **Janssen** · grants [7] ● **Merck** · Open Payments, $45,000 [9] ● **Gilead** · Open Payments, $10,000 [9]
Prof. David Glidden	● **Merck** · advisory board [2] ● **Gilead** · consultant [4]
Prof. Roy Gulick	● **Merck** · grants; principal investigator of ACTG A5391, funded in part by Merck. "Roy M. Gulick, MD, MPH, has disclosed that he has received grants for clinical research from Abbott, Boehringer Ingelheim, Merck, Pfizer, Schering, and Tibotec, and has received grants for educational activities from Gilead and Monogram. Dr. Gulick has also disclosed that he has served as an ad-hoc advisor or consultant to Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Pfizer, Schering, and Tibotec." [10] ● **Pfizer** · grants and ad-hoc advisor or consultant [10] (deleted from current version [11]) ● **Gilead** · grants and ad-hoc advisor or consultant [10] (deleted from current version [11]) ● **GlaxoSmithKline** · ad-hoc advisor or consultant [10] (deleted from current version [11]) ● **NIAID/NIH** · grants [12]
Prof. Susanna Naggie	● **Gilead** · grants and travel or meeting support [8] ● **AbbVie** · grants [8] ● **NIH** · grants [8] ● **Vir Biotechnology** · advisory board [1] ● **Vir Biotechnology** · stockholder [1] ● **Ivermectin trial** · $155 million grant after the insufficient-evidence recommendation [2] ● **AbbVie** · Open Payments, $2.4 million [13] ● **Gilead** · Open Payments, $1.2 million [13] ● **Janssen** · Open Payments, $34,000 [13] ● **Merck** · Open Payments, $19,000 [13]
Prof. Andrew Pavia	● **Merck** · consultant [4] ● **Genentech** · consultant [4] ● **GlaxoSmithKline** · consultant [8] ● **Pfizer** · Open Payments, $14,000 [14] ● **Merck** · Open Payments, $5,000 [14] ● **Janssen** · Open Payments, $4,000 [14]
Dr. Stephen Cantrill	● **Gilead** · faculty/primary author for Gilead-funded COVID-19 education released March 11, 2025 (NIH guidelines have not been updated since 2023) [15]
Dr. Timothy Uyeki	● **CDC/HHS** · CDC employee and Chief Medical Officer of the Influenza Division during COVID-19 guideline development; government institutional affiliation [16]

1. NIH panel financial disclosure
2. TrialSite News
3. Adimora et al., International Journal of Maternal and Child Health and AIDS
4. NIH guidelines archive, 27 Aug 2020
5. Open Payments
6. Open Payments
7. NEJM disclosure supplement
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9. Open Payments
10. Medscape disclosure, archived 2014
11. Medscape disclosure, current version
12. ACP Journals
13. Open Payments
14. Open Payments
15. Clinical Care Options
16. WHO, August 2023

Strongyloides

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One theory for the beneficial effect of ivermectin for COVID-19 is related to strongyloides and the use of steroids — control group patients with strongyloides may be at risk due to steroid use, while ivermectin patients are protected. While this mechanism may contribute to efficacy in some cases, it is inconsistent with the data. If this was the case, we would expect to see greater benefit in late stage trials where steroids are used more often, and we would expect to see greater benefit for outcomes that occur after steroids are used. However, we see a very strong opposite effect for treatment time, and we see comparable or stronger efficacy for earlier outcomes.

The theory has gained renewed interest based on a new analysis by *Bitterman et al*. However, this analysis is confounded by treatment delay, dose, conflicts of interest, and other factors, and the effect disappears when analyzing all studies, all RCTs, or all mortality results, as shown in Fig. 32.

Although the first author has responded to the confounders on Twitter, we do not see mention of them in the paper. Author is also aware that the larger sets of all trials, all RCTs, or all mortality results do not show the effect, however we also do not see this mentioned in the paper. These omissions suggest investigator bias. Author claims they could not discuss these issues due to publication delays, however the paper was accepted Jan 31, 2022, and author was aware of the issues months before, for example discussing treatment delay and dose in Nov 2021. These confounders are also basic and not really possible to miss.

The meta-analysis for *Hashim* includes critical patients, however these patients were always allocated to the treatment arm for ethical reasons, therefore including them is not logical and introduces substantial bias. According to the author response, this appears to have been known, suggesting investigator

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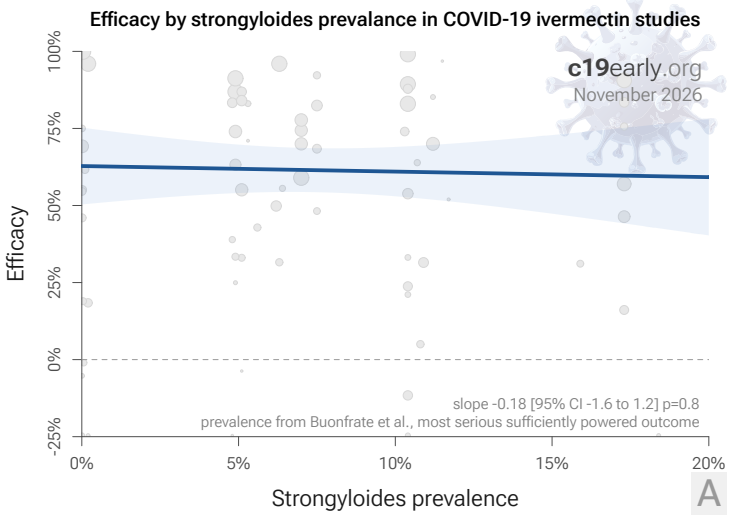
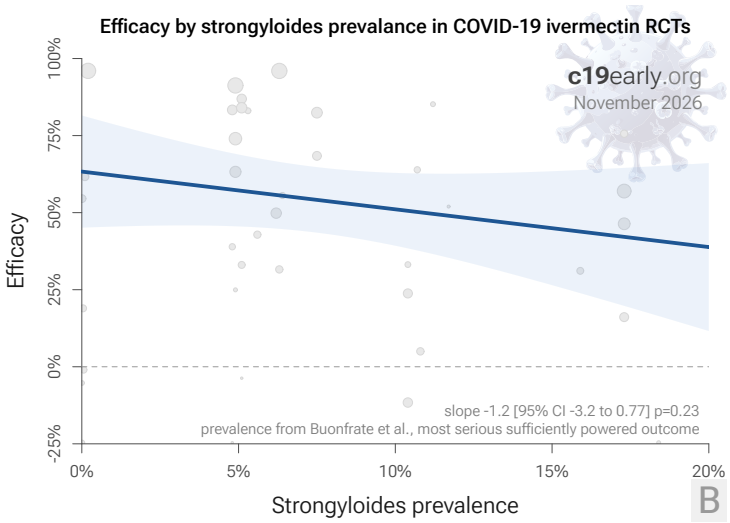
bias. Authors include *Shahbaznejad* where the only death was a critical patient that died within 24 hours of admission.

Although authors note following PRISMA guidelines, we do not see registration of the protocol or discussion thereof. We note that the current protocol is the result of multiple changes to the original methodology as posted on Twitter: from 3 groups to 2 groups, altering the included studies, and switching from using one source for prevalence estimates to selecting estimate sources on a per study basis, which allows potential bias in the selection. Notably, this resulted in moving the Together Trial (Brazil) into the low prevalence category.

Author's results rely on trials with a very small number of mortality events — the high stronglyoides prevalance group has trials with 1, 3, 4, and 13 events. Authors do mention limitations due to the small number of events and the reliability of strongyloides estimates.

Authors indicate no conflicts of interest, however the first author has been an investigator on a Pfizer trial, which may be NCT04092452, showing completion in January 2022 [358,359].





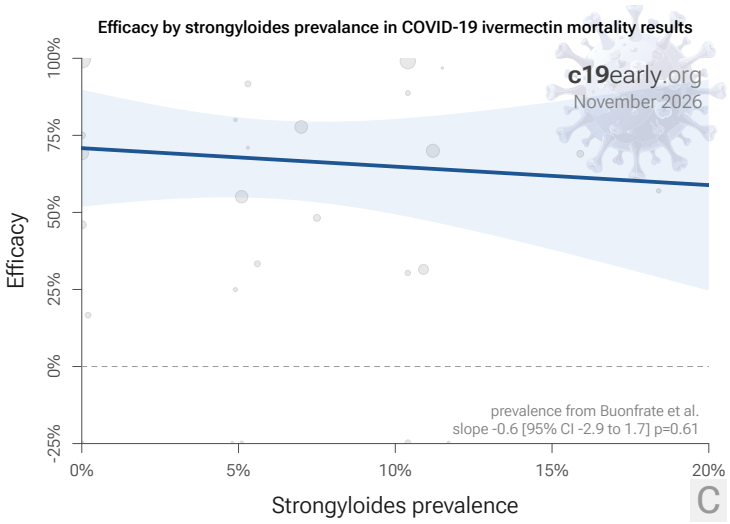


Fig. 32. Mixed-effects meta-regression showing efficacy as a function of strongyloides prevalence. **A**. all studies. **B**. all RCTs. **C**. all mortality results.

The following refers to the first author's analysis posted earlier on Twitter. The author selected 10 of the 106 studies, with 3 in a high strongyloides prevalence group where a greater benefit is seen. This was used to draw strong conclusions about the mechanism of ivermectin efficacy.

There are several limitations to this analysis. One of the 3 studies does not mention steroids in the list of SOC medications, while a second reports 6% usage for the control group. Author has added a fourth paper in a revised grouping with 11 studies.

We perfomed a similar analysis for all studies (except the 2 ecological studies), which shows no significant effect, with the high prevalence group actually showing lower improvement (50% [35-62%] vs. 65% [57-71%] for the low prevalence group). Details can be found in the supplementary data. Results are similar when restricting to mortality results or when restricting to RCTs.

Why does the smaller analysis with 11 studies show a greater benefit in high strongyloides prevalence regions? The effect is based on relatively few events - 1, 3, 4, and 13 respectively for the high prevalence group. More importantly, the result is confounded by treatment delay and dose.

Treatment delay. All meta-analyses combine heterogeneous studies which results in limitations. For example in pooled analysis we combine hospitalization and mortality. In terms of evaluating efficacy for COVID-19 treatments, reduction in hospitalization reasonably leads to reduction in mortality for high-risk populations. Both are indicators of efficacy, and both are valuable. In the largest series of COVID-19 treatment trials, hospitalization and mortality estimates are very similar. The same does not apply to treatment delay for antivirals. A trial showing efficacy with early treatment provides no information on late treatment, and a trial showing no efficacy with late treatment provides no information on early treatment. Ivermectin, as with many COVID-19 treatments, shows a strong treatment delay relationship — early treatment shows significantly higher efficacy.

The high prevalence group in the 11 study analysis has more early treatment trials, and the low prevalence group has more late treatment trials. The result is confounded by treatment delay, and reflects the greater efficacy of early treatment.

Only one trial in the high prevalence group is classified as late treatment, I-TECH, which was very close to the cutoff. Moreover, of all trials in the 11 trial analysis, this one uses the highest dose.

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Dose. The average dosage used in the high prevalence group is about twice the dose in the low prevalence group, and would be close to three times higher if the Together Trial was not moved to the low prevalence group. The result is confounded by dose, and reflects the greater efficacy of higher dosages.

Variants. Efficacy may vary based on variants. Notably, the Gamma variant was most common for one trial in the low prevalance group. This variant shows dramatically different characteristics[231], and clinicians report 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[228,229].

Conflicts of interest. Two trials have very high (>$US1B) negative conflicts of interest which may introduce bias towards null effects. The trial in the low prevalance group shows a lower effect size. The trial in the high prevalence group also shows a lower effect size for the primary outcome. This trial shows a larger mortality effect, however with only one event this has very low significance.

Summary. In summary, the greater benefit in high strongyloides prevalence regions is only seen with the small subset of 11 trials and is not seen with all trials, or after restriction to mortality results, or restriction to RCTs. Within the 11 trial sample, all trials except one in the low prevalence group have confounding due to treatment delay and/or low dosage, where a lower effect size is expected. The only remaining trial in the group is unpublished, has an unknown treatment delay (a significant percentage of patients may have been treated very late), has very high negative conflicts of interest, and the Gamma variant was most common, in addition to other issues.

In vitro evidence on required concentration

Some authors claim that *Caly* showed 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[360]. 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. Tissue concentrations of ivermectin can be much higher than plasma concentration[361,362]. 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*, authors 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[360]. Moreover, there are now 28 *In Vitro* studies that support the efficacy of ivermectin for COVID-19[50,56,59,60,62,66,76,77,81,82,85,87,119-134].

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 strong evidence of a growing negative publication bias.

As Scott Alexander said in November 2021, *"if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele."* In many locations, publishing positive ivermectin results is not conducive to maintaining employment or friendships. This can be seen in the design of recent trials, and the extreme measures taken to avoid presenting statistically significant positive results, as detailed in the study notes below.

One method to evaluate bias is to compare prospective vs. retrospective studies, although this method has become less useful with ivermectin due to the increase of prospective studies with designs favoring null results. 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. Fig. 33 shows a scatter plot of results for prospective and retrospective studies. Prospective studies show 60% [48-68%] improvement in meta-analysis, compared to 62% [51-71%] for retrospective studies, showing no significant difference. *Bryant* also perform a funnel plot analysis, which they found did not suggest evidence of publication bias.

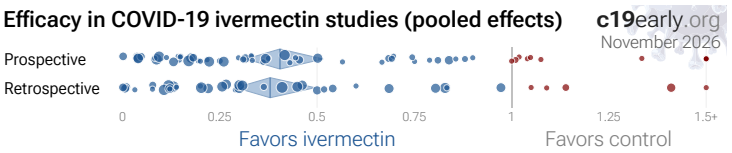

Fig. 33. **Prospective vs. retrospective studies. The diamonds show the results of random-effects meta-analysis.**

There is substantial evidence that journals are rejecting and 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[364,365]. One group performed prophylaxis and early treatment studies, with only the less positive study being formally published to date[166,170], suggesting a negative publication bias. Dr. Eli Schwartz's[328] double blind RCT was rejected without review by The Lancet and Clinical Infectious Diseases[366]. Authors of *Efimenko* do not plan to submit the very positive results to a journal, and have self-censored the conference publication, providing further evidence of a negative publication bias. Trials with pending and possibly delayed publication often involve researchers that may be restricted due to politics — publishing positive results may be incompatible with continued employment, whereas negative results can receive priority treatment at certain well-known journals, support the positions of employers or funding organizations, and receive substantial press. For more details of censorship and negative publication bias in ivermectin research see[368-370].

News coverage of ivermectin studies is extremely biased. Only studies with designs favoring null results have received significant press coverage in western media[161,162,165], all of which have multiple critical issues as discussed below, but ignored by the press.

Physician case series results

Table 4 shows the reported results of physicians that used combined early treatment protocols for COVID-19, compared to results for physicians following guidelines focusing on late treatment (Dr. Uip reportedly prescribed early treatment for himself, but not for patients[371]). The protocols vary, but include ivermectin, HCQ, vitamin D, vitamin C, zinc, melatonin, quercetin, budesonide, and other treatments. These results are subject to selection and ascertainment bias and more accurate analysis requires details of the patient populations and follow-up, however results are consistently better across many teams, and consistent with the extensive controlled trial evidence that shows a significant reduction in risk with many early treatments, and improved results with the use of multiple treatments in combination.

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Physician-reported outcomes: early vs. late treatment of COVID-19

c19early.org
November 2026

0.1% mortality with early treatment vs. **6.2%** with late treatment (49× lower)

EARLY TREATMENT
0.1%
average mortality
2.2% hospitalized

LATE TREATMENT
6.2%
average mortality
39% hospitalized

Physician	Patients	Hospitalized	Died
EARLY TREATMENT treatment on presentation			
Dr. Roberto Alfonso Acc... *0/360 deaths for treatment within 3 days*	1,265		0.6%
Dr. Mohammed Tarek Al... *patients up to 84 years old*	100		0%
Dr. Oluwagbenga Alonge	310		0%
Dr. Raja Bhattacharya *up to 88yo, 81% comorbidities*	148		1.4%
Dr. Flavio Cadegiani	3,450	0.1%	0%
Dr. Alessandro Capucci	350	4.6%	
Dr. Shankara Chetty	8,000		0%
Dr. Deborah Chisholm	100		0%
Dr. Ryan Cole	400	0%	0%
Dr. Marco Cosentino *earlier treatment results were better*	392	6.4%	0.3%
Dr. Jeff Davis	6,000		0%
Dr. Dhanajay	500		0%
Dr. Bryan Tyson & Dr. G...	20,000	0.0%	0.0%
Dr. Raphael Furtado	170	0.6%	0%
Rabbi Yehoshua Gerzi	860	0.1%	0%
Dr. Heather Gessling	1,500		0.1%
Dr. Ellen Guimarães	500	1.6%	0.4%
Dr. Syed Haider	4,000	0.1%	0%
Dr. Mark Hancock	24		0%
Dr. Sabine Hazan	1,000		0%
Dr. Mollie James	3,500	1.1%	0.0%
Dr. Roberta Lacerda	550	1.5%	0.4%
Dr. Katarina Lindley	100	5.0%	0%
Dr. Ben Marble	150,000		0.0%
Dr. Edimilson Migowski	2,000	0.3%	0.1%
Dr. Abdulrahman Mohana	2,733		0%
Dr. Carlos Nigro	5,000	0.9%	0.5%
Dr. Benoit Ochs	800		0%
Dr. Ortore	240	1.2%	0%
Dr. Valerio Pascua *one patient already on oxygen died*	415	6.3%	0.2%
Dr. Sebastian Pop	300		0%
Dr. Brian Proctor	869	2.3%	0.2%
Dr. Anastacio Queiroz	700		0%
Dr. Didier Raoult	8,315	2.6%	0.1%
Dr. Karin Ried *up to 99yo, 73% comorbidities*	237		0.4%
Dr. Roman Rozencwaig *patients up to 86 years old*	80		0%
Dr. Vipul Shah	8,000		0.1%
Dr. Silvestre Sobrinho	116	8.6%	0%
Dr. Unknown	957	1.7%	0.2%
Dr. Vladimir Zelenko	2,200	0.5%	0.1%
Early treatment	**236,181**	2.2%	0.1%
LATE TREATMENT no treatment until hospitalization			
Dr. Jake Scott (**)	1,000		10%
Dr. David Uip (*)	2,200	39%	2.5%
Late treatment	**3,200**	39%	6.2%

Early-treatment physicians treated patients on presentation, while late-treatment physicians followed official guidance with treatment only on hospitalization. Groups are not randomized. Results are subject to selection and ascertainment bias and accurate analysis requires details of the patient populations and followup, however the results are consistent across many teams, and consistent with the extensive controlled clinical evidence showing a significant reduction in risk with many early treatments, and complementary/synergistic benefits with combined treatment.

Table 4. Physicians using early combined treatment protocols had much lower hospitalization and mortality rates compared with those following guidelines focusing on late treatment. Results are subject to selection and ascertainment bias and accurate analysis requires details of the patient populations and followup, however the results are consistent across many teams, and consistent with the extensive controlled clinical evidence showing a significant reduction in risk with many early treatments, and complementary/synergistic benefits with combined treatments. (*) Dr. Uip reportedly prescribed early treatment for himself, but not for patients [371]. (**) Dr. Scott reports treating hundreds of patients and losing over a hundred, but has not provided specific numbers [372]. Dr. Scott reports following (and helping create) US guidelines.

Funnel plot analysis

Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Fig. 34 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ [373-380]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

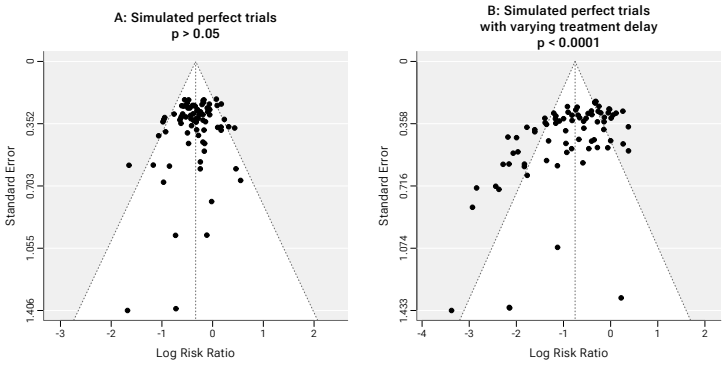

Fig. 34. Example funnel plot analysis for simulated perfect trials.

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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[161,165] — 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[161,165]. Note that biasing an RCT to produce a false positive result is difficult (suppressing adverse events is relatively easy[381]), 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.

Drug interactions

Other treatments may reduce the efficacy of ivermectin, for example dexamethasone may interfere with the pharmacokinetics of ivermectin, significantly reducing plasma concentration and efficacy[382].

Designed to fail

Several major trials 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[383]. One patient reported their experience with one of the remote outpatient ivermectin/fluvoxamine trials: they were offered enrollment 7 days after symptoms (receipt of medication would be even later), were offered $400 to participate, and reportedly target healthy people[384]. Details of issues with several trials are included in the study notes.

Notes

The 106 studies are from 96 independent research teams. 5 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. 17 of 106 studies combine treatments, for example ivermectin + doxycycline. The results of ivermectin alone may differ. 5 of 54 RCTs use combined treatment, three with doxycycline, and one with iota-carrageenan. 2 of 106 studies currently have minimal published details available.

Reviews

Many reviews cover ivermectin for COVID-19, presenting additional background on mechanisms, formulations, and related results, including[3,61,70,72-75,78,83,88,283,286,287,289,290,363,368,385-418].

Limitations

Summary statistics from meta-analysis necessarily lose information. As with all meta-analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses for specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

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

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials with conflicts of interest may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone[103,119,120,122,124,129,132,142,207,236-251]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Meta-analyses

Typical meta-analyses involve subjective selection criteria, effect extraction rules, and study bias evaluation, which can be used to generate a preferred outcome. In order to avoid bias we include all studies and use a pre-specified method to extract results from all studies, in addition to presenting results for higher-quality studies after exclusions. Results to date are overwhelmingly positive, consistent, and insensitive to potential selection criteria, effect extraction rules, and/or bias evaluation. Additional meta-analyses confirming the effectiveness of ivermectin can be found in *Kory, Lawrie, Bryant, Nardelli, Hariyanto, Ragó*. *Kory et al.* also review epidemiological data and provide suggested treatment regimens.

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 5 and Table 6 compare the amount of evidence for ivermectin compared to that used for other COVID-19 approvals, and that used by WHO for

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the approval of ivermectin for scabies and strongyloidiasis. Table 7 compares US CDC recommendations for ibuprofen and ivermectin. Fig. 35 compares the results of different meta-analyses.

WHO ivermectin approval status

c19early.org
November 2026

Indication	Studies	Patients	Status
Strongyloidiasis [420]	5	591	Approved
Scabies [420]	10	852	Approved
COVID-19	106	220,588	Pending
COVID-19 RCTs	54	17,836	Pending

Table 5. WHO ivermectin approval status.

Evidence base for COVID-19 approvals

c19early.org
November 2026

Medication	Studies	Patients	Improvement	Status
Molnupiravir (UK)	1	775	50%	Approved
Budesonide (UK)	1	1,779	17%	Approved
Remdesivir (USA EUA)	1	1,063	31%	Approved
Casirivimab/imdevimab (USA EUA)	1	799	66%	Approved
Ivermectin	**106**	**220,588**	**61%** [53-67%]	**Pending**

Table 6. Evidence base used for other COVID-19 approvals compared with the ivermectin evidence base.

Comparison of CDC recommendations

c19early.org
November 2026

	Lives saved	Deaths per year	Evidence base	CDC recommended
Ibuprofen	0	~450	0 RCTs	Yes
Ivermectin (for scabies)	0	<1	10 RCTs 852 patients	Yes
Ivermectin (for COVID-19)	>500,000	<1	54 RCTs 17,836 patients	No

Table 7. Comparison of CDC recommendations [420].

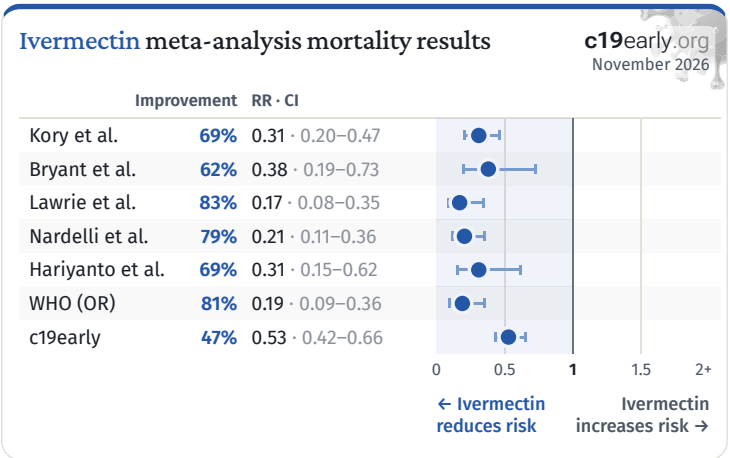

Fig. 35. Comparison of meta-analysis results.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 500+ host and viral proteins and other factors [38-45], providing many therapeutic targets. Over 12,000 compounds have been predicted to reduce COVID-19 risk [46], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Fig. 36 shows an overview of the results for ivermectin in the context of multiple COVID-19 treatments, and Fig. 37 shows a plot of efficacy vs. cost for COVID-19 treatments.

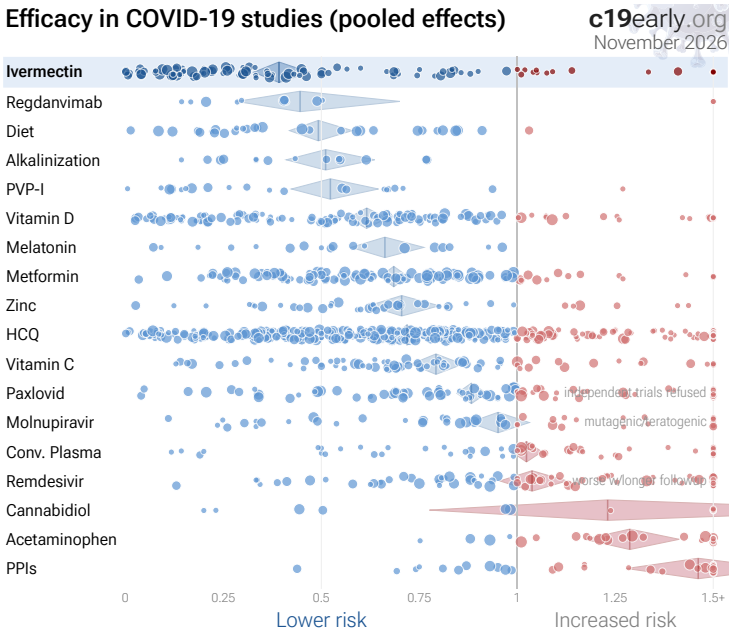

Fig. 36. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random-effects meta-analysis. 0.5% of 12,000+ proposed treatments show efficacy [421].

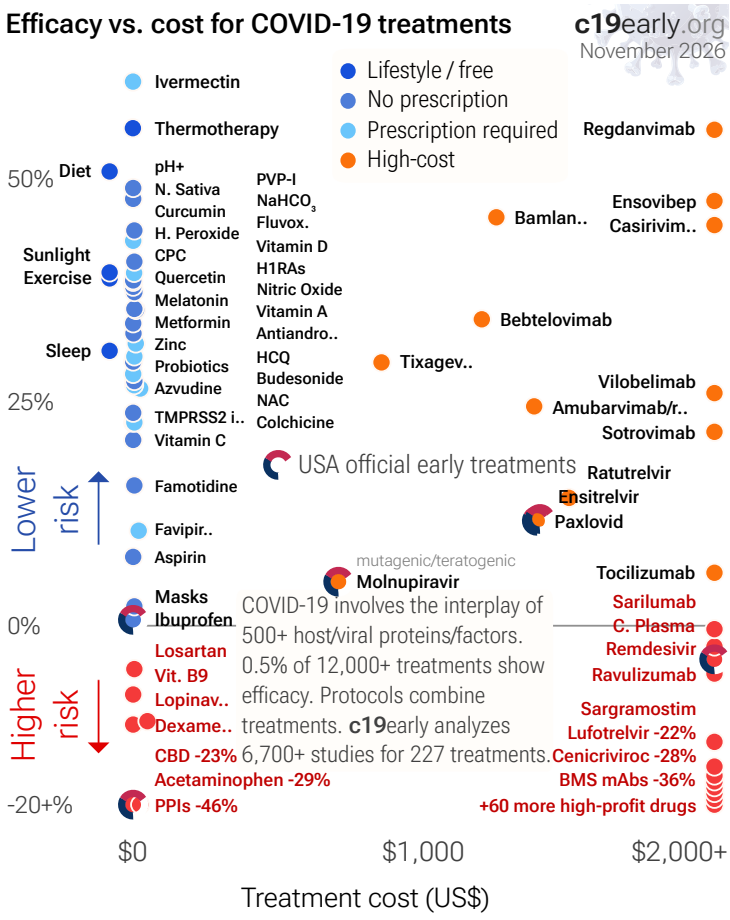

Fig. 37. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Ivermectin is an effective treatment for COVID-19. Treatment is more effective when used early. Meta-analysis using the most serious outcome shows 62% [52-70%] and 84% [75-89%] lower risk for early treatment and prophylaxis, with similar results for higher quality studies, primary outcomes, peer-reviewed studies, and for RCTs. Significantly lower risk is seen for mortality, ventilation, ICU admission, hospitalization, recovery, cases, and viral clearance. All remain significant for higher quality studies. 66 studies from 60 independent teams in 28 different countries show significant improvements.

Results are very robust—in worst case exclusion sensitivity analysis 65 of 106 studies must be excluded before statistical significance is lost. Emergent results matching biological mechanisms confirm efficacy: meta-regression of efficacy vs. treatment delay ($p = 0.0038$), efficacy gradient across stages ($p < 0.0000001$), and fed vs. fasting administration ($p = 0.03$).

Optimal use of ivermectin may involve synergy with combined treatments, administration taking into account the lipophilic nature, and sublingual, spray, or inhaled formulations for direct treatment to the respiratory tract. Pharmacokinetics show significant inter-individual variability [1]. Injectable formulations may reduce variability and provide much faster onset of action [130]. Liposomal formulations show increased antiviral activity and lower cytotoxicity [125]. Synergistic results are seen with polytherapy [122,124,129]. Efficacy varies depending on the manufacturer [2], underdosed and contaminated ivermectin is common [422-425], and fake tablets with no active ingredient have been reported [395,426].

Contact. Contact us on X at @CovidAnalysis.

Funding. We have received no funding or compensation in any form, and do not accept donations. This is entirely volunteer work.

Conflicts of interest. We have no conflicts of interest. We have no affiliation with any pharmaceutical companies, supplement companies, governments, political parties, or advocacy organizations.

Disclaimer. We do not provide medical advice. No treatment is 100% effective, and all may have side effects. Protocols combine multiple treatments. Consult a qualified physician for personalized risk/benefit analysis.

AI. We use AI models (Gemini, Grok, Claude, and ChatGPT) tasked with functioning as additional peer-reviewers to check for errors, suggest improvements, and review spelling and grammar. Any corrections are manually verified. Our preference for em dashes is independent of AI.

Updates. Our COVID-19 meta-analyses involve the extraction of over 229,000 datapoints from thousands of papers for 227 treatments. We thank the thousands of scientists, physicians, and other contributors that have provided updates, suggestions, feedback, and corrections. These are all welcome and can be submitted at https://c19early.org/imeta.html.

Dedication. This work is dedicated to top evidence-based physicians that worked tirelessly to analyze evidence and greatly reduce mortality and morbidity during the pandemic. In alphabetical order: Dr. Thomas J. Borody, Dr. Mary Talley Bowden, Dr. Flavio Cadegiani, Dr. Shankara Chetty, Dr. Ryan Cole, Dr. George Fareed, Dr. Sabine Hazan, Dr. Pierre Kory, Dr. Tess Lawrie, Dr. Robert Malone, Dr. Paul Marik, Dr. Peter McCullough, Dr. Didier Raoult, Dr. Harvey Risch, Dr. Jackie Stone, Dr. Brian Tyson, Dr. Joseph Varon, and Dr. Vladimir Zelenko.

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TLDR

As Scott Alexander says: "*if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele.*" The extreme politicization means we can only evaluate the data directly.

With 106 controlled studies, 54 RCTs, and extensive supporting evidence, few people have the time and experience to analyze all or most of the evidence. However, the PRINCIPLE trial [164] provides a single large trial showing efficacy. Despite being perhaps the most biased trial, with extreme bias against showing efficacy in the design, operation, analysis, and reporting, authors failed to eliminate efficacy and hid the results for 600 days (810 days from the expected announcement time, which resulted in a pause and a supply issue claim that was contradicted by the manufacturer, and continuation with increased bias).

PRINCIPLE showed 36% lower long COVID (pre-specified ongoing persistent COVID-19 specific symptoms), $p < 0.0001$ [164] (43%, $p < 0.0001$ if excluding the more common fatigue that may be unrelated). The primary recovery outcome shows superiority of ivermectin with significantly faster recovery and a probability of superiority > 0.999. These results are remarkable given the design for failure—very late low-dose incorrectly-administered truncated treatment with low-risk patients. Significantly better results are expected with recommended usage. The authors claim the significant improvements in this trial are unlikely to be "clinically meaningful", likely for the reason Scott Alexander illuminates. However, they are not consistent across their own trials with this interpretation, and we cannot find anyone that agrees that 36% lower long COVID is not meaningful (even among known paid industry representatives). Further, from all 227 treatments we cover, improved recovery is very significantly associated with lower mortality, $p < 0.0000000001$, as shown in Fig. 38.

Widely cited RCTs show efficacy

Despite very poor design and many critical issues, the RCTs typically used to claim a lack of efficacy all report either efficacy or strong signs of efficacy.

PRINCIPLE [164]	36% lower ongoing persistent COVID-19 specific symptoms, p<0.0001, hidden on page 358 of the appendix [164]. The primary outcome shows superiority of ivermectin with significantly faster recovery and a probability of superiority > 0.999.
TOGETHER [161]	*"There is a clear signal that IVM works in COVID patients.. that would be significant if more patients were added.."* - co-principal investigator [161].
ACTIV-6 [162]	99%, 98%, 97% superiority for time unwell, progression @14,7 days [162] (clinical progression reported in the preprint [428], video [429], and slides [430]—changed in the journal version, unexplained for over 1,400 days).
COVID-OUT [163]	61% lower hospitalization (ivermectin vs. placebo, unreported) [163]. Authors detail why the hypoxemia results are unusable, however analysis shows the ER results are similarly uninformative and not related to symptoms.
I-TECH [431]	69% lower mortality, $p = 0.09$, (75% lower, $p = 0.02$ among severe patients). This is the only one of the commonly cited RCTs that correctly used fed administration, which shows 3.1 times higher efficacy [427].

Results vary as expected across studies—only possible with a real treatment effect

While meta-analysis shows very strong confidence in efficacy, emergent results across studies that match biological mechanisms provides additional confirmation.

Treatment delay	Meta-regression of efficacy as a function of treatment delay matches expectations ($p = 0.0038$).
Gradient across stages	Preclinical studies show mechanisms relevant to all stages: blocking initial infection, minimizing viral replication, and mitigating secondary complications; therefore we expect benefits to combine and increase for earlier treatment, and again for prophylaxis—as intervention is delayed the benefit of specific mechanisms is reduced or lost. Meta-regression confirms this relationship with $p < 0.0000001$. (Specifically, for blocking initial infection: spike-ACE2 disruption [59], lipid raft attachment inhibition [76], glycan binding [60,209], and CD147 inhibition [72-75]; for minimizing viral replication: importin-α/β nuclear transport blockade [47,49,51,58], 3CLpro inhibition [66], and RdRp interference [67]; and for mitigating secondary complications: inhibiting fibrin clots [65], reducing lung fibrosis [63,79,80], protecting against myocarditis [69,81], and dampening cytokine storm [77,78]).
Fed vs. fasting	Administration with a high-fat meal is expected to significantly increase bioavailability, but also support distribution to the lung, bypassing hepatic first-pass metabolism. Studies specifying fed vs. fasting administration show 3.1 times greater efficacy, interaction $p = 0.03$).

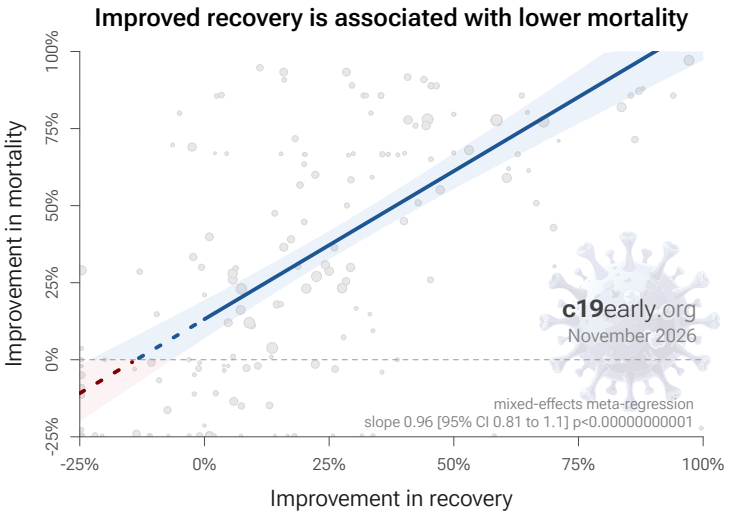

Fig. 38. Improved recovery is associated with lower mortality. Meta-regression across 227 treatments.

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Responses

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% (18 of 18) positive effects. Early treatment shows 85% (33 of 39) 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 73% (36 of 49) 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 82% (87 of 106) positive effects, compared to 81% (86 of 106) in the main protocol analysis.

BBC

The team referenced in this article is unreliable. Dr. Kyle Sheldrick posted a schedule A statement as a result of a defamation lawsuit admitting to false and defamatory claims regarding one of the world's most highly published and respected critical care physicians [432]; Dr. Nick Brown has called for trials for crimes against humanity for scientists that *"tried to scam the world with their fake treatments"* including vitamin D [433,434]. Gideon Meyerowitz-Katz has posted many false claims detailed below [435].

Update: authors indicated that their data would be available "soon" as of Sep 14, 2021, however it has not been released over 1,800 days later [436], therefore it is not possible to analyze their methods regarding ivermectin research in detail. However, Dr. Sheldrick posted false and defamatory accusations regarding a highly respected physician that has saved countless lives before and during the pandemic. In this case, detailed methods were published, revealing highly flawed analysis, and a basic misunderstanding of statistics, as detailed by multiple statisticians [437,438]. Author deleted the blog post. Further, we note that the team's disregard for major issues with the Together Trial, ACTIV-6, López-Medina et al., and Beltran Gonzalez et al. suggest substantial bias.

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, one was withdrawn by a preprint server, and another has been reported as pending retraction, although the journal reports 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. 61%, or 65 of 106 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.

	Prophylaxis	*Early treatment*	*Late treatment*
With GMK/BBC exclusions	83% [71-90%]	68% [60-75%]	50% [35-62%]
RCTs w/GMK/BBC exc.	85% [54-95%]	64% [52-73%]	39% [18-55%]

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 [439], 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 109 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 1299 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 109 studies, authors have not reported their results for all 26, and authors have not pro-

vided their data after repeated requests. Currently they 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 [440] (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 138 vitamin D COVID-19 treatment studies, author suggests only one trial is worth looking at [441]. 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 138 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 *Reis* 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, Elijah, Lawrie (B), Campbell*.

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

GidMK

On September 6, 2021, author is on video saying *"what this web site does is it goes through all of those 10 things, finds the positive one, and only reports the positive one ... they'll pick a number that is the lowest number"* [446] @46:48. This is false, we report individual outcome analyses, and for pooled results we use the most serious outcome with a detailed protocol. Notably, author knows this is false, having posted the protocol on Twitter a month earlier. Moreover, in most cases there could be no ambiguity on the most serious outcome even without a detailed protocol. At the time of author's statement, the most serious outcome was actually the worst of multiple reported outcomes 26% of the time.

Author indicated their data would be released "soon" on Sep 14, 2021. The data was used for conclusions in the BBC and BMJ along with a message that data transparency is needed. No data has been released over 1,800 days later [436].

TLDR

As a quick way to assess reliability, consider that author describes the Together Trial as "*incredibly well-done*" and a "*masterpiece of science*". The trial actually reported multiple impossible numbers, has refused to release data despite pledging to do so, has extreme conflicts of interest, and had blinding failure, randomization failure, and multiple protocol violations as detailed below. Author similarly disregards major issues with many other trials, including ACTIV-6, López-Medina et al., and Beltran Gonzalez et al. This suggests substantial bias.

SEE ALSO

The Potemkin Argument: How Scott Alexander and GidMK Caricatured the ...
The Potemkin Argument, part I (extension): The Sullying of Babalola et al.

Incorrect, misleading, hyperbolic, and unsupported statements have been made by an influential anti-treatment Twitter personality, journalist, and PhD student known for defending Monsanto Roundup against carcinogenic claims (later settled for $US 11 billion). Author is notable as the only known researcher that reports having read a majority of the 109 (including retracted) studies, but does not find the evidence to be positive. However, their opinion appears to have been formed before reading the studies — they first referred to ivermectin as "*something else to debunk*". We note that the author has made 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.

Analysis with GMK's recommended exclusions can be found in the supplementary data, which shows 46% [35-56%] improvement, $p = 0.00000000077$.

Author has been paid for writing anti-treatment articles, and has also referred to ivermectin as a "*horse dewormer*". Author has experienced personal tragedy with multiple family members having died of COVID-19, which may introduce a bias against acknowledging errors in treatment advice.

Author's attempt to discredit the scientists performing ivermectin research centers on the 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 a 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? 61%, or 65 of 106 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 (only one has been retracted, 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 11 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 [439]. 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.

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On Sep 14, 2021, author indicated that their team had reviewed about 30 ivermectin studies and their data would be available soon, however it has not been released five years later.

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 have the authors declined to release IPD that they previously pledged to release, there was not even a preprint when GMK made the statement, and the trial has many critical and serious flaws, extremely high conflicts of interest, and a history of inaccurate reporting prior to publication for another treatment arm. GMK has subsequently published a paper with one of the original co-lead's of the Together Trial (who later joined the trial DSMC).

Author has disregarded treatment delay in analysis, which results in incorrect conclusions. For example, author claims that the RECOVERY trial proved that another treatment is not effective, and would provide definitive data if the same was done for ivermectin. The trial provided valuable data on very late use (9 days after symptoms) with an excessively high dose and very late stage patients. However, it did not provide information on early treatment. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours [222,223]. Paxlovid was tested with a maximum of 3 days from symptom onset (the mean delay is unknown). For ivermectin, author believes the PRINCIPLE trial will provide strong data on efficacy, however this trial includes low risk patients less than 15 days from symptom onset, and may only provide information on late treatment in a low risk population with lower risk variants. Fig. 39 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 227 treatments. Efficacy declines rapidly with treatment delay.

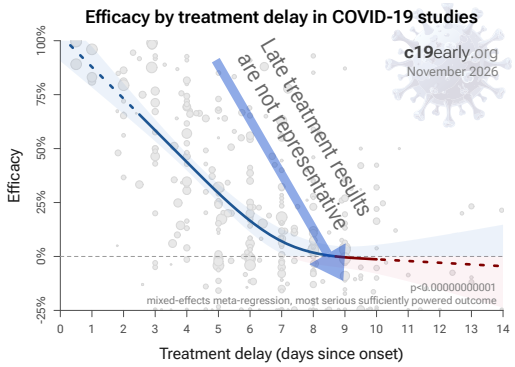

Fig. 39. **GMK believes that results for treatment delayed 9 days from symptom onset provides definitive information on treatment efficacy.** However early treatment is critical for antivirals, as shown with antivirals for other respiratory diseases, and in meta-regression of studies from 227 COVID-19 treatments.

Author has an unwarranted focus on a specific outcome (mortality) and a specific subset of trials (RCTs). This would be reasonable in many cases when sufficient high-quality data is available, however this is not the case for off-patent COVID-19 treatment trials, where RCTs often involve delayed treatment, low-risk patients where mortality is rare, or very high conflicts of interest. Widely accepted and effective (for specific variants) treatments like casirivimab/imdevimab, bamlanivimab, and sotrovimab were all approved without statistically significant mortality benefits. 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.

Most errors have not been corrected by the author over five years later. Many false, misleading, and defamatory statements continue to be available, highly-ranked in search results, and highly influential. Other errors include:

- that excluding Elgazzar et al. completely changes the results and could be "*the most consequential medical fraud ever committed*". Excluding 1 of 109 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 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 [302,447-449]).
- 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 [450]. Plasma half-life is longer in some studies, and significant plasma concentration can persist for over 2 weeks in some patients [451]. More importantly, ivermectin is highly lipophilic and may accumulate in the lung and other tissues where concentrations may be many times higher [452,453].
- 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 [364,365]).
- suggesting that it is not reasonable to combine evidence from mortality and hospitalization (for example), but happily combining late treatment and early treatment in order to obscure efficacy. If a treatment reduces disease

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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 in one study, 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 [228-230], and mortality (for example Gamma vs. non-Gamma aHR 4.73 [1.15-19.41] [231]).

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 is similar to 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 have not even interacted with them, but are connected to other users reporting on their errors. Author ackowledges using a tool called MegaBlock that blocks all people that liked a specific tweet.

The author is also against vitamin D. Of the 138 vitamin D COVID-19 treatment studies, author suggests only one trial is worth looking at [441]. 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 one of least useful studies from the 138 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 [279].

Five years later, the author has still not contacted us, making 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.

Scott Alexander

Feb 2, 2023 update: Scott acknowledges that his analysis was incorrect, that the topic is outside his *"expertise and competence level"*, and that his self-and-GidMK-filtered subset of a 29 study subset of 106 studies actually shows much stronger efficacy than previously claimed. Scott further acknowledges several false and defamatory claims, while standing by others. Scott acknowledges that the strongyloides theory is not very strong. Scott now relies on publication bias to discredit the 670 scientists reporting efficacy, without even reading many of their studies.

For publication bias, author is saying that the statistically significant positive studies were chance events, i.e., there are actually >1,000 ivermectin studies, but there is an extremely strong bias towards publishing only the positive studies.

This is in direct opposition to the evidence on publication bias. High profile journals refuse to publish positive ivermectin studies, while negative ivermectin studies are guaranteed acceptance, widespread press, and fame, just as Scott has received fame for his negative article. As Scott said in November 2021, *"if*

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you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele." Ivermectin has the strongest negative publication bias we have ever seen.

Scott finally points at our overview of efficacy across treatments, claiming that multiple effective treatments is proof of publication bias. As if somehow the existence of several effective treatments is impossible.

Scientists have identified over 2,000 compounds potentially beneficial for COVID-19. It is trivial to disable SARS-CoV-2 *in vitro*, hundreds of compounds do so, many with existing known and positive safety records. What is the chance that none of these can safely reach the location of SARS-CoV-2 infection? In the nasopharynx, oropharynx? Lung? Other tissues?

Is it really surprising that PVP-I for example, very effective *in vitro*, can be applied to the nasopharynx/oropharynx in effective concentrations, and is helpful, especially if used before infection spreads further?

Are there really no inputs to the human system that improve functioning of the immune system?

Does Scott really believe that paxlovid, casirivimab/imdevimab, sotrovimab, tixagevimab/cilgavimab, bebtelovimab, ensovibep, molnupiravir, and remdesivir are actually ineffective, all were approved in error because hundreds of other studies were not published?

While Scott dismisses the work of over 11,100 scientists reporting statistically significant positive effects of low-cost treatments (over 600 for ivermectin), he appears to have blind faith in trials having perhaps the highest moral and financial conflicts in the history of medicine, while simultaneously missing many critical issues (ACTIV-6, TOGETHER, COVID-OUT, PRINCIPLE) creating unreliable results, and signs of efficacy despite best efforts to avoid it.

Extreme moral conflicts arise for authors and institutions that played a critical role in the suppression of early treatments — they share responsibility for the results of any mistakes that impacted policies. The extreme financial conflicts come from authors and institutions associated with companies where billions of dollars of profit relies on no effective inexpensive treatments existing.

We challenge Scott to do a more serious analysis. For example: examine all of the studies rather than only 27%; directly examine studies rather than relying on a personality that thinks a study treating patients 9 days after onset is conclusive (a study so extremely late that 17% were on ventilation/ECMO); take into account major issues with studies like ACTIV-6, TOGETHER, COVID-OUT, and PRINCIPLE; and review the ~100 additional supporting papers for understanding of the mechanisms of action, censorship, and other issues.

Previous response: For a much better and more thorough analysis of Scott Alexander's essay, including numerous errors, extreme bias, incorrect statistical analysis, contradictory standards, and failure to make corrections, see the Potemkin Argument series. Part 21 illustrates the potentially catastrophic result of humanity's difficulty in objectively creating and evaluating scientific evidence related to critical world problems.

SEE ALSO

The Potemkin Argument: Index
The Potemkin Argument, Part 2: The Devil's Advocate
The Potemkin Argument, Part 3: The Misportrayal of Dr. Flavio Cadegiani
The Potemkin Argument, Part 4: How Scott Alexander and GidMK Caricatur...
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The Potemkin Argument, Part 6: The Erratic Disciples of Dr. John Carlisle
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The Potemkin Argument, Part 16: Worm Games
The Potemkin Argument, Part 17: Viral Funnel Plot Blues
The Potemkin Argument, Part 18: Scott's Scientific Takeaway
The Potemkin Argument, part 19: My Scientific Takeaway -or- Why You Still ...
The Potemkin Argument, Part 20: Scott's Sociological Takeaway—or—The ...
The Potemkin Argument, Part 21: The Political Takeaway
Ivermectin: Much Less Than You Needed To Know

The analysis by SSC / Scott Alexander has a number of major issues. For many other uncorrected errors in SSC's analysis, see *doyourownresearch.substack.com (B), twitter.com (E)*.

Analysis with SSC's recommended exclusions can be found in the supplementary data.

Update: after exclusions chosen by SSC, exclusions by GMK, excluding all late treatment, and excluding all prophylaxis studies, SSC found the results in Fig. 40, showing statistically significant efficacy of ivermectin with $p = 0.04$. The method for computing this p value is not specified. We used the same event results and performed random-effects inverse variance DerSimonian and Laird meta-analysis as shown in Fig. 41, finding much higher significance with $p = 0.005$. We note that the effect extraction appears biased against ivermectin, choosing the excessive dose arm in Buonfrate, and using the post-hoc exclusion in López-Medina. The Krolewiecki treatment count appears to have been scaled for the different group sizes. We do not know where SSC's Mahmud counts are from.

	Outcome	Placebo	Ivermectin	
Mahmud	Nonrecovery	120	89	
Ahmed	Fever nonrecovery	3	0	
Chaccour	Viral culture +	1	1	
Ravakirti	Death	4	0	
Bukhari	PCR-7+	25	4	
Mohan	Clinical worsening	5	3	
Lopez-Medina	Hospitalization	6	4	
Krolewiecki	PCR-5+	11	8	
Vallejos	Hospitalization	21	14	
Together	Death	95	86	
Buonfrate	Hospitalization	0	3	

***Fig. 40.* SSC's analysis.** SSC reports $p = 0.04$, with an unspecified method.

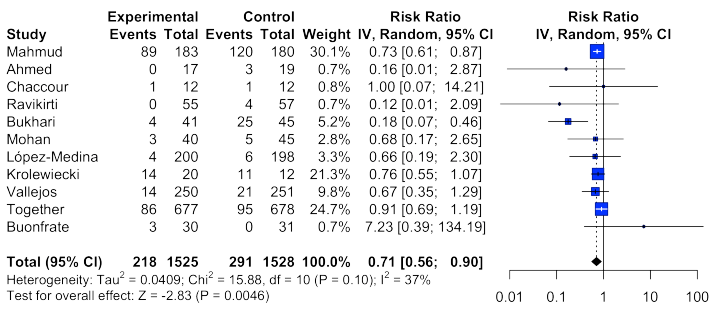

***Fig. 41.* Random-effects meta-analysis per SSC's chosen results, finding much higher significance.**

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Author appears to be against all treatments, labeling them all *"unorthodox"* and *"controversial"*, even those approved by western health authorities, including casirivimab/imdevimab, bamlanivimab, sotrovimab, and paxlovid. *Update: author's original article still refers to all treatments we follow as unorthodox and controversial, however they report that they actually recommend fluvoxamine, paxlovid, casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab, and suggest that they support all western health authority approved treatments which additionally includes remdesivir, budesonide, bebtelovimab, tixagevimab/cilgavimab, and molnupiravir. Author also has positive comments for zinc (but reports there is no proof). i.e., author appears to actually support at least 11 of the 227 treatments we follow. We note that the methodology is the same for all treatments.*

We encourage the author 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 dismissing everything as *"unorthodox"*. Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all variants — we need to embrace all safe and effective means.

The third-party analysis that author references for the strongyloides theory is confounded by treatment delay and dosage — the high prevalence group has more early treatment trials and a higher average dose, i.e., the analysis reflects the greater efficacy of early treatment and the greater efficacy of higher dosage. More details can be found in the strongyloides section.

Author refers to studies with positive but not statistically significant results as *"negative"* [297], or *"[the] original outcome would also have shown ivermectin not working"* [165], which are incorrect conclusions [439]. *Update: author believes this means we abandon statistical significance. We do not know where this comes from — all of our results report confidence intervals, and the first two words of this paper are "statistically significant". What is incorrect is making a negative conclusion based on an insignificant result. For example, if one study reports 50% lower mortality without reaching statistical significance, this does not mean that the treatment is useless. Consider if there are 10 studies all reporting ~50% lower mortality, the combined evidence may be strong even if each individual result is not statistically significant.*

Author notes that: *"if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists"*, suggesting an environment that may bias the information that the author sees, and could unconsciously bias analysis. We note that similar environments influence the design, operation, and publication of some existing (and many upcoming) ivermectin trials.

Author looks at 29 of the 106 studies, which we note is much better than most commenters, but still ignores the majority of studies, including the prophylaxis studies.

The author finds efficacy at $p = 0.04$ in their analysis of 11 of the 29 studies they looked at. We note that simply looking at the other 77 studies will result in much higher confidence in efficacy. We also note that even at $p = 0.04$ with 11 independent studies, a rational risk-benefit analysis results in immediate adoption into protocols (pending stronger data with other combinations of treatments), and immediate collection of more data from sources without conflicts of interest.

However, ultimately the author at least partially supports the two prevailing theories that are commonly used by those against treatment. These theories require disregarding extensive contradictory evidence:

The steps required to accept the *no-significant-effect* outcome are extreme — one needs to find a reason to exclude most of the studies, disregard the strong treatment-delay response relationship, and disregard all prophylaxis studies. Even after this, the result is still positive, just not statistically signficant. This does not support a negative recommendation. Widely accepted and effective (subject to dependence on viral variants) treatments like casirivimab/imdevimab, bamlanivimab, and sotrovimab were all approved without statistically significant mortality benefits.

The steps required to accept the *strongyloides-mechanism-only* conclusion are also extreme - we need to disregard the majority of outcomes occuring before steroid use, and disregard the strong treatment-delay response relationship which is contradictory. Fig. 32 shows analysis by strongyloides prevalence. The third-party analysis referenced by the author is confounded by treatment delay and dosage.

Author seems biased against believing any large effect size. We note that large effect sizes have been seen in several COVID-19 treatments approved by western health authorities, including paxlovid which the author is very positive about, and also that better results may be expected when studies combine multiple effective treaments with complementary mechanisms of action (as physicians that treat COVID-19 early typically do). *Update: author confirms this bias but appears to disregard it for paxlovid.*

Author is suspicious about a study based on the country of the researchers, and also appears biased against non-native speakers, with comments such as *"unreadable"* for one paper, compared to *"written up very nicely in real English"* for another. *Update: author confirms being biased against certain countries.*

Author calls a physician that has reported zero deaths and 5 hospitalizations with 2,400 COVID-19 patients *"a crazy person"* that *"put his patients on every weird medication he could think of"*.

Author disregards the dramatically higher mortality for Gamma vs non-Gamma variants (aHR 4.73 [1.15-19.41] [231]), instead concluding that higher mortality indicates fraud in one instance, while in another instance assuming that the related confounding by time in the Together Trial is not significant.

Author's review of the 29 studies appears relatively cursory, for example author appears unaware that the ivermectin dosage is very different in the ivermectin + doxycycline arm of Ahmed.

Author appears to accept the analysis and accusations of GMK as correct, however that author is often incorrect.

Author is concerned that we detail problems with *López-Medina*, while correctly noting that the outcomes in this trial are actually positive and in favor of ivermectin (while not statistically significant in isolation).

Author is concerned that we specifically comment on *Reis, López-Medina*. We note that it has been others that have focused on these trials — we comment on them because they have received special attention, including being held up as sole evidence overriding all other trials, despite having major issues.

Author claims that nobody can find issues with *Vallejos*, which suggests that they have not read the study, or our analysis.

Elgazzar

This study was withdrawn and was removed from this analysis on the same day. There was no significant change (excluding 1 of 109 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.

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Merino

This preprint was censored by the original preprint host. Censors claim that the government treatment program, which used approved medications and saved over 500 people from hospitalization, was unethical. In part they also indicate that studies of "the effects of a medication on a disease outcome" are outside the scope of their site.

The author's response (not provided by the censors) can be found here: *twitter.com (F)*. Author's provide the data and code for the study, and the results have been independently verified.

Pott-Junior

This paper appears to have been censored at the request of the journal's founding editor[457]. An external review is mentioned but is not provided, and there is no reply from the authors, or indication that the authors were notified. Conclusions in this study are limited due to the small size, however we should consider all information in the context of the full body of research.

Efimenko

The conference publication for this analysis was self-censored by the authors, not due to any error in the analysis, but because authors believe ivermectin "has proven to be ineffective in clinical trials". This is incorrect, 66 studies show statistically significant positive results for one or more outcomes (39 prospective and 27 retrospective studies, including 29 Randomized Controlled Trials).

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 83% [71-90%]. 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[459].

Study Notes

For discussion of all studies see c19early.org/i. A few studies have received special attention, with some considering them to be very strong evidence overriding the other 105 studies. We note limitations of these studies here.

PRINCIPLE

Ivermectin for COVID-19 in adults in the community (PRINCIPLE): an open, randomised, controlled, adaptive platform trial of short- and longer-term outcomes

SEE ALSO

The Last of The "Big Seven" Fraudulent Ivermectin Trials Has Finally Been P...
Ivermectin and the Research Cartel
Four Years Later – The Toughest COVID Pill to Swallow
Can Scientific Misconduct Be Criminally Prosecuted?

Significantly improved recovery and significantly lower risk of long COVID with ivermectin, despite very late treatment, low-risk patients, and poor administration.

36% lower ongoing persistent COVID-19 specific symptoms, p<0.0001 (details below). The primary recovery outcome shows superiority of ivermectin (probability of superiority > 0.999), missing from the abstract (details below). The *p* values for sustained recovery, early sustained recovery, alleviation of all symptoms, and sustained alleviation are all < 0.0001.

The efficacy seen here is despite testing about the worst possible usage: very late, low-dose, incorrectly administered, truncated treatment with low-risk patients. Recommended usage shows much better results.

The tables below compare the same principal investigator's trials of oseltamivir and molnupiravir, which show notable differences in design, analysis, and interpretation. A list of major issues in the trial follows.

Contrasting trial designs—ivermectin vs. molnupiravir

Trial design may favor detecting or not detecting efficacy. The contrast is clear in this case—these trials are for the same disease, from the same investigator, and overlap in time.

	MOLNUPIRAVIR (PANORAMIC) [460,461]	IVERMECTIN (PRINCIPLE) [462]
Investigator	Prof. Chris Butler	Prof. Chris Butler
	Favors detecting efficacy	Favors not detecting efficacy
Treatment delay	up to 5 days from onset	up to 14 days from onset
Population	50+ or 18+ w/comorbidities — high-risk patients	18+ (mid-trial change) — low-risk patients
Treatment	5 days, 2x per day	3 days, 1x per day, dose below real-world use
Administration	Per recommendation (with or without food)	Opposite of recommendation for COVID-19 - without food, greatly reducing concentration [1,463]
Patients	183 patients per day (25,783)	11 patients per day (3,963 inc. concurrent control)
Publication delay	4 months	1.6 years (2.2 years from expected end)
Enrollment	Dec 2021 - Apr 2022	May 2021 - Jul 2022
Mutagenic	Yes [464-478]	No
Trial funder stance	Approved	Denied—efficacy confirms liability for prior errors
Cost	$707 [479]	<$1 [480]
Merck profit	>$8B sales to date [481], estimated $18 to produce [482]	No potential, many low-cost manufacturers

Contrasting trial designs—ivermectin vs. oseltamivir

Trial design, analysis, and interpretation may favor detecting or not detecting efficacy.

	OSELTAMIVIR (ALIC⁴E) [483]	IVERMECTIN (PRINCIPLE) [164]
Investigator	Prof. Chris Butler	Prof. Chris Butler
	Favors detecting efficacy	Favors not detecting efficacy
Treatment delay	≤72 hours from symptom onset	≤14 days from symptom onset
Treatment	5 days, 2x/day	3 days, 1x/day, dose below real-world use
Administration	Per recommendation (with or without food)	Opposite of recommendation for COVID-19 - without food, greatly reducing concentration [1,463]
Primary recovery definition	Self-reported return to usual activities + fever/headache/muscle ache minor/absent; those minor symptoms and other symptoms of any severity may remain	Self-reported recovery, not limited to specific symptoms. Slower-resolving symptoms, e.g., those related to tissue repair rather than ongoing viral replication, may delay recovery and reduce sensitivity to improvement for other symptoms
Bayesian shrinkage	Priors shrink subgroup effects toward overall response; no strong null-centered overall treatment-effect shrinkage	Strong skeptical prior appears to shrink recovery HR toward 1; Prof. Sander Greenland estimates ~1.19 → 1.15 [484]
Clinically meaningful threshold	Trial explicitly powered to detect a 1-2 day benefit; no additional meaningful threshold	HR ≥1.20 specified as meaningful for futility decisions
Recovery benefit	1.02 days faster [0.74-1.31]	2.06 days faster [1.00-3.06]
Long-term morbidity	Not tested	Significantly lower long-term morbidity
Interpretation	Recovered one day sooner; clinicians may consider treatment; accelerates recovery; even 0.7 days in a subgroup is described as an oseltamivir benefit	Unlikely to be clinically meaningful; further trials unwarranted

Severity	*Issue (most recent update 60 days ago)*
CRITICAL	1. 36% lower long COVID hidden in appendix

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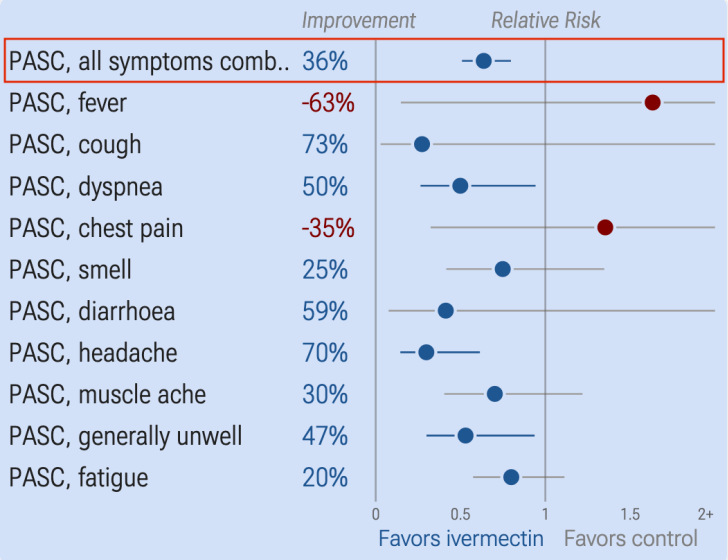
CRITICAL	2. Undisclosed null-biased Bayesian prior masks superiority
CRITICAL	3. Ad-hoc "clinically meaningful" threshold contradicted by same authors later in the same year for an ARI RCT
CRITICAL	4. False claims for long-term outcomes and recovery
CRITICAL	5. Significantly improved recovery is strongly associated with significantly lower mortality
CRITICAL	6. Superiority of ivermectin hidden
CRITICAL	7. Mid-trial allowance of mAbs/antivirals invalidates hospitalization/death data
CRITICAL	8. Superiority of budesonide not hidden
CRITICAL	9. Budesonide press release within 12 days
CRITICAL	10. Similar results, opposite conclusion
CRITICAL	11. Pre-specified "meaningful effect" only for interim futility
CRITICAL	12. Meaningful effect was 1.5 days for other arms
CRITICAL	13. Pre-specified "meaningful effect" probability changed 0.01->0.25
CRITICAL	14. Hospitalization/death probability of meaningful effect
CRITICAL	15. 10x lower accuracy in reported results
CRITICAL	16. Adverse event data missing
CRITICAL	17. Mortality results missing for concurrent control arm
CRITICAL	18. Details of hospitalization/death missing, many could be prior to treatment
CRITICAL	19. False claim on administration
CRITICAL	20. Results delayed 600 days
CRITICAL	21. Authors coverage of prior research extremely biased and cherry-picked
CRITICAL	22. Very late treatment
CRITICAL	23. Inclusion changed from 50+ to 18+ w/COVID dyspnea or comorbidity before start of ivermectin arm
CRITICAL	24. Mid-trial change to include lower risk patients
CRITICAL	25. Exteme conflict of interest
CRITICAL	26. Pause due to supply but medicine was stored at every study site
CRITICAL	27. Supply issue contradicated by manufacturer
CRITICAL	28. Design favors null result in contrast to molnupiravir trial by the same chief investigator
CRITICAL	29. Other arm results delayed over 5 years
CRITICAL	30. Inclusion changed from 7 to 14 days
CRITICAL	31. "Gate-keeping" protection of serious outcome evaluation
CRITICAL	32. Long delay between registration and enrollment
CRITICAL	33. Subject to participant fraud
CRITICAL	34. Inconsistent analysis - Bayesian vs. frequentist statistics
CRITICAL	35. Age 65+ reduced from 47% to 16% for ivermectin
CRITICAL	36. Contradictory interpretation of results *(60 days ago)*
SERIOUS	37. Fatigue not included in secondary outcome symptoms, dominates long COVID results
SERIOUS	38. Superiority and futility rules not mutually exclusive
SERIOUS	39. Delivery delay reduces perceived effect
SERIOUS	40. Recovery subgroup forest plot for all arms except ivermectin
SERIOUS	41. Even faster recovery with greater baseline severity
SERIOUS	42. Lack of recovery inverted to reduce effect size
SERIOUS	43. Slow delivery
SERIOUS	44. Administration on an empty stomach
SERIOUS	45. Mismatch with original proposal
SERIOUS	46. Eligibility criteria worse than concurrent favipiravir arm
SERIOUS	47. Recruitment questions varied
MAJOR	48. Ivermectin from source chosen has shown lower efficacy
MAJOR	49. Ability to pickup medication quickly removed from information sheet
MAJOR	50. Only three different doses, lower µg/kg dose for higher weights
MINOR	51. Duration == 7 missing
COMMENT	52. Efficacy not due to open label design

Responses: authors have not responded to any of these issues.

CRITICAL **36% lower long COVID hidden in appendix.** Page 358 in the appendix shows 36% lower ongoing persistent COVID-19 specific symptoms (p<0.0001) when combining the individual symptom results. The paper reports a 28% reduction (p=0.015), not mentioned in the abstract or conclusion. This appears to be a one of any symptom analysis, effectively increasing the weight of the more common "fatigue", reducing the perceived effect (the difference does not appear to be due to adjustments - the adjustments in Table S6 to Table S39 make minimal difference). The effect may be diluted by including fatigue due to unrelated causes. If fatigue is excluded, the data on page 358 shows 41% lower long COVID, which may be more accurate. This is for very late and poorly administered treatment taken by only 89% of patients in a relatively low-risk population - benefits may be much greater with recommended usage and in high-risk patients.



CRITICAL ***Undisclosed null-biased Bayesian prior masks superiority.*** Prof. Sander Greenland reports (starting on slide 38) [484] that the Bayesian model applied an extremely tight, null-centered prior that was not reported in the paper. This prior pulls the frequentist hazard ratio for time-to-recovery down and slashes the posterior probability that the benefit reaches the trial's own "clinically meaningful" threshold of HR≥1.2. Even with the shrinkage, the posterior probability of any benefit exceeds 0.9999, well above the protocol's 0.99 superiority bar, however authors label ivermectin "unlikely to provide clinically meaningful improvement." Greenland argues that the unexplained prior acts like a hidden penalty, lacks empirical justification, and biases the analysis toward the null, thereby allowing the authors to downplay results their own decision rules would otherwise classify as superior. Author notes the strong priors are not justified by previous trials and suggests that they reflect social pressure to discredit ivermectin.

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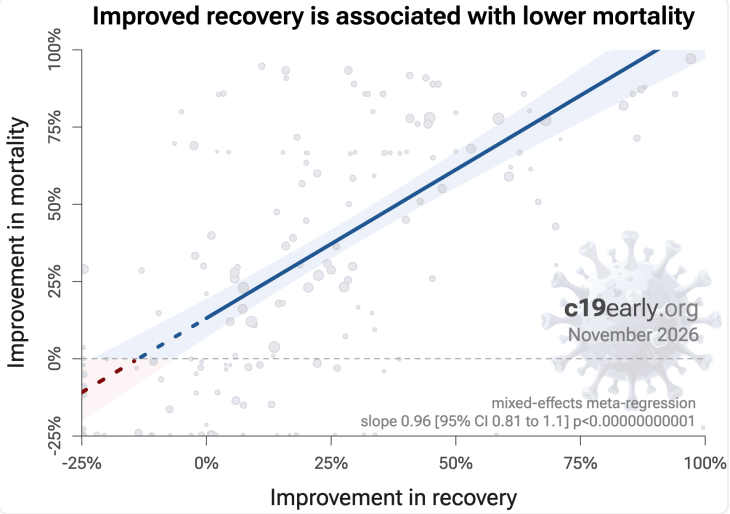
- **Estimated mean-ln(1.1) normal prior needed to shrink 1.12,1.26 to 1.07,1.23 has 95% limits 1.03,1.18, Pr(HR≥1.2) = 0.5%**
- **Such strong priors were not justified by previous trials; instead they reflect social pressure to discredit ivermectin.**

CRITICAL **Ad-hoc "clinically meaningful" threshold contradicted by same authors later in the same year for an ARI RCT.** In the Immune Defence RCT on common acute respiratory illness (ARI) [521], with two of the same senior investigators including the PI for PRINCIPLE, a similar reduction in illness-days from over-the-counter nasal sprays is highlighted as a clear therapeutic success without any extra "clinically meaningful" hurdle, is referred to as "clinically significant", and is promoted in the abstract and discussion [522]. By contrast, PRINCIPLE imposes a bespoke threshold and a very tight sceptical prior. This inverts the expected risk-benefit logic: improved recovery and minimizing viral replication is likely to be more significant for COVID-19, which showed higher risk of severity, systemic viral spread, and long-term sequelae.

CRITICAL **False claims for long-term outcomes and recovery.** Authors claim that ivermectin is *"unlikely to provide clinically meaningful improvement in recovery, hospital admissions, or longer-term outcomes"*, which is contradicted by their results. 36% (or the 28% from the author's calculation) lower long COVID is clearly clinical and very meaningful - it would represent an enormous global reduction in morbidity if adopted. The significantly faster recovery is also clearly clinically meaningful.

CRITICAL ***Significantly improved recovery is strongly associated with significantly lower mortality.*** Authors report highly statistically significant improved recovery but claim no clinical relevance. Across all 227 treatments we cover, improved recovery is very significantly associated with lower mortality, p<0.000000001 (from all studies that report both).



CRITICAL **Superiority of ivermectin hidden.** The protocol states *"If the Bayesian posterior probability of superiority (a log hazards ratio greater than 0 corresponding to quicker recovery) for a treatment versus Usual Care is sufficiently large (e.g. ≥ 0.99), the null hypothesis will be rejected and the intervention will be deemed superior.."*. The intervention is superior (probability > 0.9999), yet there was no press release and immediate call for use, and this is not even mentioned in the abstract or conclusion.

CRITICAL **Mid-trial allowance of mAbs/antivirals invalidates hospitalization/death data.** Authors note: *"From 16 Dec 2021, a minority of extremely clinically vulnerable patients could also access antiviral treatment or a monoclonal antibody infusion"*. However, there is no information on treatments provided or procedures for determining eligibility. This change invalidates hospitalization/death data after 16 Dec 2021. Hospitalization/death events occured in a small minority of patients and are expected to be strongly biased towards the extremely clinically vulnerable patients. Patients randomized to usual care are more likely to obtain alternative treatment. During the trial extension period sotrovimab was the most common treatment, with paxlovid and molnupiravir also being used [523]. Sotrovimab showed very high efficacy during this period [524,525]. It is normal to provide details of other treatments used in cases like this, the lack of disclosure suggests that the data confirms alternative treatment use significantly biased the results.

CRITICAL **Superiority of budesonide not hidden.** The same trial's budesonide arm did not hide the superiority: *"There was a benefit in time to first self-reported recovery ... with a probability of superiority greater than 0·999, meeting the prespecified superiority threshold of 0·99"* (in the abstract).

CRITICAL **Budesonide press release within 12 days.** The superiority for recovery for budesonide was announced within 12 days of trial completion [516,526]. Slow but perhaps acceptable. Ethical and moral obligations mandate release as soon as possible. However for ivermectin, the results were hidden for around 600 days, and then misrepresented.

CRITICAL **Similar results, opposite conclusion.** Of the 6 arms reporting results (HCQ is still missing), three show superiority on the primary recovery outcome. Comparing ivermectin and budesonide, which both show probability of superiority >0.999 and similar results - several individual recovery results are better for ivermectin than budesonide - concurrent and COVID+: time to alleviation of all symptoms, time to sustained alleviation of all symptoms, WHO5 wellbeing at day 28, all concurrent: time to allevation of all symptoms, time to sustained alleviation of all symptoms, and time to initial reduction of severity all show better results for ivermectin than budesonide. However the conclusions for each are the opposite - for budesonide authors concluded superiority, for ivermectin they conclude that ivermectin *"is unlikely to provide clinically meaningful improvement in recovery"*. Note improvements are higher with ivermectin and the primary recovery outcome for several subgroups related to baseline severity - illness duration, baseline severity, and respiratory illness.

CRITICAL **Pre-specified "meaningful effect" only for interim futility.** The protocol (even the post-hoc versions) only mentions clinically meaningful effects in terms of interim futility analyses: *"If the Bayesian posterior probability of a clinically meaningful treatment effect is sufficiently small (e.g. < 0.01) for the first co-primary endpoint (time to recovery), the intervention arm may be dropped from the study for futility"*. In the body of the paper authors do note that the pre-specified HR of ≥1.2 was only for futility evaluation, however the abstract drops this, implying that there was a pre-specified HR of 1.2 for superiority.

CRITICAL **Meaningful effect was 1.5 days for other arms.** Authors did not mention a "meaningful effect" for budesonide, but added a "meaningful effect" of 1.5 days for colchicine, azithromycin, and doxycycline - which was sufficient to ensure very low probabilities for those arms. For ivermectin they show an improvement of 2.06 days, i.e., clinically meaningful according to the authors for all prior arms (for most other people, smaller improvements are also clinically meaningful, and as above the improvements translate into lower mortality for high-risk patients). Additionally, the poor design of the trial means the actual improvement for recommended usage is likely much greater.

CRITICAL **Pre-specified "meaningful effect" probability changed 0.01->0.25.** In June 2022, in view of interim (if not all at the time) results, authors changed the 0.01 probability to 0.25 (just above the 0.22 for the one outcome at the time). Authors note this change is only for ivermectin and favipiravir, and will return to 0.01 for future arms (appendix page 169). Authors claim a rationale for the change is in "Appendix A" but this appears to be missing.

CRITICAL **Hospitalization/death probability of meaningful effect.** For hospitalization/death authors previously used a threshold of 2% for calculating the probability of meaningful effect. For ivermectin they changed it to 20%. Consid-

er the families of 20% or 2% of COVID-19 deaths, perhaps 4 million or 400,000 people based on an estimated 20 million total. Do they believe those deaths were not clinically meaningful?

CRITICAL **10x lower accuracy in reported results.** For budesonide authors reported key results with 10x greater accuracy, for example 10.9 vs. 13.3 days time to recovery, wherease for ivermectin all times are reported as integers, e.g., 14 vs. 16 days. This may be used to hide differences and to reduce efficacy (e.g., 3.6 vs. 5.4 becomes 4 vs. 5 and 3.6 vs. 4.4 becomes 4 vs. 4).

CRITICAL **Adverse event data missing.** Other than a count of hospitalizations, no adverse event data was reported.

CRITICAL **Mortality results missing for concurrent control arm.** Authors do not provide the main mortality results for the concurrent control arm.

CRITICAL **Details of hospitalization/death missing, many could be prior to treatment.** Authors provide no details on the hospitalizations and deaths. Given the remote nature of the trial, the enrollment of very late stage patients, the very low event rate, and the very delayed time between patients signing up and actual enrollment indicated by some participants, many of the hospitalizations may have happened before medication was delivered and taken. This is supported by the subgroup analysis showing that patients >7 days from onset (likely >8-9 days to treatment initiation) contributed more to the ivermectin events. The patient information sheet for molnupiravir states that medication will be delivered by the next day[461,527], while the patient information sheet for ivermectin has deleted "next day" only stating that medication will be delivered[528].

CRITICAL **False claim on administration.** Authors falsely claim that *"the influence of food on absorption is not known"*[463]. Guzzo et al.[1] show that the plasma concentration of ivermectin is much higher when administered with food (geometric mean AUC 2.6 times higher). This is from 2002 and well-known among ivermectin researchers.

CRITICAL **Results delayed 600 days.** Results were delayed around 600 days from the expected announcement time, with no reasonable excuse for hiding such positive results (or any results).

CRITICAL **Authors coverage of prior research extremely biased and cherry-picked.** Authors perform extreme cherry-picking on their discussion of previous research, and even then highly misrepresent those studies. For example, authors discuss the TOGETHER trial, without mentioning the known impossible data, refusal to release data despite pledging to, external sharing of results during the trial, randomization/blinding failure, and many protocol violations; and without mentioning that the principal investigator said that "*There is a clear signal that IVM works in COVID patients.*." in private[161].

CRITICAL **Very late treatment.** Patients were enrolled up to 14 days after the onset of symptoms. Extensive research for COVID-19 and other viral diseases show that early antiviral treatment is critical.

CRITICAL **Inclusion changed from 50+ to 18+ w/COVID dyspnea or comorbidity before start of ivermectin arm.** Inclusion was originally 50+ w/comorbidity or 65+, but was changed to 18+ w/COVID dyspnea or comorbidity or 65+ before the start of the ivermectin arm. The move to low-risk patients was specific to the ivermectin and favipiravir arms only[529].

CRITICAL **Mid-trial change to include lower risk patients.** Inclusion criteria were modified mid-trial to allow enrolling anyone 18+, i.e. very low risk patients. This change is first seen in protocol 9.0 on July 12, 2021[501]

CRITICAL **Exteme conflict of interest.** The chief investigator is also chief investigator for the PANORAMIC molnupiravir trial, with overlapping dates, and 7.2B+ financial conflict of interest between the two treatments.

CRITICAL **Pause due to supply but medicine was stored at every study site.** The trial claimed to pause due to a supply problem but medicine was stored at every site[530], It is unlikely that all sites would have run out, if there was no supply in some locations, recruitment could have continued at other locations.

CRITICAL **Supply issue contradicated by manufacturer.** The trial was paused with a reported supply issue, however the manufacturer stated that there were no supply issues.

CRITICAL **Design favors null result in contrast to molnupiravir trial by the same chief investigator.** Treatment delay, inclusion criteria, dosing, administration, and target size all show a design better for efficacy for molnupiravir, and worse for efficacy for ivermectin. Both trials have the same chief investigator and overlapping dates.

CRITICAL **Other arm results delayed over 5 years.** The HCQ arm results were withheld for over 5 years[512], consistent with extreme bias against reporting efficacy of low-cost treatments that were denied to the public by the funder.

CRITICAL **Inclusion changed from 7 to 14 days.** Inclusion was originally within 7 days of symptoms, but was changed to 14 days, compared to the molnupiravir trial which was started with 5 days[531].

CRITICAL **"Gate-keeping" protection of serious outcome evaluation.** Authors declare a "gate-keeping" strategy to prevent evaluation of hospitalization/death if the recovery time difference is not significant[463]. Authors claim benefit for serious outcomes is unlikely without statistically significant benefit for recovery time, which is not logical, especially with low prevalence of progression - consider for example an intervention that prevented progression to mortality by 100%, but has no effect on resolution of a specific symptom, e.g., cough. The trial did not always have this gate-keeping strategy - protocol 4.0 had hospitalization/death as the primary outcome and protocol 5.0 added the new strategy (this was a post-hoc change for azithromycin and doxycycline related to the recruitment of low-risk patients and low event rates).

CRITICAL **Long delay between registration and enrollment.** One participant reports filling out a form for the trial at the time of receiving a positive PCR result and not being called until much later on day 11 of COVID to complete enrollment[532]. A second participant reports waiting 9 days after online registration to receive an enrollment phone call[533,534].

CRITICAL **Subject to participant fraud.** There is no requirement for participants to have a face-to-face visit as part of trial participation. The self-reported design and the potential lack of professional medical examination results for many patients opens this kind of remote trial to participant fraud, which may be significant due to extreme politicization in the study country. Participant fraud has been reported for two other remote trials[535,536], involving submission of fake surveys and repeated signups. Authors do not provide any information on attempts to limit participant fraud.

CRITICAL **Inconsistent analysis - Bayesian vs. frequentist statistics.** The protocol specifies Bayesian analysis which is used for some outcomes. However, authors have used frequentist statistics for other outcomes, with no known reason. This results in avoiding reporting Bayesian probability of superiority showing superiority of treatment for those outcomes.

CRITICAL **Age 65+ reduced from 47% to 16% for ivermectin.** From the non-concurrent to concurrent populations (Table 1), we can see a dramatic change in the population. 47% of patients were over 65 in the control group prior to the ivermectin arm. For ivermectin this was reduced to 16% (focusing on low-risk patients is one method to reduce the chance of showing a benefit).

CRITICAL **Contradictory interpretation of results.** The same principal investigator ran an oseltamivir for influenza trial, which found 1.02 days faster recovery[483]. Authors suggest that clinicians may consider treatment, describe the result as accelerating recovery, and even describe 0.7 days in a subgroup as beneficial. In contrast, the 2.06 days benefit in this trial (and the 36% lower long COVID) is described as unlikely to be clinically meaningful, and authors state that further trials are unwarranted.

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SERIOUS **Fatigue not included in secondary outcome symptoms, dominates long COVID results.** The protocol (page 17 of 55, section 2.3.2.2, appendix page 119) does not include fatigue as a symptom. It's unclear if this was added later to dilute long COVID results (the included long-term follow-up SAP is post-hoc, dated June 2023). The more general fatigue, which may not be related to COVID-19, is by far the most common long-COVID symptom reported and dilutes efficacy—excluding fatigue ongoing persistent COVID-19 specific symptoms are 43% lower with treatment.

SERIOUS **Superiority and futility rules not mutually exclusive.** The superiority and futility rules are not even mutually exclusive—the treatment can be considered superior and futile at the same time (superiority: Pr(HR > 1) ≥ 0.99, "meaningful-effect" futility: Pr(HR ≥ 1.2) ≤ 0.01"[537]).

SERIOUS **Delivery delay reduces perceived effect.** Recovery is defined as the time from randomization, however there are additional delays between randomization and delivery, and between delivery and the patient taking the medication. This has the effect of reducing the perceived effect of treatment. For example, the median time to alleviation of all symptoms was 4 and 5 days respectively, or 20% faster with treatment. If the delay until treatment is one day, this becomes 3 and 4 days, for 25% improvement, with progressively greater improvement with longer delays. The patient information sheet for molnupiravir states that medication will be delivered by the next day[461,527], while the patient information sheet for ivermectin has deleted "next day" only stating that medication will be delivered[528].

SERIOUS **Recovery subgroup forest plot for all arms except ivermectin.** The main paper shows a forest plot with subgroups of the primary recovery outcome for all arms (colchicine, budesonide, azithromycin, doxycycline) except ivermectin. For ivermectin, authors only show the hospitalization/death forest plot in the main paper. The recovery results show superiority of ivermectin.

SERIOUS **Even faster recovery with greater baseline severity.** Figure S2a shows that longer duration, at least one baseline major severity item, and respiratory illness all show greater improvement for recovery, consistent with the greater room for improvement in more severe cases. If authors truly believed that HR 1.2 is a required and valid threshold, they should not be ruling out use for higher-risk cases.

SERIOUS **Lack of recovery inverted to reduce effect size.** Authors report the number of patients fully recovered at 3, 6, 12 months. It is typical to compare the risk of bad outcomes (failure to recover, hospitalization, death, etc.), however authors compare good outcomes. Authors method shows a significant improvement of 6% at 12 months, however the typical analysis shows a much larger 18% reduction in failure to recover. Consider a recovery rate of 90% in the control group, by the author's method it would be impossible for any intervention to create the HR ≥1.2 that they added.

SERIOUS **Slow delivery.** The patient information sheet for molnupiravir states that medication will be delivered by the next day[461,527], while the patient information sheet for ivermectin has deleted "next day" only stating that medication will be delivered[528].

SERIOUS **Administration on an empty stomach.** Authors instructed patients that *"no food should be taken two hours before or after administration"*[463]. Guzzo et al.[1], from 2002 and well known to ivermectin investigators, shows that the plasma concentration of ivermectin is much higher when administered with food (geometric mean AUC 2.6 times higher).

SERIOUS **Mismatch with original proposal.** The original proposal for the trial starts with: *"COVID-19 disproportionately affects people over 50 years old with comorbidities and those over 65 years old. The infection causes considerable morbidity and mortality in this population group in particular."*[538], yet authors later modified the trial to include anyone 18+.

SERIOUS **Eligibility criteria worse than concurrent favipiravir arm.** In addition to inferior eligibility compared with molnupiravir, eligibility was even inferior to the concurrent favipiravir arm, with ivermectin further favoring a null result. As of July 8, 2021 favipiravir started at 50+ while ivermectin started at 18+ w/ dyspnea or comorbidity as per the trial newsletter[539].

SERIOUS **Recruitment questions varied.** Recruitment questions varied, for example the video instructions for ambulatory care show the system asking about only two symptons - cough and fever. Notably, cough may be less responsive to treatment and increased enrollment based on cough may reduce the chance of showing efficacy[540].

MAJOR **Ivermectin from source chosen has shown lower efficacy.** Authors chose to source ivermectin from Edenbridge, which ranked 7 out of 11 brands in In Vitro tests for antiparasitic efficacy[2], requiring 5 days compared to 2 days for the best performing brand, and 3 days for 4 other brands.

MAJOR **Ability to pickup medication quickly removed from information sheet.** Earlier versions of the patient information sheet (e.g., v3.1[541]) allowed patients to pickup the medication from a local pharmacy instead of waiting for delivery. This was removed sometime before the ivermectin arm and the sheet now only lists delivery, excluding the possibility of very quick pickup of the medication after enrollment[542].

MAJOR **Only three different doses, lower µg/kg dose for higher weights.** Only three different doses were used: 45-64kg (18mg), 65-84kg (24mg), and ≥84kg (30mg)[463]. Patients with higher weights will have progressively lower µg/kg dosing.

MINOR **Duration == 7 missing.** The subgroup forest plot shows illness duration <7 and >7, without specifying what happens with == 7. The papers for other arms shows ≤7 and >7.

COMMENT **Efficacy not due to open label design.** Some people with strong prior claims of no efficacy have claimed that the efficacy here is due to the open label design. *Moustgaard et al.* showed there was no evidence to support this from analysis of 142 meta-analyses covering 1,153 trials. However, in this case we have multiple arms from the same exact trial that show this is not the case (which authors acknowledge in the paper, noting no evidence from the other arms). Moreover, any effect would be reversed because at the time and in the study country, the government and almost all media claimed that ivermectin was ineffective (and contrary information was censored).

The PANORAMIC trial for molnupiravir and the PRINCIPLE trial for ivermectin provide a good example of extreme bias in trial design. For molnupiravir investigators randomized 25,000 patients a median of 2 days from onset[485]. For ivermectin, they allow inclusion up to 14 days after onset — a delay incompatible with the recommended use of antiviral treatments, and incompatible with current real-world protocols. This delay alone would normally be more than enough to guarantee a null effect for an early treatment. However, authors also bias the population, treatment dose and duration, treatment administration, and sample size to favor a null result with ivermectin.

PANORAMIC and PRINCIPLE have the same chief investigator and primary contact[460,462], and the molnupiravir and ivermectin arms overlap in time.

It is unclear why results were not released December 2021, why a reported supply issue was contradicted by the manufacturer, why the trial continued, and why results were delayed 19 months[486].

Ivermectin was added to the PRINCIPLE trial on May 12, 2021[487] (June 2021 according to[488]), and favipiravir on April 26, 2021[487]. 4,731 patients were enrolled as of April 8, 2021[489], by which time the azithromycin, doxycycline, and budesonide arms had completed. The colchicine arm had been running for one month and was later terminated with 156 patients. With an estimated enrollment of 1,000 per arm for ivermectin, favipiravir, and concurrent control, the trial would end when total enrollment reached around 8,000.

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8,010 patients were enrolled and ivermectin was removed from the list of treatments under investigation on the website on or before Dec 2, 2021 [490,491], suggesting that enrollment was complete and results would be available shortly thereafter.

By Dec 9 ivermectin was added back to the list [492] with a note that the arm was paused due to supply issues. MedPage Today reported on the pause on Dec 14 [493]. Notably, Merck's statement at the time shows a significantly softer stance compared to their previous comments [493,494].

The reported supply issue is unusual - trials normally secure medication in advance, the reported trial manufacturer stated there were no supply issues [495], investigators did not respond to journalist queries, there was reportedly no response to Freedom of Information requests [496], alternate sources of ivermectin in the specified dosage were readily available, and there was no need for an identical match in appearance. The trial manufacturer was Edenbridge [497], participants received standard standard foil strips [498,499].

The trial later restarted the ivermectin arm. As of January 27, 2022, the trial was paused without explanation. As of February 11, 2022, the trial was open intermittently (twice daily between Sunday and Thursday), a change which further decreases the chance of participants receiving relatively early treatment. Delaying and restarting the trial at a later time may also reduce observed efficacy due to less severe variants in combination with the trial design.

We are pre-specifying subgroup analysis for enrollment up to Dec 2, 2021, for treatment within 2 days of onset, and for treatment of high risk patients (as originally defined by the trial).

PRINCIPLE trial timeline

Date	*Change*
March 22, 2020	Inclusion ≤7 days, age 50+ w/comorbidity or 65+.
June 16, 2020	Inclusion changed to ≤14 days.
February 14, 2021	Inclusion changed to 18+ w/COVID dyspnea or comorbidity or 65+ [500].
May 12, 2021	Ivermectin listed as current intervention in protocol [487].
June 2021	Ivermectin added according to web site [488].
Jul 12, 2021	Inclusion changed to 18+ [501].
December 2021	Anticipated completion of ivermectin arm.
December 3, 2021	Ivermectin arm ends, removed from web site between Dec 2 and Dec 3 [491,502,503].
December 2021	No press release or rapid top-tier publication, indicating positive results.
December 9, 2021	Ivermectin added back to web site with claim of pause due to supply issues.
December 14, 2021	Trial does not respond to MedPage Today regarding supply problems. A statement from Merck is dramatically different to their previous position and is consistent with them knowing that a trial they cannot ignore has positive results and them being unsure if they can suppress the results [504].
December 25, 2021	The trial supplier, Edenbridge, denies any supply issue. Prof. Chris Butler declines to comment [505]. The trial used standard widely available tablets [498,499].
January 14, 2022	Prof. Paul Little, TSC chair, is removed from the trial in protocol version 13 [506]. The TSC is responsible for reporting ethical issues.
January 27, 2022	Trial paused without explanation [507].
February 11, 2022	Trial only open intermittently (twice daily between Sunday and Thursday), adding further enrollment delays [508].
July 8, 2022	Extended ivermectin arm ends [509].
July 2022	No press release or rapid top-tier publication, indicating positive results.
June 2, 2023	Sometime between May 2 and June 2, authors add a note on the web site indicating that, against protocol, they are delaying and will release in a rigorous and transparent way after extended 1 year followup ends in July [510,511]. Note that the analysis code for professional trials is written and tested in advance.
November 6, 2023	Links to the protocol, amendments, and other supporting documents were removed from the web site.

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December 2023	Still no results or update. A link was added to a version 14 of the protocol dated August 8, 2022 (after all arms had completed). The link does not work, pointing to an internal University of Oxford site. The latest version available is 13.0, dated January 14, 2022 [506] (during the ivermectin arm, after the expected end in December 2021).

PRINCIPLE trial selective reporting delays

Results for effective but politically inconvenient treatments were withheld for very long periods.

	TREATMENT PATIENTS	DURATION	RESULTS DELAY
HCQ [512]	413	2 months	Over 5 years [512]
Azithromycin [513]	540	6 months	56 days [514]
Budesonide [515]	1,073	4 months	12 days [516]
Doxycycline [517]	780	5 months	42 days [514]
Colchicine [518]	156	3 months	120 days [519]
Ivermectin [164]	2,157	14 months	600 days (810 days from ~1,000 per arm enrollment)
Favipiravir [520]	~2,250	15 months	780 days (1,000 days from ~1,000 per arm enrollment)

Together Trial

Effect of Early Treatment with Ivermectin among Patients with Covid-19

Extreme COI, impossible data, blinding broken, randomization/blinding failure, uncorrected errors, protocol violations, no response from authors, refusal to release data

SEE ALSO

The TOGETHER Files 1: The Andrew Hill connection - How the principal inv...
Fraudulent Trial On Ivermectin Published By The World's Top Medical Journal
The False, Sinister, and Duplicitous Statements of the TOGETHER Ivermecti...
10 Questions for the TOGETHER Trial Investigators
The Potemkin Argument, Part VII: TOGETHER vs. Carvallo, A Tale of Two St...
Did the Placebo Group in the TOGETHER Trial Take Ivermectin?
Demonstrating Randomization Failure in the TOGETHER Trial
FDA Reveals Concerns About the Conduct of the TOGETHER Trial, Joining ...
When Characteristics of Clinical Trials Require Per-Protocol as Well as Inten...

Many major issues including multiple impossible numbers, randomization failure, blinding broken (even externally), protocol violations, refusal to release the data, and many more serious issues as detailed below.

The metformin arm has been retracted due to impossible data and compromised integrity [544]. The ivermectin arm has far more serious issues, however neither the journal nor the authors respond.

Private comments:

"There is a clear signal that IVM works in COVID patients.. that would be significant if more patients were added.. you will hear me retract previous statements where I had been previously negative" — Ed Mills, Together Trial co-principal investigator [545].

"I'm not interested in this question as its not the correct way to interpret the outcome" — Ed Mills, responding to a per-protocol death count request [546].

*"F*ck you" "F*ck off" "Glory to Satan" "You are one of these f*ckers.." "You f*cking *sshole"* — Ed Mills, responding to various emails on the trial and ivermectin research [546].

Public comments:

"There was no indication that ivermectin is clinically useful" — Ed Mills, Together Trial co-principal investigator.

"..the question of whether this study was stopped too early in light of the political ramifications of needing to demonstrate that the efficacy is really unimpressive.. really could be raised.." — Frank Harrell, *"I totally agree with Frank"* — Ed Mills [547].

CRITICAL	1. Patient counts for reported period impossible
CRITICAL	2. Placebo counts vs. fluvoxamine not possible
CRITICAL	3. Impossible baseline data
CRITICAL	4. Metformin arm retracted for incorrect data and compromised integrity
CRITICAL	5. Randomization violation, significant confounding by time
CRITICAL	6. Blinding broken
CRITICAL	7. Blinding failure
CRITICAL	8. Data pledge violation, unavailable over 1,800 days from protocol, over 1,600 days from publication
CRITICAL	9. DSMC not independent
CRITICAL	10. Extreme conflicts of interest
CRITICAL	11. Three conflicting death counts
CRITICAL	12. Placebo adverse event conflicts with fluvoxamine arm
CRITICAL	13. Conflicting adverse event counts
CRITICAL	14. 3-day dosing patients before March 23 missing
CRITICAL	15. Multiple false statements by investigators
CRITICAL	16. Investigators not responding to concerns
CRITICAL	17. ICODA reports never having the data
CRITICAL	18. Indications of ivermectin use in the placebo arm
CRITICAL	19. Conflicting and inconsistent PP/ITT groups
CRITICAL	20. Refusal to release per-protocol mortality and hospitalization data
CRITICAL	21. Conflicting descriptions of the placebo group
CRITICAL	22. Failure of NEJM to publish letters reporting errors and issues

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CRITICAL	23. Placebo tablets may not match treatment tablets
CRITICAL	24. Viral load protocol violation, high Ct may hide efficacy
CRITICAL	25. 162 control patients missing onset data vs. 1 for peginterferon lambda
CRITICAL	26. Contradictory inclusion/exclusion of vaccinated patients, changes, and confounding
CRITICAL	27. Impossible data in the metformin arm
CRITICAL	28. Conflicting information on FTX funding
CRITICAL	29. Metformin/fluvoxamine conclusions opposite of COVID-OUT, but matching earlier studies on each team
CRITICAL	30. Paper silently modified without notification or explanation
CRITICAL	31. Team selected dose below what they believe is required
CRITICAL	32. Viral clearance results mismatch
CRITICAL	33. FDA concerns regarding trial conduct for peginterferon lambda
CRITICAL	34. Co-principal investigator agrees with political need to demonstrate poor efficacy
CRITICAL	35. Private comments on efficacy contradict public comments
CRITICAL	36. Mid-trial change adds patients showing lower efficacy
CRITICAL	37. Funding from Gates Foundation
CRITICAL	38. Conflicting reports on trial end date
CRITICAL	39. Author calls for censorship of 670 scientists reporting positive results
CRITICAL	40. Impossible data identified in three COVID-19 trials by author
SERIOUS	41. Side-effect prevalence consistent with treatment error
SERIOUS	42. Screening to treatment delay unknown
SERIOUS	43. Unknown onset patients show statistically significant efficacy
SERIOUS	44. 317 unknown onset patients, onset required for inclusion
SERIOUS	45. Unknown onset patients treated late
SERIOUS	46. Conflicting comorbidity counts
SERIOUS	47. Unexplained >6 month delay
SERIOUS	48. Placebo patients receiving an injection not blinded
SERIOUS	49. Major imputation error
SERIOUS	50. Single dose results missing
SERIOUS	51. Incorrect conclusion
SERIOUS	52. Missing age information
SERIOUS	53. Mid-trial protocol changes
SERIOUS	54. COI: designed by Cytel
SERIOUS	55. COI: co-principal investigator works for Cytel and the Gates Foundation
SERIOUS	56. COI: pharma funding and denial of independent investigator
SERIOUS	57. COI: Gates Foundation
SERIOUS	58. COI: Certara
SERIOUS	59. COI: MMS Holdings
SERIOUS	60. COI: analysis company works closely with Pfizer
SERIOUS	61. COI: Fast Grants funding closely related to companies that censored scientific research
SERIOUS	62. Unexpected differences in missing data
SERIOUS	63. Out of funding claim contradicted by funder
SERIOUS	64. Misrepresentation of dosing recommendation
MAJOR	65. Mean delay likely excluding unknown onset
MAJOR	66. Per-protocol placebo much more effective
MAJOR	67. Multiple conflicting randomization protocols
MAJOR	68. Dominated by Gamma variant with different characteristics, no discussion
MAJOR	69. Incorrect dose reporting, patients at higher risk due to BMI may have received lower per kg doses, and show lower efficacy
MAJOR	70. Conflicting target enrollment and reasons for termination
MAJOR	71. Primary outcome subject to bias, selected after single dose arm
MAJOR	72. Reported terminated due to futility, but threshold not reached
MAJOR	73. Subgroup analysis protocol violations
MAJOR	74. Many pre-specified outcomes missing
MAJOR	75. Single-dose recruiting continued after change
MAJOR	76. Funding list incorrect, missing Gates Foundation and Unitaid
MAJOR	77. Statistical analysis plan dated after trial start
MAJOR	78. Imputation protocol violation
MAJOR	79. Expected analyses missing
MAJOR	80. Conflicting reasons for dose change
MAJOR	81. Details of placebo unspecified
MAJOR	82. Antigen test requirement
MAJOR	83. Bayesian probability of superiority, featured for FLV, hidden in appendix
MAJOR	84. Two different per-protocol counts
UNKNOWN	85. Source of ivermectin unspecified (fluvoxamine source specified)
UNKNOWN	86. 100% adherence reported for 3-day placebo
UNKNOWN	87. No confirmation of placebo manufacturing

Author responses

84. modified without explanation

No response for all other items

CRITICAL **Patient counts for reported period impossible.** Authors claim the ivermectin and control patients were all from on or after March 23, 2021, however independent analyses of the enrollment graph (contained in this presentation [568]) require including patients prior to this date to reach the reported numbers [557,569]. The enrollment graph shows much higher enrollment to ivermectin near the start of the trial. The only way that the number of placebo patients can be the same as the number of treatment patients is if placebo patients were taken from an earlier period [566,570], which creates a nonconcurrent control group [571] and substantial confounding by time as below.

CRITICAL **Placebo counts vs. fluvoxamine not possible.** The IVM placebo arm has 679 patients and the FLV arm has 756. The 679 should be shared between the arms, with 77 extra patients for FLV. For FLV, there were 34 placebo patients requiring mechanical ventilation, for IVM there was only 25, indicating that 9 of the extra 77 placebo patients for FLV had mechanical ventilation, a much higher percentage during a period that had lower deaths and CFR (and included vaccinated patients). Placebo all-cause hospitalization shows 95/679 for IVM and 99/756 for FLV, i.e., only 4 of the extra 77 patients were hospitalized, but the paper reports an additional 9 patients with mechanical ventilation.

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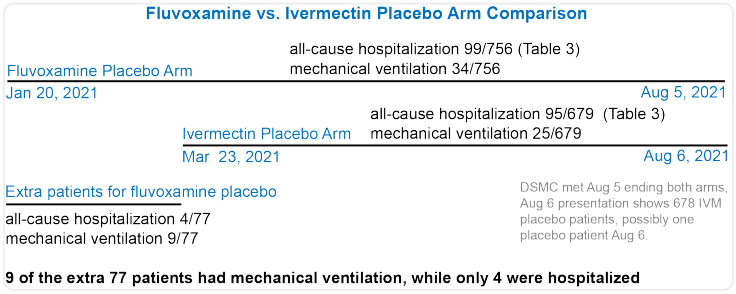
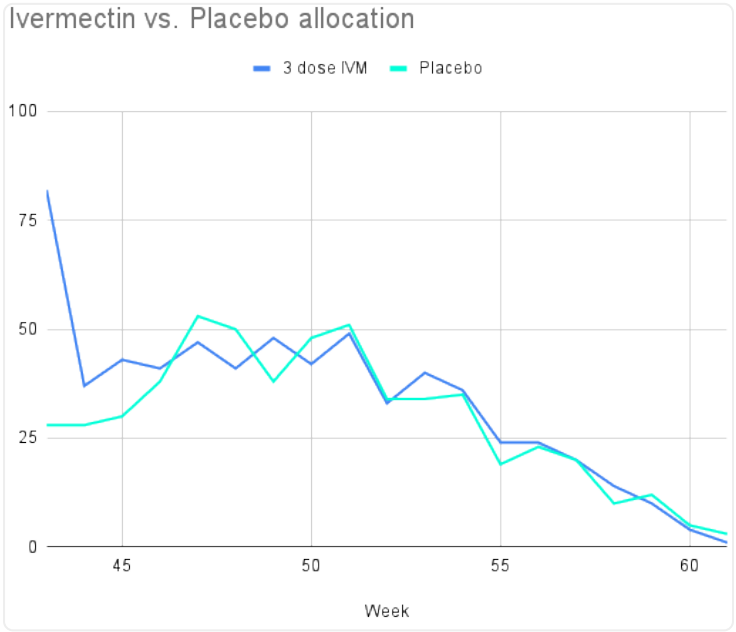


CRITICAL **Impossible baseline data.** Analysis of baseline data by Marinos shows conflicting data and points to data being changed to hide randomization failure and incomparable groups. For details see [572].

CRITICAL **Metformin arm retracted for incorrect data and compromised integrity.** The metformin arm has been retracted due to impossible data and compromised integrity [544]. The ivermectin arm has far more serious issues, however neither the journal nor the authors respond (the metformin arm was published in a different journal).

CRITICAL **Randomization violation, significant confounding by time.** Unequal randomization, significant confounding by time. The trial reports 1:1:1:1 randomization, however independent analysis shows much higher enrollment in the ivermectin treatment arm towards the start of the trial [557,573]. This introduces very significant confounding by time due to the major change in the distribution of variants. *Zavascki* show dramatically higher mortality for Gamma vs non-Gamma variants (28 day mortality from symptom onset aHR 4.73 [1.15-19.41]). Many more patients were randomized to ivermectin vs. placebo in the first few weeks, for example the first week shows 82 ivermectin vs. 28 placebo patients, 2.9x higher. The period of excess ivermectin enrollment coincides closely with a period of significantly higher deaths and CFR in Brazil.



CRITICAL **Blinding broken.** Leaked documents show that blinding was broken, with interim results available not only within the team, but shared externally with a group of 90+ people, many from other ivermectin trials, in meetings organized by Dr. Andrew Hill. Unreleased leaked emails also indicate sharing with higher-up individuals at the NIH. As below, protocol changes were made mid-trial to add additional bias against ivermectin [574].

CRITICAL **Blinding failure.** Ivermectin/placebo blinding was done by assigning a letter to each group that was only known to the pharmacist. If a patient received a 3-dose treatment, investigators immediately know that the patient is more likely to be in the treatment group than the control group, because 3-dose placebo was relatively rare (~46% from PP). If a patient received non-3-day treatment, investigators immediately know that the patient is not an ivermectin treatment patient. Moreover, by observing the frequency of allocations, investigators can easily determine which letter corresponds to active ivermectin 3-day treatment, thereby removing all blinding. For example, consider 3-dose-ivermectin and 3-dose-placebo being identified by the letters G and K. If allocations to date have been G:11 and K:20, there is a very high probability that K is ivermectin. Note that this blinding failure is only obvious because the journal required the authors to restrict to the 3-day placebo group. Also note that it would have been trivial to avoid if desired, for example by using a unique identifier for all medication bottles. Note that there may be additional reasons for blinding failure, for example the paper specifies identically shaped bottles, but does not appear to specify identical appearance tablets [575], and patients receiving a placebo injection.

CRITICAL **Data pledge violation, unavailable over 1,800 days from protocol, over 1,600 days from publication.** The trial registration states that data was to be available at termination and upon request [576], however authors have not responded to a request for the data. Even funders of the trial have been unable to access the data [577]. Requests can be sent to thetogethertrial@gmail.com, let us know the outcome. For a detailed timeline of requests and the denial to release data see [578] (appendix A).

CRITICAL **DSMC not independent.** Reviewer 1 of the protocol notes that the DSMC is not independent [579]. Prof. Thorlund is Vice President of the contract research organisation (CRO, Cytel), professor at the sponsoring university, and an author of the protocol. Dr. Häggström is an employee of the CRO. *doyourownresearch.substack.com (D), twitter.com (O)* reveals many other conflicts. Prof. Thorlund has written >100 papers with Prof. Mills. Prof. Singh has written 29 papers with Prof. Mills. Prof. Orbinski has written 9 papers with Prof. Mills. The first version of the web site showed Prof. Mills and Prof. Thorlund as joint leads. Emails pointed to a company MTEK Sciences, founded by Prof. Mills and Prof. Thorlund (MTEK is hypothesized to stand for Mills, Thorlund, Edward, Kristian). MTEK received grants from the Gates Foundation. MTEK also employed Dr. Häggström. MTEK was acquired by Cytel in 2019. Dr. Häggström works for the Gates Foundation. Two members of the DSMC have published a paper with members of a well known anti-ivermectin research group [581] and Dr. Hill, whose meta analysis has reports of external influence [582-584]. The trial protocol reports that *"an independent DSMC will be established, composed of scientists of unrivalled reputation and expertise, without involvement with this research protocol."*

CRITICAL **Extreme conflicts of interest.** Disclosed conflicts of interest include: Pfizer, Merck, Bill & Melinda Gates Foundation, Australian Government, Medicines Development for Global Health, Novaquest, Regeneron, Astrazeneca, Daichi Sankyo, Commonwealth Science and Research Organization, and Card Research. Many conflicts of interest appear unreported. For example, Unitaid is a sponsor [585,586].

CRITICAL **Three conflicting death counts.** In the original paper, Table 3 shows 21 and 24 deaths, while Table S6 shows 20 and 25 [587]. In Table 3, death and grade 5 events showed the same 21/24 numbers, but different effect sizes, with 0.81 being closer to the 20/25 counts and the previously reported number. This is consistent with one death being moved between arms after manuscript generation, but not updated in Table S6 or the Table 3 AE RR. This cannot be explained by the safety population excluding patients with zero doses because the AE control deaths are higher. In email, a co-principal investigator suggested that the discrepancy was due to one being COVID-19 deaths and the other being all-cause deaths [545]. That explanation does not fit the data because one arm increases while the other arm decreases. Both co-principal investigators report in the paper that *"they had full access to all the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol."* A third set of death counts, 20 and 24, with RR 0.84, was presented by a co-principal investigator on Mar 18, 2022 [588]. In total, 4 different death relative risks have been presented: Mar 18, 2022 presentation: 0.84, Mar 30 paper: 0.88 (T3), 0.81 (T3 AE), and 0.80 (TS6, presented as 20 and 25 only

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without group sizes). 6 days after publication, the paper was updated, with no information given on what was changed. In this version, a "respiratory, thoracic and mediastinal disorders" death was removed from the control arm and an "infections and infestations" death was added to the ivermectin arm. The paper still indicates RR 0.81 for death AE.

CRITICAL **Placebo adverse event conflicts with fluvoxamine arm.** For FLV, there were 11 grade 1 AEs, for IVM there were 12, with 77 less patients. For FLV, there were 50 grade 3 AEs, for IVM there were also 50, meaning the 77 extra patients had 0% grade 3 AEs vs. an expected 7.4%. For FLV, there were 54 CKD patients according to Figure 3 and eTable1 (2 according to Table 1). For IVM there was 5.

CRITICAL **Conflicting adverse event counts.** Table 3 and Table S6 adverse event counts do not match for any grade, e.g., grade 1/2 in Table S6 shows 82 for IVM, while Table 3 shows 65[589]. The Apr 5 update changed the grade 5 events without explanation, however the other grades remain conflicting.

CRITICAL **3-day dosing patients before March 23 missing.** The co-principal investigator wrote on March 6 that 3-day dosing was being administered, and that the clinicaltrials entry was out of date at that time[590]. This earlier start of the 3-dose arm would resolve an oustanding major inconsistency. Analysis of the trial randomization shows that reaching the 3-day placebo count requires patients from March 4[591], and it would be logical for the 3-day placebo and 3-day active arms to have started on the same day. This reinforces existing concerns as to which patients were included in the analysis, and adds additional questions regarding what happened to the patients prior to March 23, and if patients were treated prior to ethics approval. Ethics approval for the dose change was received on March 21 according to the paper[592], with the regulator document dated March 15[593].

CRITICAL **Multiple false statements by investigators.** There has been multiple false statements by investigators raising questions about their ethics and the reliability of their work[546].

CRITICAL **Investigators not responding to concerns.** After details of major data errors and protocol violations became known, investigators appear to have stopped responding to all researchers regarding serious concerns with the trial[546,594] (and have still not responded to us).

CRITICAL **ICODA reports never having the data.** Investigators report that the data is available via ICODA: *"The final trial dataset will be accessible by written request to the study principal investigators (G Reis or EJ Mills). There are no contractual agreements to limit access to final trial data. All data collected by the TOGETHER Trial will be shared with the International COVID-19 Data Alliance"*. Not only has there been no reports of successful access to the data, but an ICODA manager reports that they have never had the data[595].

CRITICAL **Indications of ivermectin use in the placebo arm.** Recent ivermectin use was not in the exclusion criteria, however community use was widespread. Ivermectin was available OTC, was recommended by the government for COVID-19, and had nine times higher sales[596]. Authors claim they ensured patients did not use ivermectin via "extensive screening", but do not explain why this was not an exclusion criterion, or how this unwritten exclusion was ensured even though there is extensive missing data related to written exclusion criteria. Similar unwritten exclusions were not mentioned for other arms[597], a primary investigator previously stated such an exclusion should not be an issue[598], and it is not mentioned in the interview sheets[599]. After publication, a co-principal investigator reportedly wrote that *"even if some patients did access IVM, the fact that it is blinded should still maintain balance"*, which is incorrect, placebo patients taking ivermectin are expected to improve, treatment patients that already have significant tissue distributions may have positive, neutral, or negative responses to additional treatment. Further, there are contradictory reports of how patients with prior ivermectin use were handled, and there is an indication that patients who had taken, or "were likely to take" ivermectin for COVID-19 were re-allocated to fluvoxamine or placebo[600].

CRITICAL **Conflicting and inconsistent PP/ITT groups.** Conflicting and inconsistent decreases in PP vs. ITT groups between different tables and between the treatment and control arms[578].

CRITICAL **Refusal to release per-protocol mortality and hospitalization data.** Refusal to release per-protocol mortality and hospitalization results although they were reported for fluvoxamine and their importance was emphasized by coauthor Dr. Boulware[578].

CRITICAL **Conflicting descriptions of the placebo group.** There are multiple conflicting statements regarding the placebo group[578].

CRITICAL **Failure of NEJM to publish letters reporting errors and issues.** NEJM has refused to publish any of the many letters submitted by scientists reporting errors and critical issues with the trial. For details see[578].

CRITICAL **Placebo tablets may not match treatment tablets.** Authors do not specify the appearance of the placebo tablets, suggesting that they may not match the treatment tablets, providing an additional reason for blinding failure. A Brazilian investigator reports that, at the time of the trial, there was only one likely placebo manufacturer, and they reportedly did not receive a request to produce identical placebo tablets[575]. They also report that compounded ivermectin in Brazil is considered unreliable.

CRITICAL **Viral load protocol violation, high Ct may hide efficacy.** The protocol has change in viral load as an outcome, however only viral clearance is reported, and without any details (for example, using a high Ct value would have limited relevance). Notably, the same trial did report viral load results for a commercial drug where one of the principal investigators is a founder of the company[601].

CRITICAL **162 control patients missing onset data vs. 1 for peginterferon lambda.** 162 control patients are missing time from onset (Figure 2), however for peginterferon lambda (which overlaps with ivermectin in time) authors claim only one control patient is missing time from onset[601] (page 25).

CRITICAL **Contradictory inclusion/exclusion of vaccinated patients, changes, and confounding.** The trial changed from including vaccinated patients to excluding them on Mar 21, 2021[602,603], and on Jul 5 the exclusion was changed to specify >14 days. As discussed, meeting the reported placebo counts likely requires taking placebo patients from the earlier period, which has significant confounding due to variant changes. The vaccine inclusion change adds additional confounding, which also favors the placebo group. The original vaccine inclusion criterion is shown in both the protocol and the clinicaltrials.gov record[604,605]. Note that the paper, master protocol, Brazilian protocol, and trial registration report contradictory information on vaccine inclusion/exclusion and changes over time[606].

CRITICAL **Impossible data in the metformin arm.** Data for the primary outcome in the metformin arm of this trial appears to be impossible[607]. For example, considering the metformin arm and the ITT population: 24 were hospitalized and 8 had an ER visit (tables S2/S3), therefore the number for combined ER or hospitalization must be between 24 and 32. However, authors report 34 events for ER/hospitalization.

CRITICAL **Conflicting information on FTX funding.** There is conflicting information and statements regarding FTX funding of the trial[608].

CRITICAL **Metformin/fluvoxamine conclusions opposite of COVID-OUT, but matching earlier studies on each team.** The Together trial and COVID-OUT both tested metformin and fluvoxamine. Notably, they came to opposite conclusions. In Together, authors found efficacy for fluvoxamine, but the metformin results were so negative that the trial was terminated early. In COVID-OUT it was the opposite, authors (although not the journal editor) found efficacy for metformin, while the fluvoxamine results were so negative that the trial was terminated early[609]. Note that the Together authors include researchers that

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found fluvoxamine effective in earlier studies, while the COVID-OUT authors include researchers that found metformin effective in earlier studies.

CRITICAL **Paper silently modified without notification or explanation.** *Apr 5:* The paper was silently updated, with no indication or explanation of the changes. Changes include: age range, placebo description, per-protocol count, and death counts (as above). *May 5:* The paper was silently updated again. A new summary notes that authors *attempted* to screen for previous ivermectin use, contradicting both the discussion section, where authors claim they *ensured* no use *for COVID-19*, and the exclusion criteria and interview forms, which do not specify ivermectin use.

CRITICAL **Team selected dose below what they believe is required.** Dr. Craig Rayner, a senior investigator on the trial, previously published research indicating that a higher dose is required [610], raising the question of why the dose and fasting administration was chosen, for both the single day and 3 day dose regimens. Clinical equipoise [611] raises ethical questions about running a trial where the invesigators do not believe the chosen dose is effective. *Krolewiecki* show an antiviral effect only with plasma concentrations above 160ng/mL. Figure S5 shows that the authors expected the mean concentration to be well below this level [612]. Dosage requirements are likely to vary significantly depending on many factors including the variant encountered, time of administration, mode of administration, patient genetics, concomitant medications, SOC, and the distribution of the infection in different tissues. However, the dose used is far below what is recommended by clinicians for post-infection treatment with the Gamma variant — about 2.5 - 6.5x lower, depending on the recommendation and which estimate of fasting/fed administration is used. The trial used fasting administration, however Merck's product information reports that *"administration of 30mg ivermectin following a highfat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30mg ivermectin in the fasted state."* [613].

CRITICAL **Viral clearance results mismatch.** In Figure S3, the numbers in the table do not match the graph, for example day 0 to day 3 for ivermectin shows a 30% decline in viral detection in the table, while the graph shows only a 4% decline [614]. Table 3 results do not match either of these results. For example at day 3, table 3 reports 7.4% clearance for ivermectin. In Table 3, about 15% more patients have viral clearance results in the control arm, suggesting likely confounding by time. Authors provide no details on which patients were tested in each arm, however the confounding may be very significant. Notably, a July 2021 change adds viral load testing for the IV arms [615], suggesting that placebo viral results may have a significant number of patients from a very different time period [615] where patient characteristics [616], viral variants, and outcomes may be very different.

CRITICAL **FDA concerns regarding trial conduct for peginterferon lambda.** The peginterferon lambda arm of this trial generated positive results, however the FDA denied a request for a pre-EUA meeting, citing concerns about the conduct of the trial [617]. Reportedly, the *"FDA will not consider an EUA application based on results generated from the TOGETHER study"* [617]. Details of the FDA's concerns were not provided.

CRITICAL **Co-principal investigator agrees with political need to demonstrate poor efficacy.** Frank Harrell commented that "..the question of whether this study was stopped too early in light of the political ramifications of needing to demonstrate that the efficacy is really unimpressive.. really could be raised..", and co-principal investigator Prof. Ed Mills responded *"I totally agree with Frank"* [547].

CRITICAL **Private comments on efficacy contradict public comments.** Co-principal investigator Prof. Ed Mills said the following in private communication: *"There is a clear signal that IVM works in COVID patients.. that would be significant if more patients were added.. you will hear me retract previous statements where I had been previously negative"* [545], while public comments are contradictory, e.g. *"There was no indication that ivermectin is clinically useful"*.

CRITICAL **Mid-trial change adds patients showing lower efficacy.** Authors modified the inclusion criteria mid-trial to allow adding more low-risk patients <50 [618]. Comparison with the metformin placebo arm shows many more patients <50 were included in the later part of the trial. Notably, the primary outcome shows much higher efficacy for patients ≥50, which would be statistically significant if there was about 50% more patients ≥50.

CRITICAL **Funding from Gates Foundation.** Analysis suggests funding of the ivermectin arm in part by the Gates Foundation by way of Certara and Prof. Rayner [619], in addition to previously disclosed funding of the overall trial. Authors list only FastGrants and Rainwater in the ivermectin paper. The Gates Foundation was cited as a funder on the web site until Sep 13, 2021 [620] (after completion of the trial). Correspondence regarding fluvoxamine and fluoxetine notes that Certara support for the TOGETHER study was funded by the Gates Foundation [621].

CRITICAL **Conflicting reports on trial end date.** There are conflicting reports on when enrollment into the ivermectin and fluvoxamine arms ended [622], with the master protocol showing the end as July 26 and the web site confirming an end in July. However, the papers report August 5 and 6.

CRITICAL **Author calls for censorship of 670 scientists reporting positive results.** 66 studies by 670 scientists report statistically significant positive results for ivermectin treatment of COVID-19 [623]. One author claimed that reporting efficacy is 'disinformation' and distributed a request to report and censor a US legislator [624-626]. While discussion is warranted for all studies, a call for censorship without analysis raises concern for potential bias. Author provides no basis for the results of the 670 scientists being incorrect and warranting censorship.

CRITICAL **Impossible data identified in three COVID-19 trials by author.** One author is a co-author of three ivermectin COVID-19 trials [161-163] and impossible data has been identified in all of these trials, suggesting caution regarding the reliability of the results.

SERIOUS **Side-effect prevalence consistent with treatment error.** The side effects (e.g., gastrointestinal side effects were lower in the ivermectin arm) suggest that many ivermectin patients may not have received authentic ivermectin, or that placebo patients may have taken ivermectin. For comparison, there was a 3.6 times greater incidence of diarrhea in the treatment arm in *Lim*.

SERIOUS **Screening to treatment delay unknown.** Most Together Trial master protocols show an additional day delay in already late treatment for most patients. The Aug 5, 2021 protocol published with the metformin paper [627], shows treatment administration one day after screening, baseline, and randomization (Table 2, schedule of study activities). This can also be found in the protocol dated Mar 11, 2021 [628]. The protocol attached to the ivermectin paper, dated Feb 15, 2021, shows a different schedule, stating that the treatment *should* be administered on the same day of randomization. There is no explanation of when this change was made, how the overlapping metformin and ivermectin arms could use different schedules, or how this change was implemented (there are many tasks in the screening and baseline visits). There is no reporting for how many patients received treatment on the same day. The form for the first treatment visit asks if there were clinical events including >6hr ER visits since the baseline visit, which would not be possible if this visit was immediately after randomization. Time of first treatment was recorded [599], but no information has been reported. According to *Forrest*, WhatsApp messaging and video was used for recruitment, raising the question of how medication was delivered in cases where recruitment was done online. The Brazilian versions of the protocol do not match the master protocol, with all showing administration on the same day. The first Brazilian version of the protocol stated the drug *"must be administered on the same day"*, however in March 2021 and later versions, this was changed to *"should be administered on the same day"*.

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	Screening Visit (D-0)	Baseline and Randomization (1) D-0	Day 1
Informed Consent	X		
SARS-CoV-2 Rapid Test	X[1]		
Eligibility Criteria Review	X[2]		
Pregnancy Test	X[3]		
Demographics	X[5]		
Co-morbidities and Risk Factors	X		
Medical History	X		
WHO Clinical Worsening Scale	X		X
Exposure to Index Case Information		X	
Substance Abuse		X	
PROMIS Global Health Scale		X[6]	
ECG		X	
Height and Weight		X	
Nasopharyngeal Swab		X	
Randomization		X	
Concomitant Medications		X	X
Investigational Treatment Administration			X[7]

SERIOUS **Unknown onset patients show statistically significant efficacy.** For the known time since onset subgroups, both groups show worse results than the overall results[630], with the missing 317 patients showing significant efficacy RR 0.51, p = 0.02 (compared to 1.00 and 1.14 for known patients).

SERIOUS **317 unknown onset patients, onset required for inclusion.** Figure 2 shows that the time from onset was unknown for 317 patients, however time from onset is required for the inclusion criteria.

SERIOUS **Unknown onset patients treated late.** After imputation, the percentage of patients in the late treatment subgroup went from 46% to 56%. 87% of the unknown patients were predicted to be in the late group. This is reasonable and expected — patients that do not recall when the onset was are more likely to have had onset further in the past. What is not clear is how these patients could be enrolled in the trial, how many of these patients had onset >7 days, how this very late 317 patient subgroup could show much greater efficacy as above, and why authors did not report this result, analyze this in greater detail, or recommend further research.

SERIOUS **Conflicting comorbidity counts.** The companion fluvoxamine arm ran from Jan 20 to Aug 5, 2021, while this trial ran from March 23 to Aug 6, 2021 — most control patients should be shared, with an additional 10% for fluvoxamine from the earlier start. The Aug 6 presentation, which has a date of 9:38am Aug 6 local trial time[631], shows 678 placebo patients, indicating that either 0 or 1 placebo patients were randomized on Aug 6. Zero patients should have been randomized on Aug 6, because authors cannot add patients after unblinding. The fluvoxamine control arm shows 16/756 control patients with asthma. The ivermectin control arm has a subset of these patients (679), but shows a much higher prevalence of asthma (60 patients). This might be possible due to imputation if there was a very high percentage of missing data, however imputation does not appear to be a good explanation. For example, placebo CKD goes from 2 to 5 (FLV->IVM). First, it is not logical to impute CKD on patients based on the other variables. Second, the protocol specifies imputation only with up to 20% missing data, making it unlikely that imputation would add 150% of CKD patients. Third, the degree of change between FLV and IVM varies dramatically, with IVM reporting 666%, 275%, 150%, and 43% more patients for CPD, asthma, CKD, and CCD, without any clear explanation for similar differences in the percentage of missing data (all were collected on the same interview form).

SERIOUS **Unexplained >6 month delay.** The paper was delayed over 6 months with no explanation. The companion fluvoxamine arm, completed at the same time, was published Aug 23, 2021. The very long delay, high profile of the topic, and other issues above raise questions. The paper was submitted to NEJM in Sep 2021[632]. COI forms suggest that additional authors were added after submission and the corresponding author changed from Prof. Mills to Dr. Rayner[633], whose conflicts include Pfizer, Merck, the Gates Foundation, and the Australian Goverment.

SERIOUS **Placebo patients receiving an injection not blinded.** One-day placebo patients, which study documents repeatedly report as being included in the placebo group, would include those receiving a single injection, and are therefore not blinded[578].

SERIOUS **Major imputation error.** In the paper authors use imputation in Table 1 but not in Figure 2. Authors also released a version of Figure 2 with imputation[634], where the numbers for age and BMI now match the imputed numbers in Table 1. However, the time from onset numbers are very different, with the treatment arm showing 302 patients for 0-3 days, and the imputed version of Figure 2 showing 367[635].

SERIOUS **Single dose results missing.** Results for the single dose ivermectin arm have not been reported.

SERIOUS **Incorrect conclusion.** The conclusion states that ivermectin *"did not result in a lower incidence of [hospitalization] or of [ER observation >6hr]"*. This is incorrect, hospitalization was 17% lower, which is not statistically significant with the sample size and typical statistical analysis. For the Bayesian analysis the authors use, the ITT probability of superiority for ivermectin was 79.4%, which is a positive result, the opposite of the conclusion.

SERIOUS **Missing age information.** According to Figure 2, 98 patients are missing age information[636].

SERIOUS **Mid-trial protocol changes.** There were several mid-trial protocol changes on July 5, 2021[637]. The number of patients for viral load analysis was reduced, only for the ivermectin arm. All-cause, cardiovascular, and respiratory death outcomes were deleted (all-cause was reported). Exclusions were modified to allow enrolling patients vaccinated within the last 14 days. Inclusion criteria were modified to allow enrolling healthy young people — the criterion *"fever >38C at baseline"* was added, allowing enrollment independent of increased risk.

SERIOUS **COI: designed by Cytel.** The trial was designed by Cytel, a company that helps pharmaceutical companies get approval and that works very closely with Pfizer[638,639]. Cytel's software and services are used by the top 30 pharmaceutical companies[640].

SERIOUS **COI: co-principal investigator works for Cytel and the Gates Foundation.** A co-principal investigator works for Cytel and the Gates Foundation[641]: *"The majority of the time I work for a company called Cytel, where I design clinical trials, predominantly for the Bill & Melinda Gates Foundation"*.

SERIOUS **COI: pharma funding and denial of independent investigator.** Reportedly, the first author's center is funded by pharmaceutical companies, and independent investigators tried to participate in the trial but were denied[642].

SERIOUS **COI: Gates Foundation.** The Gates Foundation is a founding partner of GAVI, which took out Google ads telling people not to use ivermectin[643], and a major funder of Unitaid, which may have modified the results of the Hill meta analysis in a way that prevented adoption[582-584].

SERIOUS **COI: Certara.** One of the senior investigators was Dr. Craig Rayner, President of Integrated Drug Development at Certara - another company with a similar mission to MMS Holdings. They state on their website that: *"Since 2014, our customers have received over 90% of new drug and biologic approvals by the FDA."* One of their clients is Pfizer[644].

SERIOUS **COI: MMS Holdings.** The trial is associated with MMS Holdings[568], whose mission includes helping pharmaceutical companies get ap-

proval and designing scientific studies that help them get approval. One of their clients is Pfizer [645].

SERIOUS **COI: analysis company works closely with Pfizer.** All analyses were done by Cytel. Cytel is a statistical modelling company that helps pharmaceutical companies get approval — they work very closely with Pfizer [639]. Cytel's software and services are used by the top 30 pharmaceutical companies [640].

SERIOUS **COI: Fast Grants funding closely related to companies that censored scientific research.** Fast Grants funding is closely related to tech companies that censored ivermectin and other early treatment research. These companies have a strong conflict of interest in not admitting that their censorship was harmful [646,647].

SERIOUS **Unexpected differences in missing data.** Age is unknown for 98 patients, however according to Figure 2, BMI is missing for only 11 patients, smoking status is unknown for only 2 patients, lung disease is unknown for only one patient, and cardiovascular disease is known for all patients.

SERIOUS **Out of funding claim contradicted by funder.** A co-principal investigator has reported that the trial was stopped because they ran out of funding, however this is contradicted by the Rainwater Foundation, which reported that they would have given more money to finish the trial if the investigators had asked [648].

SERIOUS **Misrepresentation of dosing recommendation.** Investigators have misrepresented an email from the FLCCC regarding recommended dosing [648].

MAJOR **Mean delay likely excluding unknown onset.** The reported mean number of days from symptoms to randomization probably only includes known onset patients and therefore is likely to significantly underestimate the actual average (in addition to not including the time between randomization and treatment).

MAJOR **Per-protocol placebo much more effective.** The 3-dose per-protocol placebo group shows greater efficacy [566,649]. This could be consistent with placebo patients accidently receiving treatment.

MAJOR **Multiple conflicting randomization protocols.** *twitter.com (AO)* reviewed the randomization protocol, finding three different algorithms, and conflicting versions in the papers.

MAJOR **Dominated by Gamma variant with different characteristics, no discussion.** The trial took place in an area of Brazil and time when the Gamma variant was dominant. 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 [228,229].

MAJOR **Incorrect dose reporting, patients at higher risk due to BMI may have received lower per kg doses, and show lower efficacy.** The paper reports 400µg/kg for 3 days, however the protocol indicates that this was only up to 90kg, meaning that the dose received for higher-risk high BMI patients was even further reduced from dosage which is already far below clinician recommendations for the dominant variant [651]. 50% of patients had BMI ≥30. Much greater efficacy was seen in the low BMI subgroup (RR 0.77 vs 0.98).

MAJOR **Conflicting target enrollment and reasons for termination.** There are conflicting target enrollment numbers. The protocol showed 800 patients per arm as of Mar 21, 2021 (after the trial started) [652,653], the co-principal investigator reported 800 per arm in an interview published June 14, 2021 [654], and the protocol changed to 681 on June 22 [655]. However, the trial record from Jan indicates 2724 (681*4) patients [604], suggesting that the 800 goal was later, and was kept for fluvoxamine but reverted for ivermectin. The fluvoxamine arm which started two months earlier was terminated at the same time, and was terminated due to superiority [656] after 741/756 patients. Note that Gamma was declining significantly around the termination point, which likely favors improved efficacy if the trial continued, given the late treatment and dosage used. The co-principal investigator reports three different reasons for stopping the trial [657]: a) because they ran out of money, b) because third parties were not supportive, and c) it was done by the DSMC and was out of their control.

MAJOR **Primary outcome subject to bias, selected after single dose arm.** The subjective "emergency room visit for >6 hours" criterion shows higher risk (RR 1.16), while hospitalization is lower (RR 0.83 all-cause, RR 0.84 COVID-19). The primary outcome results were set on March 21, 2021, after the single dose ivermectin arm. Given the known public biases of some investigators, this may have been specifically chosen to reduce efficacy. Authors claim that the 6hr threshold did not include waiting time, however the emergency visit form has no mention of waiting time, only recording presentation and discharge times [599].

MAJOR **Reported terminated due to futility, but threshold not reached.** The trial was reportedly terminated due to futility [658], however the futility thresholds were 20%, 40% and 60%, and all published probabilities are >60% (ITT 79.4%). Additionally, the fluvoxamine arm did not have the higher 60% threshold, only using 40%. Note the DSMC was not independent as below.

MAJOR **Subgroup analysis protocol violations.** The presented subgroup analysis is inconsistent with plans and with the fluvoxamine paper, including not presenting pre-specified subgroups, presenting subgroups that were not pre-specified, presenting different subgroups to the contemporary fluvoxamine paper, and modifying subgroup definitions [659].

MAJOR **Many pre-specified outcomes missing.** Many outcomes specified in the protocol appear to be missing, including the co-primary outcome of COVID-19 mortality (only all-cause mortality is provided, specific AE details not provided), time to clinical failure, days with respiratory symptoms, mortality due to pulmonary complications, cardiovascular mortality, COVID-19 symptom scale assessment, WHO clinical worsening scale assessment, and 14 day mortality.

MAJOR **Single-dose recruiting continued after change.** The trial had requested moving to 3-dose treatment by Feb 15/19, when only 19 patients had been recruited, however the trial continued recruiting an additional 59 patients to single dose treatment [660].

MAJOR **Funding list incorrect, missing Gates Foundation and Unitaid.** The paper does not include the Bill and Melinda Gates Foundation or Unitaid as funders, however the protocol shows the Gates Foundation [661] and the web site shows Unitaid [585].

MAJOR **Statistical analysis plan dated after trial start.** The statistical analysis plan appears to be dated after the trial started [662].

MAJOR **Imputation protocol violation.** The protocol specifies multiple imputation with up to 20% of missing data, however imputation was done with time from symptom onset, which has >23% missing data [663].

MAJOR **Expected analyses missing.** Authors do not provide time from onset analysis for either mortality or hospitalization, only the combined measure including the ER visits where anomalous results are seen. Authors do not provide per-protocol or mITT results for mortality or hospitalization. Per-protocol mortality results were provided for the companion fluvoxamine trial.

MAJOR **Conflicting reasons for dose change.** Conflicting reasons have been given for the change from 1-day to 3-day dosing. In email from March 6, the co-principal investigator says the change was "based on emerging trials from Andrew Hill's synthesis" [664]. The paper says the change was made "on the basis of feedback from advocacy groups". Neither of these match the report that the dosing change was made at the request of one of the trial funders [546].

MAJOR **Details of placebo unspecified.** The placebo appears to be unspecified in the paper and protocol. The initial trial announcement indicated the placebo was vitamin C[638], which would be an active treatment according to the results of 72 studies (mortality RR 0.81 [0.73-0.91]). The metformin arm reports using talc, however fluvoxamine and ivermectin do not appear to report details of the placebo, which could potentially be different, for example based on manufacturer limitations for matching active treatment tablets.

MAJOR **Antigen test requirement.** The protocol indicates that patients with a negative test may be included if they become positive a few days later, potentially resulting in a long unreported delay between randomization and treatment, depending on how investigators interpreted the protocol. The requirement for a positive antigen test excludes the possibility of early treatment in many cases - tests have very high false negative rates in the early stages of infection, and symptoms may appear before the test becomes positive.

MAJOR **Bayesian probability of superiority, featured for FLV, hidden in appendix.** The bayesian probability of superiority figure, featured in the main paper for FLV, MET, HCQ, was hidden in the appendix for IVM[665].

MAJOR **Two different per-protocol counts.** Figure 1 shows 228 per-protocol for the control arm, while Table 2 shows 288. This was modified in the Apr 5 update without explanation.

UNKNOWN **Source of ivermectin unspecified (fluvoxamine source specified).** Authors do not specify the source of the ivermectin used in the trial, whereas they do specify the source for the fluvoxamine arm (Luvox, Abbott). Depending on the source, Ivermectin has been reported to be of unreliable quality in Brazil.

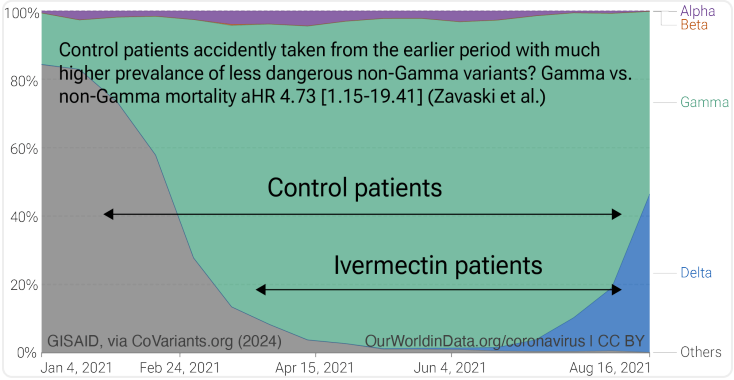
UNKNOWN **100% adherence reported for 3-day placebo.** Reported numbers indicate that there was 100% adherence among 288 patients assigned to 3-day placebo, which is unexpected[546,591].

UNKNOWN **No confirmation of placebo manufacturing.** A local Brazilian investigator reports that, at the time of the trial, there was only one likely placebo manufacturer, and they reportedly did not receive a request to produce identical placebo tablets[575]. They also report that compounded ivermectin in Brazil is considered unreliable. The protocol reports that "*the study medication used will come from pharmaceutical plants that hold a commercial authorization for their production, already approved by ANVISA.*"

The following comments are prior to the publication and may be out of date. We note that authors claim they have not included patients prior to the time period for the 3 dose ivermectin patients, however this conflicts with previously reported data as per the analyses above.

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[548]. 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[549]. 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[548], 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.



An investigator from Brazil notes that the gamma variant became prevailing in the state of Minas Gerais later than in the rest of the country, with the time when gamma prevailed for the trial locations being more closely aligned with the start of the ivermectin arm[550]. Due to the substantial differences in disease course and risk between the variants, authors need to consider only patients recruited during the same time period.

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[228,229,551]. Treatment was administered on an empty stomach, greatly reducing expected tissue concentration[1] 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[552], and prior use of ivermectin is not listed in the exclusion criteria.

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.

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[440], 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.

The same trial's results for a previous treatment were initially reported as RR 1.0 [0.45-2.21][553], while the final paper reported something very different — HR 0.76 [0.30-1.88][554].

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"[439,555]. Prior statements: odysee.com.

The local Brazilian investigator also reports that nitazoxanide was tested in the same location, however very few patients reportedly experienced urine discol-

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oration, while all are expected to experience this side effect. They also suggest that 6-hour observation is a poor choice because it is almost impossible to stay less than 6 hours in Brazil.

For additional issues see: *stevekirsch.substack.com*, *cato.org*, *longhaulwiki.com*, *trialsitenews.com (B)*, *covid19criticalcare.com*, *doyourownresearch.substack.com (C)*, *twitter.com (L)*, *web.archive.org (N)*, *web.archive.org (O)*, *twitter.com (M)*, *Marinos*, *Marinos (B)*. Protocols, approvals, and statistical analysis plans can be found here *togethertrial.com*.

Revisions: added the median number of days to clinical recovery outcome.

ACTIV-6

Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19: A Randomized Clinical Trial

Extreme COI, data inconsistencies, uncorrected errors, no response from authors, participant fraud, refusal to release data

SEE ALSO

ACTIV-6 Trial on Ivermectin: NIH Scientists Behaving Badly
The Story Of A Real ACTIV-6 Patient
ACTIV-6 Dosing & Timing: A Fox In The Henhouse

RCT low-risk outpatients with very late treatment (median 6 days, 25% ≥8 days) in the USA, showing 98% probability of efficacy for clinical progression at day 14, a treatment delay-response relationship, and significant efficacy for patients with severe symptoms at baseline.

The posterior probability that ivermectin reduces COVID-19 risk was 99%, 98%, 97% for mean time unwell and clinical progression @14 and 7 days. Clinical progression results in the preprint [666] were changed in the journal version without disclosure. The preprint analysis is the correct prespecified analysis. The two dose arms were reported separately [667]. When not specified, comments refer to the 400*µg*/kg arm.

There are many critical issues as below. Design, presentation, and analysis shows a strong bias against treatment. Submit Updates or Corrections

CRITICAL	1. Prespecified primary outcome not reported; protocol violation
CRITICAL	2. Treatment adverse effects are considered to be unresolved COVID symptoms
CRITICAL	3. Requiring all symptoms to resolve hides faster recovery of most symptoms
CRITICAL	4. Sustained recovery requirement further biases towards null/harm
CRITICAL	5. Clinical progression analysis changed between preprint and journal; protocol violation; no disclosure
CRITICAL	6. Impossible data
CRITICAL	7. 16% of patients missing (600*µg*/kg)
CRITICAL	8. Randomization failure - higher severity in ivermectin arms
CRITICAL	9. Adverse events consistent with potential medication error
CRITICAL	10. Mean time unwell analysis capped at day 12; appears only in protocol v4.0
CRITICAL	11. Very late treatment
CRITICAL	12. Superiority found, not reported
CRITICAL	13. Mismatch in number of patients receiving medication
CRITICAL	14. Adverse events similar for active and placebo
CRITICAL	15. Adverse event count mismatch
CRITICAL	16. Participant fraud
CRITICAL	17. 0.4% AE for newly added patients versus 8.0%
CRITICAL	18. Interim analyses not reported, likely showed superiority
CRITICAL	19. Death incorrectly reported in mITT, medication not received
CRITICAL	20. Death in 600*µg*/kg was accidental
CRITICAL	21. Ivermectin source unknown, specified for other trial medications
CRITICAL	22. More patients took medication than received it
CRITICAL	23. Non-identical placebo
CRITICAL	24. Post-hoc protocol
CRITICAL	25. Closest reported outcome to the unreported primary outcome shows superiority
CRITICAL	26. Prespecified primary 14 day outcomes not reported, clinical status shows 30% benefit
CRITICAL	27. Hospitalization/death mismatch
CRITICAL	28. 90 day followup results not provided
CRITICAL	29. Key clinical question consistent with unreported prespecified primary outcome but not the reported outcome
CRITICAL	30. Patients with symptoms >7 days included
CRITICAL	31. Data unavailable over 1,500 days from publication
CRITICAL	32. Outcomes reported do not match protocol
CRITICAL	33. Primary outcomes changed after publication
CRITICAL	34. Different hosp./urgent care numbers between paper and presentation
CRITICAL	35. Recovery dated to the third of three symptom-free days rather than the first; protocol violation
CRITICAL	36. Dose below 400µg/kg
CRITICAL	37. Effective dose ~130µg/kg, administration on empty stomach
CRITICAL	38. Clinical progression details for other arms but not ivermectin
CRITICAL	39. COVID-19 mortality/hospitalization not reported
CRITICAL	40. Many prespecified outcomes missing
CRITICAL	41. Full protocol unavailable before October 2022
CRITICAL	42. IDMC not independent, extreme conflict of interest
CRITICAL	43. Shipping and PCR delays largely enforce late treatment
CRITICAL	44. Very slow shipping
CRITICAL	45. Blinding failure
CRITICAL	46. Extreme conflicts of interest
CRITICAL	47. Treatment delay-response relationship
CRITICAL	48. Asymptomatic patients included
CRITICAL	49. Disingenuous conclusion
CRITICAL	50. Significant missing data, not mentioned in paper
CRITICAL	51. Statistically significant efficacy for severe patients removed
CRITICAL	52. Statistical analysis plan dated after trial end
CRITICAL	53. 31% more severe cases in the ivermectin arm
CRITICAL	54. Many conflicting exclusion counts
CRITICAL	55. Population incorrect
CRITICAL	56. Early treatment incorrect

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CRITICAL	57. Author calls for censorship of 670 scientists reporting positive results
CRITICAL	58. Impossible data identified in three COVID-19 trials by author
SERIOUS	59. Bias due to false positive antigen tests
SERIOUS	60. Participant pickup delay
SERIOUS	61. Treatment initiation unknown
SERIOUS	62. Randomization failure
SERIOUS	63. Low-risk patients
SERIOUS	64. No adherence data or per-protocol analysis
SERIOUS	65. Skeptical prior not justified
SERIOUS	66. Missing symptom severity mismatch
SERIOUS	67. Not enough tablets provided
SERIOUS	68. Monotherapy with no SOC for most patients
SERIOUS	69. Over 2x greater severe dyspnea at baseline for ivermectin
SERIOUS	70. Safety conclusion removed, suggests bias
SERIOUS	71. Authors suggest high-income country healthcare is better, however almost all patients received no active SOC
SERIOUS	72. No breakdown of severe outcomes
SERIOUS	73. Missing subgroup counts
MAJOR	74. Overlapping fluticasone placebo shows very different event numbers
MAJOR	75. Overlapping fluticasone placebo shows unexpected baseline numbers
MAJOR	76. Inconsistent calendar time subgroups
UNKNOWN	77. Outcome graph presented does not match either medication tested

Responses: authors have not responded to any of these issues.

CRITICAL **Prespecified primary outcome not reported; protocol violation.** The prespecified primary outcome - which should be a much better measure of recovery - was not reported. Protocol v2.0 section 10.6.1 defines the primary outcome as a daily ordinal variable - symptom count, with hospitalization as count+1 and death as count+2, measured daily, with the estimand being the common odds ratio from a proportional odds model (section 10.6.4). This outcome is not reported anywhere in the paper. The published primary endpoint is time to sustained recovery, which the protocol lists as secondary.

CRITICAL **Treatment adverse effects are considered to be unresolved COVID symptoms.** The symptom list includes nausea, vomiting, and diarrhea - known ivermectin adverse effects. Because sustained recovery requires all symptoms to resolve, drug-induced GI symptoms delay the endpoint in the treatment arm only. This biases results towards harm.

CRITICAL **Requiring all symptoms to resolve hides faster recovery of most symptoms.** Unlike the prespecified primary outcome, sustained recovery requires every symptom to resolve. A single symptom not resolving hides any effect against all other symptoms. For example, consider symptoms where recovery involves tissue repair or resolution of inflammation, and not just stopping viral replication, such as anosmia and cough - these control the recovery date regardless of any treatment effect against other symptoms.

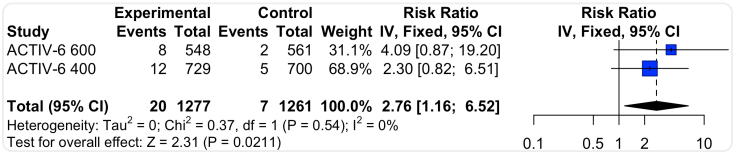
CRITICAL **Sustained recovery requirement further biases towards null/harm.** The protocol's original primary outcome has no sustained-resolution requirement. The three-day sustained recovery rule further biases towards null (or towards harm for side-effects of treatment). Any symptom logged once within three days delays recovery, including side-effects of the treatment and symptoms requiring tissue repair that are less amenable to antiviral treatment.

CRITICAL **Clinical progression analysis changed between preprint and journal; protocol violation; no disclosure.** The protocol (section 10.6.8) specifies a covariate-adjusted proportional odds model for the clinical progression scale, and section 10.6.2 shows the cumulative-probability form $Pr(Y \geq y \mid X) = expit(\alpha_y + X\beta)$. The preprint's analysis matches this specification. The preprint shows probability of superiority at days 7 and 14 of 97% and 98% respectively. In the journal version the model was changed resulting in lower probabilities - 88% and 89%. The preprint version is the correct prespecified analysis.

CRITICAL **Impossible data.** There are major data mismatches[670]. For the ivermectin 600 arm clinicaltrials.gov (CT) indicates that 718 patients started and 708 completed the arm[671], while the paper claims that only 668 were randomized to ivermectin, of which 66 did not even receive the medication[672]. Baseline age, ethnicity, and race data all differ between CT and the paper, for example CT indicates 3 patients in the ivermectin arm were American Indian or Alaska Native, whereas the paper shows 9, despite reporting on a much smaller number of patients. Many results also differ between CT and the paper. A second version of the paper makes some values match but adds new data problems as below.

CRITICAL **16% of patients missing (600µg/kg).** *Naggie (C)* confirms that 16% of patients were missing in the 600µg/kg paper. It's not clear how the trial could have such a large error for the number of patients randomized, why the correction took over a year, or why the many other errors have not been corrected.

CRITICAL **Randomization failure - higher severity in ivermectin arms.** The most severe baseline symptom reported is severe dyspnea. For both 600µg/kg and 400µg/kg, the ivermectin arm has higher incidence of severe dyspnea, which is statistically significant across both arms (p = 0.02). This suggests that known and potentially unknown blinding failures are material.



CRITICAL **Adverse events consistent with potential medication error.** Placebo adverse events are expected to be similar for the 400µg/kg and 600µg/kg arms. The populations are similar and patients are not taking any study treatments. The 600µg/kg arm has a lower overall hospitalization rate. However, the 600µg/kg placebo arm reports 44/604 (7.3%) adverse events, while the 400µg/kg arm reports only 27/774 (3.5%), over 2 times higher. This is a significant increase in adverse events, p = 0.002, without explanation or discussion. Comparing 400µg/kg and 600µg/kg, adverse events are over 2x higher for both the active and placebo arms. The overall increase in adverse events with the higher dosage (total 3x higher) matches expectations, however we expect the increase in the active treatment arm, not both active and placebo arms. One hypothesis is that patient arm classifications are incorrect, i.e., many patients received the opposite of their designated arm. This kind of error is possible in all placebo controlled trials and happened for example in *López-Medina* (discovered and excluded in that case). This hypothesis is consistent with both the adverse events and the 600µg/kg results, with the very small remaining effect explainable by the 10% non-matching placebo patients. We recommend that participants retain any leftover medication for analysis.

CRITICAL **Mean time unwell analysis capped at day 12; appears only in protocol v4.0.** The mean time unwell outcome appears only in protocol v4.0, dated Dec 20, 2021, by which point most of the ivermectin arm had already been enrolled. This analysis is capped at day 14, although symptoms were collected until day 33 for patients who have not reached sustained recovery. However, authors count recovery as the last of three symptom-free days, so a day-14 cutoff corresponds to symptoms resolving on day 12. Because recovery requires resolution of all 13 symptoms including minor symptoms, fatigue, lingering cough, etc. the time to recovery is much longer than trials that look at

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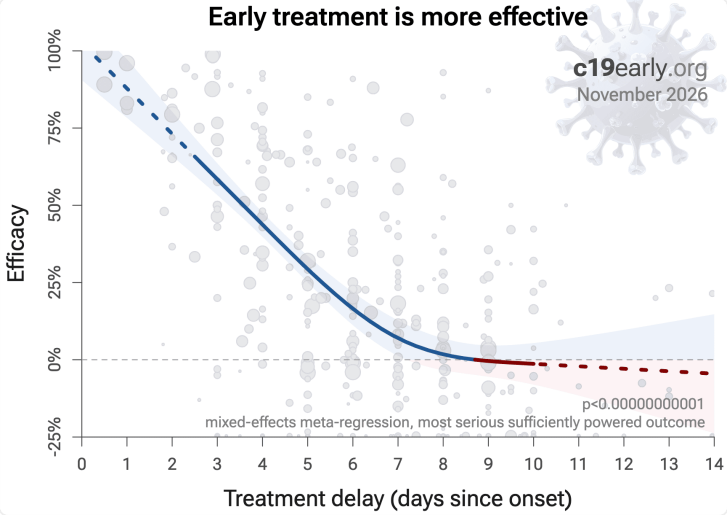
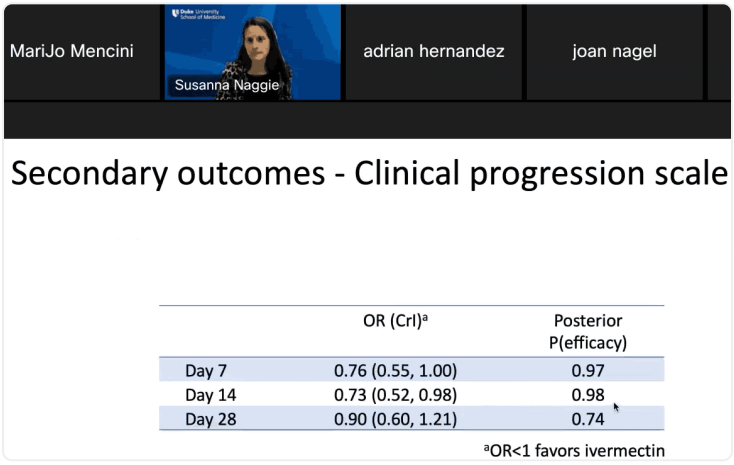
resolution of major COVID-19 symptoms - the KM plot shows only ~82% have recovered by day 28 and the curves separate most around days 14-19, with more patients recovering in the treatment arm. Capping at day 14 discards all symptom days beyond that point, attenuating any differential recovery occurring in the second half of the follow-up window. Over 40% of patients have no recovery by day 14. As an example, if one arm's participants typically recover on day 16 and the other's on day 20, both contribute an identical 14 unwell days and the difference disappears entirely from the estimate. There is no explanation for why this analysis was capped at day 14, whereas the primary endpoint is up to day 28. Authors use this analysis as a quantification of benefit, without noting the cap at day 14 (effectively day 12).

CRITICAL **Very late treatment.** Patients were treated a median of 6 days late, with 25+% 8+ days late. Extensive research for COVID-19 and other viral diseases shows that early antiviral treatment is critical. While authors recommend further study, they do not recommend or perform the obvious step of doing an early treatment trial, as is done for NIH recommended treatments like Paxlovid, suggesting a strong negative bias.



CRITICAL **Superiority found, not reported.** Day 7 and day 14 clinical progression results and mean time unwell show superiority of ivermectin (400µg/kg arm preprint [666], results were changed in the journal version, however the preprint analysis is the correct prespecified analysis as detailed above). In the presentation [429], author shows a slide containing these results while stating *"this was, um, not statistically significant"* (@22:36). These results were seen despite 107 patients having no symptoms at baseline and the use of the skeptical prior [674].



CRITICAL **Mismatch in number of patients receiving medication.** The first version of the 600µg/kg paper reports that 138 patients did not receive the study medication, while the second (which includes many patients incorrectly excluded in the first version) claims that only 27 did not receive the medication (from Figure 1 in each version).

CRITICAL **Adverse events similar for active and placebo.** For the 600µg/kg arm authors report that 9% of patients experienced an adverse event, similar to placebo (7%, no significant difference). However significantly more side effects are expected at this dosage (the total dosage is 3x greater due to the longer duration). The 600µg/kg arm in *Buonfrate* reports much higher adverse events. Overall reporting is higher in this trial, which may include lower severity items, especially within 'general disorders'. However looking specifically at eye disorders, a known side effect of higher doses of ivermectin, *Buonfrate* show 46% vs. 3% for ivermectin vs. control. The lack of higher side effects for ivermectin in ACTIV-6 suggests that patients may not have taken authentic ivermectin at the dosage reported. GMK [435] notes that data was self-reported by patients in ACTIV-6. Highly inaccurate reporting by patients would also apply to the symptomatic results, similarly invalidating the trial.

CRITICAL **Adverse event count mismatch.** The paper reports 44 of 604 placebo patients had an adverse event in the 600µg/kg arm [672] (44 of 724 in the second version), whereas clinicaltrials shows 5 of 724 placebo patients had an adverse event [671].

CRITICAL **Participant fraud.** A paper on the operation of the trial [536] reveals that there was participant fraud - authors identified participants that signed up repeatedly, and participants that withdrew when not randomized to their preferred arm. Authors indicate that they tried to prevent repeat signups but provide no details on the algorithms or the evaluation thereof. It is possible that they only caught a small fraction of the fraud, and possible that improvements to detection were added only later in the trial during or after the ivermectin arms. Individuals may have been gaming the system related to the politicization and extreme financial implications. This information was not disclosed previously. Patients were allowed to specify treatments that they accept or decline to be a part of. One author indicates this was most commonly used by patients to specify only ivermectin [675], which could be related to fraud targeting ivermectin. There are known paid groups of individuals targeting ivermectin, and it would be simple to bias results towards null without having to break the blinding. Participant fraud has also been reported for a similar remote trial [535] where known fake surveys were submitted. The self-reported design and absence of professional medical examination opens these kind of trials to participant fraud, which may be significant due to extreme politicization in the study country.

CRITICAL **0.4% AE for newly added patients versus 8.0%.** The first version of the 600µg/kg paper reports that 8.0% of patients had an adverse event (96/1206, eTable2). The second version reports 97/1430 indicating that only 0.4% of the added patients had an adverse event.

CRITICAL **Interim analyses not reported, likely showed superiority.** The original protocol specified interim analyses every 200 patients, this was later modified to every 300 patients. However the paper claims *'Because the rate of enrollment was so rapid, it was not possible to complete the interim analyses'*. This is not realistic - the analysis code is written and tested in advance for trials like ACTIV-6 which have professional statisticians. Based on the clinical progression results showing superiority, it is likely that one or more of the interim analyses showed superiority on the original primary outcome.

CRITICAL **Death incorrectly reported in mITT, medication not received.** Authors report one death in the ivermectin 400µg/kg arm in the mITT population (817 patients that received the drug within 7 days), however in the presentation [429] (@21:15) author reports that the patient that died did not receive the drug because they were admitted prior to receipt. The reported mITT death is therefore incorrect. Similarly, at least one and potentially many or all hospitalizations may have occurred before receiving the drug.

CRITICAL **Death in 600µg/kg was accidental.** For 600µg/kg, authors note that the death was accidental, however the abstract and results table report the

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death with no acknowledgement that the result is unrelated to efficacy of the treatment.

CRITICAL **Ivermectin source unknown, specified for other trial medications.** Authors do not specify who provided the ivermectin and ivermectin placebo tablets. This information is specified for the other ACTIV-6 medications (fluticasone and fluvoxamine). For both other medications, active and placebo were provided by the same source.

CRITICAL **More patients took medication than received it.** The first version of the 600μg/kg paper reports that 566 of 602 treatment patients took the medication (eTable 2), however Figure 1 shows that only 536 of 602 received the medication.

CRITICAL **Non-identical placebo.** The protocol states that the ivermectin placebo tablets will be identical to the ivermectin tablets, however the paper states only that packaging was identical. In contrast, the preprints for fluvoxamine and fluticasone both state that the placebo was identical.

CRITICAL **Post-hoc protocol.** An incorrect post-hoc protocol is included with the paper published October 21, 2022 which differs significantly from the prespecified protocol [676]. The post-hoc protocol is dated December 20, 2021, long after the trial started and after scheduled interim analyses. Metadata shows the author of the protocol files to be Jenny Jackman. The protocol for the ivermectin arm is included with the fluticasone NEJM paper, and is dated May 25, 2021. Neither protocol matches the reported outcomes, however the post-hoc version has been modified to be closer.

CRITICAL **Closest reported outcome to the unreported primary outcome shows superiority.** The protocol shows the primary symptom outcome using a longitudinal statistical model with an ordinal variable based on symptom count and hospitalization/death measured daily until day 14 [676] (see section 10.6.1). This outcome is not reported. The closest reported outcome is clinical progression at 14 days, which shows superiority of ivermectin, OR 0.73 [0.52-0.98], posterior probability of efficacy 98% (changed in journal version, details above).

CRITICAL **Prespecified primary 14 day outcomes not reported, clinical status shows 30% benefit.** The prespecified primary 14 day outcomes [676] are still not reported in the journal version. However, authors now show the clinical status graphs in eFigure 2, which shows 30% benefit for ivermectin for limited activity at 14 days.

CRITICAL **Hospitalization/death mismatch.** Results show 10 and 9 events for hospitalization/death, however eFigure 1A shows 4 and 3.

CRITICAL **90 day followup results not provided.** Authors do not provide the PROMIS-29 results, stating that this is due to the 90 day followup. The 90 day followup period ended 169 days before publication (38 days before the preprint publication). The protocol also specifies 7, 14, and 28 day PROMIS-29 results.

CRITICAL **Key clinical question consistent with unreported prespecified primary outcome but not the reported outcome.** Authors report the key clinical questions for ACTIV-6 as being 'How to help someone feel better faster with newly diagnosed mild-moderate COVID-19?' and 'How to prevent hospitalizations or death in someone with newly diagnosed mild-moderate COVID-19?' [429]. The prespecified but unreported primary symptom outcome provides a measure for feeling better faster, however the reported post-hoc primary outcome is very poorly matched. For example, a treatment that resolves serious symptoms 10x faster, but does not speed up 100% resolution of cough for three consecutive days, would show zero benefit in the post-hoc primary outcome. Cough may persist long after viral clearance [677]. Note also that the trial does not address 'newly diagnosed' patients, but rather very late treatment a median of 6 days after symptoms. The very late treatment also minimizes the chance of preventing the initiation of viral cough.

CRITICAL **Patients with symptoms >7 days included.** The trial specifies symptoms ≤7 days, however subgroup results show symptoms ≤9, 11, and 13 days, and the Q3 for the ivermectin arm was 8 days, indicating 25% of patients with a treatment delay of ≥8 days. The difference is likely due to the authors not considering receipt of medication or treatment time in inclusion, i.e., due to shipping delays. However, ≤7 days treatment delay already makes the results inapplicable to real-world usage where antivirals are used early.

CRITICAL **Data unavailable over 1,500 days from publication.** Data for the study is unavailable over 1,600 days after publication.

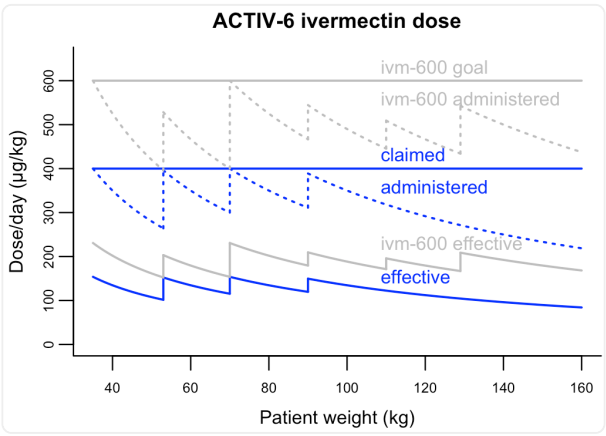
CRITICAL **Outcomes reported do not match protocol.** The reported outcomes are very different to the trial registration [678] and the prespecified protocol [676]. The trial registration shows three primary outcomes, of which zero are reported in the paper. The prespecified protocol shows the primary outcome using a longitudinal statistical model with an ordinal variable based on symptom count and hospitalization/death measured daily until day 14.

CRITICAL **Primary outcomes changed after publication.** The primary outcomes were changed from day 14 to day 28 on June 25, 2022, after publication [679]. Two of the three primary outcomes were changed to match what was reported, while the third remains unreported, and none of the prespecified primary outcomes have been reported to date.

CRITICAL **Different hosp./urgent care numbers between paper and presentation.** The paper and the later presentation show different numbers for hospitalization and urgent care/ER. In the presentation, a hospitalization was moved from the placebo arm to the ivermectin arm [429] (@21:44). The HRs did not change.

CRITICAL **Recovery dated to the third of three symptom-free days rather than the first; protocol violation.** The protocol specifies 'first of at least three consecutive days without symptoms', however the paper dates recovery to the third day, adding 2 days to every participant in both arms. This makes any reduction in recovery time appear smaller. Both the prespecified [676] and post-hoc protocols include a secondary outcome of '*symptom resolution, defined as first of at least three consecutive days without symptoms*'.

CRITICAL **Dose below 400μg/kg.** The abstract states that patients received 400μg/kg. This is incorrect, section 16.3.3 in the protocol shows that the actual dose was always below 400μg/kg, unless patients weighed exactly 35kg or 70kg, as shown below [674]. Dosage was as low as 269μg/kg for 52kg. When considering administration as below, the average dose administered is equivalent to ~130μg/kg as used in practice. Authors state: "*ivermectin was dosed by weight to achieve a goal dose of 400μg/kg, but the maximum dose of ivermectin provided by the study was 35mg. While almost 42% of participants had a weight of more than 88kg and thus did not achieve the goal dose, more than 75% of participants had a weight of less than 100kg and so received at least 90% of the target dose*". This is incorrect - the goal dose varied between ~300-400μg/kg, and the percentage that received 90+% of 400μg/kg is likely < 40%.



CRITICAL **Effective dose ~130µg/kg, administration on empty stomach.** Authors instructed patients to take ivermectin on an empty stomach (not done for fluvoxamine). Guzzo show that the plasma concentration of ivermectin is much higher when administered with food (geometric mean AUC 2.6 times higher). *"Ivermectin should be taken on an empty stomach with water"* (protocol section 16.3.3). This is not mentioned in the paper or the supplementary appendix, only in the protocol. This makes the average effective dose administered equivalent to ~130µg/kg for administration with a meal (as used in clinical protocols).

CRITICAL **Clinical progression details for other arms but not ivermectin.** Authors provide clinical progression details for fluticasone (Table S3, Figure S5) and fluvoxamine (eFigure 3), but not for ivermectin. This may be related to authors not reporting any of the prespecified primary outcomes — the same table would reveal 2 of the 3 prespecifed primary outcome results.

CRITICAL **COVID-19 mortality/hospitalization not reported.** Authors only report all-cause mortality and hospitalization. Notably, the baseline hospitalization and mortality rate for non-COVID-19 causes may account for the death and many of the hospitalizations. This may also explain why authors report only 28 day mortality/hospitalization in violation of the protocol where the primary outcomes specify 14 days[678]. Additionally, adverse events show only one case of aggravated COVID-19 pneumonia for ivermectin, versus 3 for placebo.

CRITICAL **Many prespecified outcomes missing.** Authors do not report[676]:

- OR describing the overall difference in symptoms and clinical events over 14 days (primary outcome)
- Overall clinical progression OR (only specific day 7, 14, 28 values are provided)
- Time to first urgent care, emergency care, hospitalization or death
- Risk and time to event for each component of the composite
- Mean and median time to symptom freedom
- Overall QOL OR
- Day 7, 14, 28, 90 QOL OR
- Mean difference in QOL scores at day 7, 14, 28, 90
- Mean and median time to symptom resolution (only a new sustained resolution measure is reported, which is not in the protocol)
- Day 90 mean and median symptom count

CRITICAL **Full protocol unavailable before October 2022.** The prespecified protocol[676] is missing the appendix which includes contraindications, exclusions, formulation, appearance, packaging, dispensing, dosing, and dose rationale.

CRITICAL **IDMC not independent, extreme conflict of interest.** The IDMC vice chair was reportedly on the NIH panel that did not recommend treatment despite strong evidence, and provided no quantitative analysis, no reference to the majority of the research, and no updates for new research for a very long period[680]. While not reviewing most of the evidence, the panel concluded that there was "insufficient evidence".

CRITICAL **Shipping and PCR delays largely enforce late treatment.** Authors required positive PCR before randomization, and shipped medication to participants. The delay before PCR results become positive, delay in receiving PCR results, and the shipping delay largely ensure that patients will not be treated early.

CRITICAL **Very slow shipping.** While one day or faster shipping should have been possible (~$11,000 funding per patient[681]), the shipping delays in this trial appear to be very long based on the ≤7 days inclusion criterion and subgroup analysis up to 13 days. One participant in the ivm-600 arm shared their experience showing 6 days from signing up until arrival of the medication, resulting in a total of 11 days treatment delay[682]. COVID-19 is an acute disease (which may or may not be mild). Participants cannot be expected to wait 1-2 days or longer for treatment. Chances are that patients feel better by the time medication arrives and do not take the medication, which may explain why adherence is not reported, or their condition became worse and they found alternative immediate care elsewhere.

CRITICAL **Blinding failure.** The placebo arm included multiple regimens matching different treatment arms, hence some participants will know they are not in the ivermectin arm, and others will know that there is a higher probability of them being in the ivermectin arm than the placebo arm. This may be more important given the politicization in the study country. The fluticasone arm and matching placebo use an inhaler, the fluvoxamine arm uses 10 days treatment. Matched placebo analysis should be provided.

CRITICAL **Extreme conflicts of interest.** This trial has extreme conflicts of interest, being funded by an organization that chose to recommend against treatment while providing no quantitative analysis, no reference to the majority of the research, and no updates for new research for a very long period[680]. Further, a majority of the panel providing the recommendation has major conflicts of interest[680]. Also see *trialsitenews.com (D), trialsitenews.com (E)*. The ACTIV executive committee was chaired by employees of J&J and NIH, and is now chaired by employees of Pfizer and NIH. Other members of the committee are from NIAID (Dr. Fauci), FDA, and Pfizer[668,685].

CRITICAL **Treatment delay-response relationship.** Subgroup results for treatment delays 13, 11, 9, 7, and 5 show monotonically improving results (less than 1% probability due to chance). ≤3 days may have very few patients, and is within confidence limits for monotonically improving results (any inaccurate reports of symptom onset could also be more prevalent in the ≤3 days group). Improved efficacy for earlier treatment matches extensive results for ivermectin and other COVID-19 treatments[686], however authors ignore this trend, claiming only a lack of statistical significance for one specific binary threshold (which may have few patients on one side), and authors have not initiated an early treatment trial.

CRITICAL **Asymptomatic patients included.** Study inclusion required >2 symptoms, however the subgroup analysis includes 109 patients with no symptoms, where results favored placebo. The primary outcome may reach statistical significance without these patients.

CRITICAL **Disingenuous conclusion.** The conclusion states that treatment did not lower mortality of hospitalization, however it is impossible to lower zero mortality. While authors do not indicate COVID-19 versus other hospitalization, statistically significant reduction in hospitalization would require at minimum 79% efficacy, but for COVID-19 hospitalization it is likely impossible based on expected non-COVID-19 hospitalizations. The trial is underpowered by design due to selection of a low-risk population. Note that among the 90 severe cases, statistically significant efficacy is reported.

CRITICAL **Significant missing data, not mentioned in paper.** The paper does not mention missing data, however in the presentation[429] (@44:20) authors report close to 10% missing survey data. One author indicates there was less then 10% missing survey data through day 14. However, the presentation also shows clinical progression graphs (@22:10) that contradict this, showing 650/614 patients at day 14, which is over 20% missing data.

CRITICAL **Statistically significant efficacy for severe patients removed.** The statistically significant HR 1.86 [1.10-3.16] efficacy for severe patients at baseline (using the post-hoc primary outcome) was noted in the text of the preprint[666], but has been deleted in the journal version (only seen in the appendix eFigure 3).

CRITICAL **Statistical analysis plan dated after trial end.** The statistical analysis plan included with the journal paper is dated after the end of the trial.

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CRITICAL **31% more severe cases in the ivermectin arm.** There were 31% more severe cases in the ivermectin arm at baseline (39 control vs. 51 ivermectin).

CRITICAL **Many conflicting exclusion counts.** Comparing the two versions of the 600μg/kg paper shows many conflicts in excluded patients. 10 had a drug allergy to ivermectin in the first while only 7 did in the second. 11 were on warfarin in the first version while only 4 were in the second version. 9 were hospitalized in the last 10 days in the first version while only one was in the second version. 7 had current use of ivermectin in the first version while only 4 had current or recent use in the second version. The second version claims 78 were exluded for symptom onset >7 days which is not in the first version, and both versions show patients up to 10 days from onset included (eFigure 2). In the second version, 17 fewer patients were eligible but elected not to continue.

CRITICAL **Population incorrect.** The visual abstract reports the population as patients experiencing two or more symptoms for 7 days or less. This is incorrect and refers to the time of enrollment, not the time of intervention. The study actually includes a subgroup of patients 13 days from onset, and 107 patients that had no symptoms at baseline (eFigure 3).

CRITICAL **Early treatment incorrect.** The abstract and paper claim to study *"treatment of early mild to moderate COVID-19."* This is incorrect, treatment was very late, median 6 days, 25+% 8+ days, and with subgroup results up to 13 days. For influenza and oseltamivir or baloxavir, treatment is typically considered early within 24-48 hours [687].

CRITICAL **Author calls for censorship of 670 scientists reporting positive results.** 66 studies by 670 scientists report statistically significant positive results for ivermectin treatment of COVID-19 [623]. One author claimed that reporting efficacy is 'disinformation' and distributed a request to report and censor a US legislator [624-626]. While discussion is warranted for all studies, a call for censorship without analysis raises concern for potential bias. Author provides no basis for the results of the 670 scientists being incorrect and warranting censorship.

CRITICAL **Impossible data identified in three COVID-19 trials by author.** One author is a co-author of three ivermectin COVID-19 trials [161-163] and impossible data has been identified in all of these trials, suggesting caution regarding the reliability of the results.

SERIOUS **Bias due to false positive antigen tests.** Authors accept positive antigen tests for enrollment, where the false positive rate varies depending on the prevalence of COVID-19. If the false positive rate significantly affects the results, we would expect the observed efficacy to vary with COVID-19 prevalence, with lower prevalence leading to higher false positives leading to lower observed efficacy (as more patients did not actually have COVID-19). The change in COVID-19 prevalence and efficacy over time follows this pattern in both the 400μg/kg and 600μg/kg arms. Results may be significantly affected by the inclusion of patients that do not have COVID-19 but had false positive antigen tests [688].

SERIOUS **Participant pickup delay.** A paper on the operation of the trial [536] reveals that delivery was increasingly made to centralized pickup locations and not directly to the participant. Authors indicate they use shipping logs and participant notification of drug receipt. This is unclear because if delivery was based on participant confirmation there would be no need to determine delivery based on shipping logs. This suggests that in at least some cases, delivery time may not have accounted for the time for participant pickup. Therefore, the actual treatment delay may be even longer than reported. This information was not disclosed previously. The paper reports *"the median time from symptom onset to receipt of study drug was 6 days"*, without noting that the receiver may not have been the participant.

SERIOUS **Treatment initiation unknown.** In 2025, authors reported that *"we know that some participants did not start study drug the day it was delivered, but the date of initiation could not be reliably captured."* [689]

SERIOUS **Randomization failure.** The treatment and control groups were drawn from different populations. Patients were allowed to select which medication they would like to test, while the control group contains patients assigned to other medications, some of which specifically requested that medication [690]. Additionally, drug-specific exclusions further modify the populations.

SERIOUS **Low-risk patients.** Authors focus on patients at low risk of COVID-19 severe outcomes, which ensures an underpowered trial, with only one death which may not be due to COVID-19. All-cause mortality and hospitalization become less meaningful, with a significant contribution from non-COVID-19 causes.

SERIOUS **No adherence data or per-protocol analysis.** Authors provide no adherence data. Non-adherence may de-power the trial and may harm randomization.

SERIOUS **Skeptical prior not justified.** The skeptical prior, which reduces the observed efficacy in the post-hoc primary outcome, is not justified based on the prior studies.

SERIOUS **Missing symptom severity mismatch.** The first version of the 600μg/kg paper reports that 2.4% of patients had missing symptom severity (eFigure 4). In the second version 32% of the newly added patients are missing symptom severity.

SERIOUS **Not enough tablets provided.** Participants were supplied 15 7mg tablets and instructed to take the number of tablets to approximate 400μg/kg, however not enough tablets were provided for patients with higher weights, indicating that higher risk patients received lower dosage. 41% of patients had BMI >30 and subgroups include BMI 50. In the journal version authors confirm that 42% of patients exceeded 88kg and did not receive the intended dose.

SERIOUS **Monotherapy with no SOC for most patients.** Authors perform monotherapy and the standard of care for most patients in the study country included no active treatments. Other treatments were very rare - remdesivir 0.3%, monoclonal antibodies 3%, and paxlovid 0.1%. However, extensive and growing research shows greater and synergistic benefits from polytherapy. Many studies use polytherapy and/or the standard of care includes multiple active treatments.

SERIOUS **Over 2x greater severe dyspnea at baseline for ivermectin.** There was over 2x greater severe dyspnea in the ivermectin arm at baseline (1.65% vs. 0.71%), which may be very important for analyzing mortality and hospitalization. Notably, the opposite is the case for fluticasone. The ivermectin placebo arm has less severe dyspnea than fluticasone, despite being larger.

SERIOUS **Safety conclusion removed, suggests bias.** Authors included the conclusion *"Ivermectin at 400 μg/kg was safe and without serious adverse events as compared with placebo"* in the abstract [666]. This was deleted in the JAMA paper [691].

SERIOUS **Authors suggest high-income country healthcare is better, however almost all patients received no active SOC.** Authors suggest the operation in a high-income country with an associated healthcare system is a notable strength, however the study country provided no active treatment for almost all patients in the study, in contrast to many lower income countries that provide multiple treatments. Remdesivir, monoclonal antibodies, and paxlovid were very difficult to obtain and rarely used for outpatients in the study country. High income countries also may have significantly higher conflicts of interest.

SERIOUS **No breakdown of severe outcomes.** No details are provided for the hospitalization and mortality events, which may have been more likely among patients with extremely late treatment, or influenced by the higher baseline severity in the ivermectin arm. No severe outcome results are provided for (relatively) early treatment.

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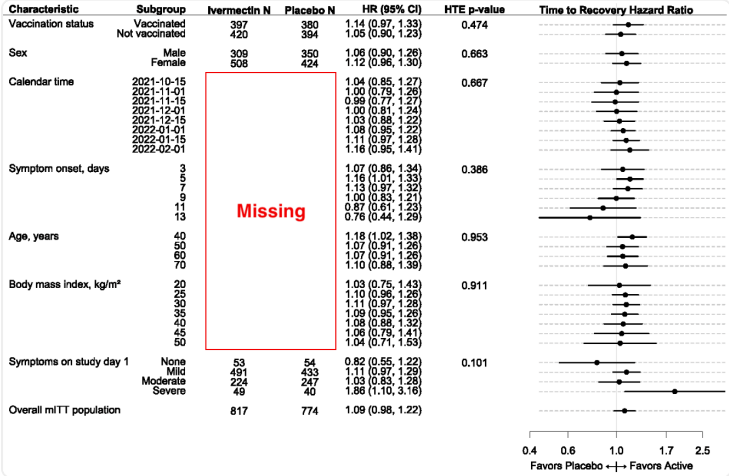
SERIOUS **Missing subgroup counts.** No subgroup counts are provided for several subgroups including treatment delay, while they are provided for baseline symptoms and vaccination status. The number of patients with symptoms ≤3 days may have been very small given the design of the trial. Authors suggest that there are no discrete categories to count the number of participants. While the graph shows estimates from a smoothed model, there are discrete numbers of participants in each group, for example patients treated within 3 days.



MAJOR **Overlapping fluticasone placebo shows very different event numbers.** The ivermectin and fluticasone arms have 79% overlap in time (Jun 23, 2021 - Feb 4, 2022 vs. Aug 10, 2021 - Feb 12, 2022). The ivermectin placebo arm is 20% larger, suggesting approximately 20% more events. However, hospitalization is 3x larger (9 vs. 3), and combined hospitalization, urgent care, ER, and death is 2.2x larger (28 vs. 13).

MAJOR **Overlapping fluticasone placebo shows unexpected baseline numbers.** The ivermectin and fluticasone arms have 79% overlap in time (Jun 23, 2021 - Feb 4, 2022 vs. Aug 10, 2021 - Feb 12, 2022). The ivermectin placebo arm is 20% larger, suggesting approximately 20% more patients for each characteristic. However, ivermectin placebo has less Latino patients than fluticasone and over 2x COPD patients.

MAJOR **Inconsistent calendar time subgroups.** The calendar time subgroups for ivermectin and fluticasone are identical, from Oct 15, 2021 to Feb 1, 2022, however these do not match the reported recruitment periods.

UNKNOWN **Outcome graph presented does not match either medication tested.** In the ACTIV-6 presentation [429] (@9:22) an outcome graph is shown, however there is no indication what treatment it is for. The deaths and hospitalizations do not match those reported for either ivermectin or fluticasone.

Efficacy was higher over calendar time, which may reflect higher efficacy with more recent variants. Efficacy was higher for vaccinated patients.

Data:

Posterior probability ivermectin is effective:

Mean time unwell: 99%
Clinical progression @14 days: 98%
Clinical progression @7 days: 97%

Clinical progression results showing superiority in the preprint [666] *were changed in the journal version - the preprint analysis is the correct prespecified analysis.*

Team comments:

"No differences were observed in relief of mild-to-moderate COVID-19 symptoms" [429] (@24:22)

"No evidence of improvement in time to recovery" [668]

ACTIV trial authors have reported a number of issues that may affect the reliability of the results in ACTIV trials including participant fraud [536], biased participant demographics [692], resource issues that may have led to protocol deviations [692], differences in trial design including inconsistent inclusion/exclusion criteria [692], participant self-selection bias [536,692], underrepresentation of older patients due to web-based recruitment [692], changes in treatment and public health policies during trials [692], treatment delay determination from shipping logs and delivery that may not be directly to the patient [536], variable placebo responses (e.g., oral vs. inhaled) [693], logistical challenges maintaining blinding [693], errors from complex data collection systems [693], unplanned design changes including endpoint changes [693], and inconsistent SoC across trial sites and time periods [693].

For additional issues see [669].

COVID-OUT

Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19

COVID-OUT remote RCT, showing no significant differences compared to a combined metformin/placebo "control" group. Results for other treatments are listed separately - metformin, fluvoxamine.

Authors include metformin patients in the control group, allowing details of adjustments to affect results. Using standard treatment vs. placebo analysis shows 61% lower hospitalization, or 75% lower for patients with onset ≤5 days (not statistically significant with only 7 and 5 events). These results are not reported in the paper or the supplementary appendix, readers need to request the data. Authors note that *"hospitalization is perhaps the most accurate and well-documented end point"*.

There are many major issues as detailed below. We provide more detailed analysis of this study due to widespread incorrect press. Submit Updates or Corrections

CRITICAL	1. Ivermectin vs. placebo analysis - 61% lower hospitalization
CRITICAL	2. Severity mismatch for ivermectin treatment but not for any other medication or control
CRITICAL	3. ER results unreliable, not related to symptoms
CRITICAL	4. Mismatch with reported death and symptoms
CRITICAL	5. Ivermectin vs. placebo symptoms consistent with efficacy
CRITICAL	6. Multiple outcomes missing, including time to recovery
CRITICAL	7. Hypoxemia results unreliable but prioritized
CRITICAL	8. Adverse events suggest authentic ivermectin not taken
CRITICAL	9. Major event counts differ between paper and registry
CRITICAL	10. Baseline data differs between paper and registry
CRITICAL	11. Control group includes metformin, adjustment protocol violation
CRITICAL	12. Primary outcome changes
CRITICAL	13. All 7 secondary outcomes deleted
CRITICAL	14. Metformin/fluvoxamine conclusions opposite of Together Trial, but matching earlier studies on each team
CRITICAL	15. Administration on an empty stomach
CRITICAL	16. Subject to participant fraud
CRITICAL	17. Severity scores not reproducible from released data

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CRITICAL	18. Author calls for censorship of 670 scientists reporting positive results
CRITICAL	19. Impossible data identified in three COVID-19 trials by author
SERIOUS	20. Results delayed 6 months (including life-saving metformin results)
SERIOUS	21. Fewer comorbidities for serious outcomes
SERIOUS	22. Control arm results very different between treatments
SERIOUS	23. COVID-19 specific symptoms hidden in appendix
SERIOUS	24. Authors claim placebo is not better than the treatments
SERIOUS	25. Incorrect claim that no treatment reduced severity
SERIOUS	26. False conclusion
SERIOUS	27. Trial outcomes modified
SERIOUS	28. Very high percentage of missing data
SERIOUS	29. Medication delivery varied significantly
SERIOUS	30. Treatment 3 days for ivermectin, 14 days for metformin and fluvoxamine
SERIOUS	31. SAP dated after trial
SERIOUS	32. Test requirement and delivery prohibits early treatment
SERIOUS	33. Conclusion modified by journal
SERIOUS	34. Symptom results contradictory
SERIOUS	35. Adherence very low
SERIOUS	36. Inconsistent blinding statements
SERIOUS	37. Author indicates a best guess can be used for onset
MAJOR	38. Ivermectin from source chosen has shown lower efficacy
MAJOR	39. Highest mean age for ivermectin, lowest for placebo
MAJOR	40. Adherence subgroups analysed but not reported
UNKNOWN	41. Maximum symptom duration not clear
UNKNOWN	42. No discontinuation due to hospitalization for ivermectin
COMMENT	43. Authors indicate up to 5 day delay in real-world usage

Author responses

20. Results sent to the US government[694]. Note most people live outside the US, and there was no action.

No response for all other items

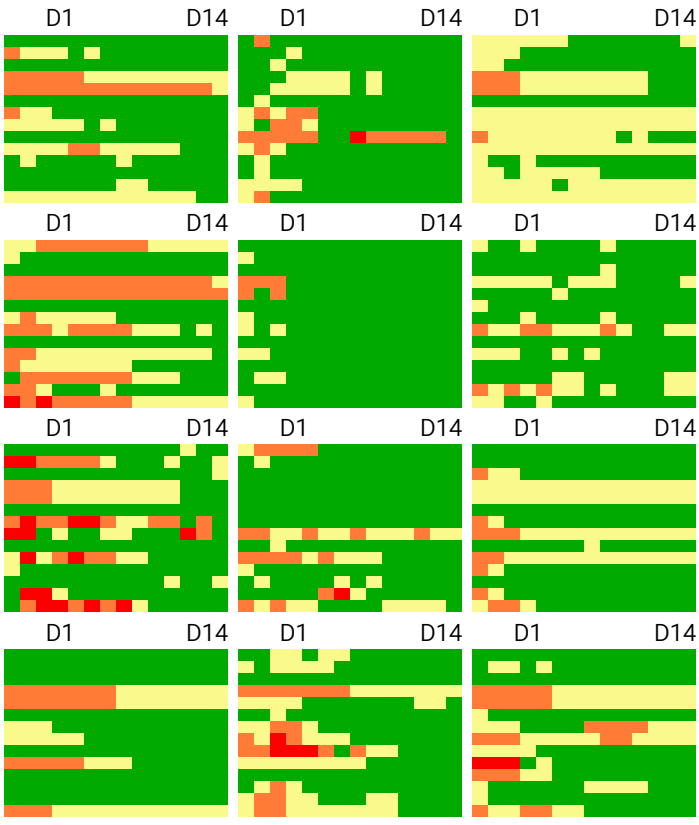
CRITICAL **Ivermectin vs. placebo analysis - 61% lower hospitalization.** Authors include metformin patients in the control group, allowing details of adjustments to affect results. Using standard treatment (ivermectin only) vs. placebo analysis shows more favorable results for ivermectin, with 61% lower hospitalization, or 75% lower for patients with onset ≤5 days (not statistically significant with only 7 and 5 events). Authors note that *"hospitalization is perhaps the most accurate and well-documented end point"*.

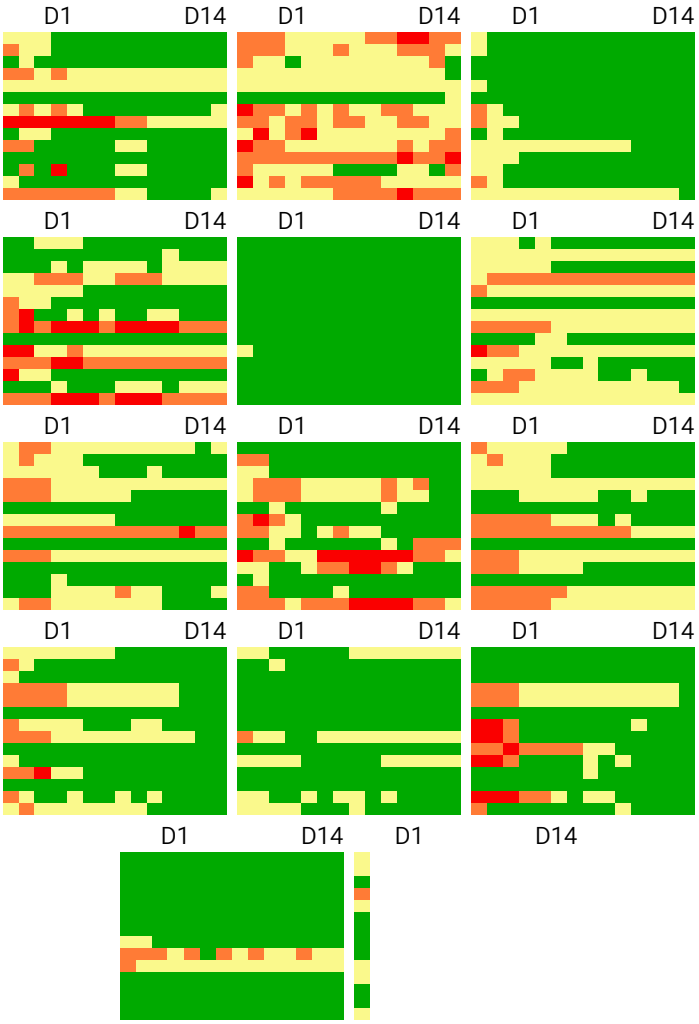
CRITICAL **Severity mismatch for ivermectin treatment but not for any other medication or control.** The table shows the percentage of patients reporting severe dyspnea for each active treatment and respective control. We expect that patients reporting ER visits would be more likely to experience severe dyspnea. This is true for all cases except for ivermectin treatment, suggesting unlucky randomization for ivermectin treatment, or a potential data error. The percentages are with respect to the total number of patients reporting symptom data in each case.

	IVM active	*IVM control*	*MF active*	*MF control*	*FLV active*	*FLV control*
ER	0.0%	9.1%	13.3%	10.0%	10.0%	14.3%
Non-ER	6.1%	6.9%	8.0%	7.8%	6.4%	8.4%

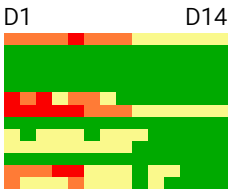
CRITICAL **ER results unreliable, not related to symptoms.** Authors detail why the main hypoxemia results are unreliable, however the ER results appear to be similarly uninformative. ER visits do not appear to be related to symptoms. The mean total COVID-19 symptom score for patients reporting an ER visit is 55 compared to 56 for patients reporting no ER visit (or hospitalization/death). Visualization of the ER patient symptoms raises the question of why most of them went to the ER. Of the 26 patients reporting an ER visit and symptom data, only one ever reported severe dyspnea, 5 more reported at most moderate dyspnea, 11 more reported at most mild dyspnea, and 9 reported no dyspnea at any time. ER patients were less likely to report severe or moderate dyspnea. The decision to go to the ER appears to be more of a personal preference rather than based on symptoms. Patients that signed up for the trial may be especially concerned about PASC for example, and seek help based on potential future problems rather than current symptoms.

Maximum dyspnea severity	*ER patients*	*Non-ER/hosp./death patients*
Severe	3.8%	6.5%
Moderate	19.2%	22.2%

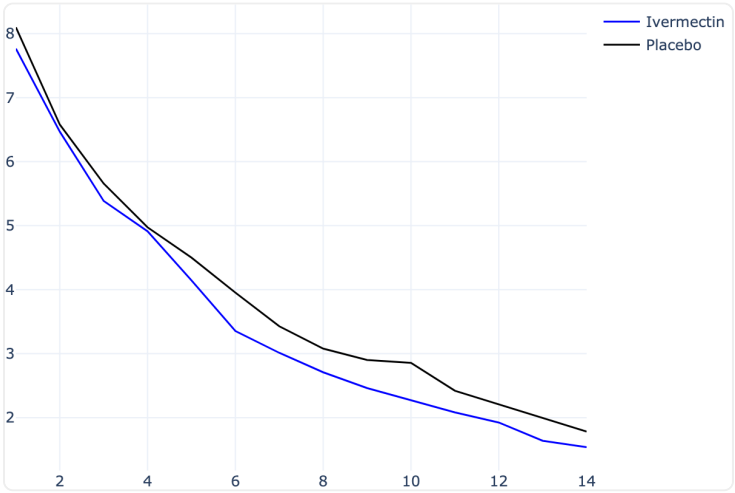




CRITICAL **Mismatch with reported death and symptoms.** There was only one death for a patient that was treated very late (7 days). The patient was not hospitalized. The death is reported within 14 days, however the patient reported symptom data for all 14 days, showing substantial recovery several days prior, with only 2 of 14 symptoms remaining and reported as mild. Data suggests that the death was not due to COVID-19.



CRITICAL **Ivermectin vs. placebo symptoms consistent with efficacy.** Authors include metformin patients in the control group, allowing details of adjustments to affect results. Using standard treatment vs. placebo analysis gives the mean COVID-19 symptom scores below, matching expectation for an effective treatment with the low-risk fast recovering population (note that administration on an empty stomach is expected to delay the time when therapeutic effects may be reached).



CRITICAL **Multiple outcomes missing, including time to recovery.** Multiple outcomes are missing, for example time to recovery (where ACTIV-6 showed superiority of ivermectin): *"Time to meaningful recovery (symptoms or severity improved by one category and sustained for at least 36 hours)"* (protocol page 91). Notably, the definition is less biased than the ACTIV-6 definition, including improvement by one category, making allowance for mild fatigue and cough, and requiring 36 hours sustained rather than 3 days. More notably, the result is not reported.

CRITICAL **Hypoxemia results unreliable but prioritized.** Authors detail why the hypoxemia results are unreliable [695] @28:30, however they are still prioritized in the presentation, and included in the abstract without mentioning that these results are unreliable.

CRITICAL **Adverse events suggest authentic ivermectin not taken.** Adverse events were notably not reported in the paper, other than to note none were serious. Partial information is contained in Table S2 and Figure S5. Notably, there is no significant increase for ivermectin for any of the expected side effects, in contrast to other trials, e.g. [431]. These results are unexpected if patients received and took authentic ivermectin at the dosage indicated. Adverse events have been reported to clinicaltrials.gov, which shows only one adverse avent (neuropathy) for all 410 ivermectin patients, which does not match Table S2 [696].

CRITICAL **Major event counts differ between paper and registry.** The main outcome event numbers are different between the paper and the clinicaltrials.gov registry. Some differences are expected - clinicaltrials shows events for each arm while the paper hides information by using control groups with other treatments instead of placebo comparisons. However, expected matches are different. For example, the paper shows 8/652 hospitalization or death for metformin, while the registry shows 18/652 for all treatment groups with metformin [696]. It appears that authors attempted to submit the combined data that hides the individual arm results (which show lower hospitalization for ivermectin versus placebo) but their submission was not allowed and they subsequently submitted false data. For discussion see [697].

CRITICAL **Baseline data differs between paper and registry.** The baseline data is different between the paper and the clinicaltrials.gov registry. For example, for ivermectin the paper shows 19/410 Asian patients, while the registry shows 13/410 [696]. For metformin, the numbers are 25/663 and 18/663.

CRITICAL **Control group includes metformin, adjustment protocol violation.** The "control" group includes patients receiving metformin, which is known to be beneficial for COVID-19 [698]. Authors present adjusted results however they do not appear to fully account for metformin efficacy. For example, the adjusted result for ivermectin ER/hosp./death is close to the unadjusted result, while a greater difference would be expected based on the metformin efficacy reported (which is not expected to be doubled in the metformin + ivermectin arm). The trial has 5 treatments arms, but is presented as if there was 3, which

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adds complexity, makes the results subject to potential interactions between treatments, and introduces the potential for investigator bias in adjustments. Notably, the protocol specifies primary and secondary adjustments (page 74), and the paper reports only one set of adjustments, which matches neither the primary or secondary adjustments in the protocol.

CRITICAL **Primary outcome changes.** The primary outcome was changed around and after the end of recruitment [699,700].

CRITICAL **All 7 secondary outcomes deleted.** All 7 secondary outcomes were deleted in the clinicaltrials.gov registry on April 18, 2023 [700].

CRITICAL **Metformin/fluvoxamine conclusions opposite of Together Trial, but matching earlier studies on each team.** The Together trial and COVID-OUT both tested metformin and fluvoxamine. Notably, they came to opposite conclusions. In Together, authors found efficacy for fluvoxamine, but the metformin results were so negative that the trial was terminated early. In COVID-OUT it was the opposite, authors (although not the journal editor) found efficacy for metformin, while the fluvoxamine results were so negative that the trial was terminated early [609]. Note that the Together authors include researchers that found fluvoxamine effective in earlier studies, while the COVID-OUT authors include researchers that found metformin effective in earlier studies.

CRITICAL **Administration on an empty stomach.** Authors instructed patients to take ivermectin on an empty stomach, but other treatments with food. Guzzo show that the plasma concentration of ivermectin is much higher when administered with food (geometric mean AUC 2.6 times higher). *"Ivermectin or matching placebo should be taken by mouth on an empty stomach with water. 1 hour before or 2 hours after a meal. All other agents should be taken by mouth at the end of a balanced snack or small meal."*

CRITICAL **Subject to participant fraud.** The self-reported design and absence of professional medical examination opens this kind of remote trial to participant fraud, which may be significant due to extreme politicization in the study country. Participant fraud has been reported for two other remote trials with a shared author [535,536], involving submission of fake surveys and repeated signups.

CRITICAL **Severity scores not reproducible from released data.** Table 3.8.1 in the appendix shows mean total symptom severity scores which cannot be reproduced from the released data. Either the data or the specified scoring system appears to be incorrect.

CRITICAL **Author calls for censorship of 670 scientists reporting positive results.** 66 studies by 670 scientists report statistically significant positive results for ivermectin treatment of COVID-19 [623]. One author claimed that reporting efficacy is 'disinformation' and distributed a request to report and censor a US legislator [624-626]. While discussion is warranted for all studies, a call for censorship without analysis raises concern for potential bias. Author provides no basis for the results of the 670 scientists being incorrect and warranting censorship.

CRITICAL **Impossible data identified in three COVID-19 trials by author.** One author is a co-author of three ivermectin COVID-19 trials [161-163] and impossible data has been identified in all of these trials, suggesting caution regarding the reliability of the results.

SERIOUS **Results delayed 6 months (including life-saving metformin results).** Results were delayed for 6 months with no explanation, with followup ending Feb 14, 2022. Results were not presented until July 8 [701], and they were still not available to the public due to a news embargo for over a month. Embargo and delay of clinical trial results during a pandemic is not consistent with a goal of minimizing mortality and morbidity. Notably authors report very positive results for metformin (although journal editors changed the conclusion as below).

SERIOUS **Fewer comorbidities for serious outcomes.** Patients experiencing serious outcomes are expected to be more likely to have comorbidities, however the opposite is seen.

Outcome	*Comorbidity prevalence*
Non-ER/hosp./death	53%
ER	45%
Hospitalization	12.5%
Death	0%

SERIOUS **Control arm results very different between treatments.** Control arm results are very different between treatments, for example considering hospitalization/death, this was 1.0% for ivermectin treatment vs. 2.7% for metformin control, however it was 1.3% for the ivermectin control. The metformin arm started earlier, however the difference in outcomes is very large given that most patients are in the shared period.

SERIOUS **COVID-19 specific symptoms hidden in appendix.** Authors present results for all symptoms in Figure 2, and for COVID-19 symptoms in the appendix Figure S4. Notably, the COVID-19 specific results are better for ivermectin and especially for fluvoxamine.

SERIOUS **Authors claim placebo is not better than the treatments.** Authors state: *Neither overall symptoms nor Covid-19–specific symptoms were reduced faster with placebo than with any of the trial drugs*. This may be true, Figure S4 shows symptoms were reduced faster with all treatments (with ivermectin and fluvoxamine showing greater improvement than metformin), but the reverse claim is very unusual — placebo is not expected to be better. Note that the graphs and data refer to the control groups including other treatments, while the statement refers to placebo only.

SERIOUS **Incorrect claim that no treatment reduced severity.** Authors claim that *"None of the trial drugs resulted in a lower severity of symptoms than identically matched placebo."* The intended meaning — compared to the "control" groups used, since that is the data reported — is incorrect, multiple results show lower severity in the treatment groups in terms of the symptom scores and severity resulting in hospitalization. Individual results may not reach statistical significance, however ER/hosp./death does in the larger metformin group.

SERIOUS **False conclusion.** Authors claim *"None of the three medications that were evaluated prevented the occurrence of hypoxemia, an emergency department visit, hospitalization, or death associated with Covid-19."* Taking the literal wording, this is false, there were no deaths with fluvoxamine. Taking the likely meaning (no treatment reduced incidence of these events), this is false, reduced incidence is seen in several results (mostly without statistical significance).

SERIOUS **Trial outcomes modified.** Trial outcomes were changed on January 20, 2022 [702], and again on March 2, 2022 [703].

SERIOUS **Very high percentage of missing data.** There is a very high percentage of missing data. 25% of patients have zero symptom data reported for all 14 days in the data file. This does not match the paper which reports 20% of patients did not contribute symptom data (Figure 2).

SERIOUS **Medication delivery varied significantly.** Medication delivery varied significantly over the trial. In this presentation [704], author indicates that delivery was initially local, later via FedEx, was much slower in August, there were delays due to team bandwidth issues, and they only realized they could use FedEx same day delivery in September.

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SERIOUS **Treatment 3 days for ivermectin, 14 days for metformin and fluvoxamine.** Treatment was 14 days for metformin and fluvoxamine, but only 3 days for ivermectin.

SERIOUS **SAP dated after trial.** The SAP is dated February 14, 2022, which authors note is one day before unblinding. However, the protocol notes that the statisticians are unblinded: *"There is one unblinded statistician with two unblinded supporting statisticians on the study team"*, and *"All analyses will be carried out by the un-blinded statisticians"*. The protocol also notes that the SAP will be developed by unblinded statisticians in one case, and blinded in a second case: *"detailed statistical analysis plan will be developed by the unblinded statisticians"*, and *"statistical analysis plan will be developed by the blinded statistician."*

SERIOUS **Test requirement and delivery prohibits early treatment.** The requirement for a positive test and delivery of medication introduces substantial delay and largely excludes the possibility of early treatment. The protocol requires verifiable results using a local laboratory standard which excludes most home antigen tests (supplementary data page 5). Note that the trial results do not generalize to real-world usage, where clinicians recommend treatment immediately on symptoms.

SERIOUS **Conclusion modified by journal.** Author statements indicate that the conclusion was modified by the journal [705,706].

SERIOUS **Symptom results contradictory.** Authors consider only metformin results to be positive (the journal editor considers none to be positive), however the symptom results in Figure S4 show the opposite: ivermectin and fluvoxamine show faster improvement (without statistical significance), while no difference is seen for metformin.

SERIOUS **Adherence very low.** Adherence was very low, with 77% overall reporting 70+% adherence, and 85% for ivermectin reporting 70+% adherence. An author has claimed 85% took all doses but that is contradicted by the 20% reported "Total Interruption or Discontinuation" in Table S2. Numbers for 100% adherence are not provided.

SERIOUS **Inconsistent blinding statements.** Protocol page 12 states that *"The research team statisticians will remain blinded"*, while the supplementary data page 40 states that *"There is one unblinded statistician with two unblinded supporting statisticians on the study team"*.

SERIOUS **Author indicates a best guess can be used for onset.** One author suggests that investigators can use a *"best guess"* if a patient gives a range for time of onset, which would allow a biased investigator to present an incorrect lower average time from onset [707].

MAJOR **Ivermectin from source chosen has shown lower efficacy.** Authors chose to source ivermectin from Edenbridge, which ranked 7 out of 11 brands in In Vitro tests for antiparasitic efficacy [2], requiring 5 days compared to 2 days for the best performing brand, and 3 days for 4 other brands.

MAJOR **Highest mean age for ivermectin, lowest for placebo.** All treatment groups show the same median age (46) in the paper, however the clinicaltrials.gov registry shows the mean ages, and the mean is notably higher in the ivermectin only group (48) versus all other groups, suggesting a skew towards older patients specifically in the ivermectin only group. The control median age for ivermectin is 45 in the paper, while the placebo mean age in the registry is 42, while no other group has a mean age below 46. There is a large difference between the ivermectin and placebo mean ages (48 vs. 42), which is hidden in the paper which shows median 46 vs. 45 ivermectin vs. control

MAJOR **Adherence subgroups analysed but not reported.** Authors indicate they performed subgroup analysis by adherence [695] @18:30, however these results have not been reported.

UNKNOWN **Maximum symptom duration not clear.** The procol excludes patients with >7 days of symptoms, i.e. patients 7 days from onset are included. The paper claims *"less than 7 days"* in one instance and *"within 7 days"* in another. The presentation reports *"<7 days"* [695].

UNKNOWN **No discontinuation due to hospitalization for ivermectin.** Table S2 shows 9 placebo patients discontinued treatment due to hospitalization, compared to zero for ivermectin. While ivermectin patients only received 3 days treatment, they received placebo tablets for the remaining days. If this number is only counting discontinuation during the first three days, the result highlights that treatment was stopped before any patients were hospitalized. The protocol notes *"Study drug will be stopped at the time of hospitalization for any reason"*.

COMMENT **Authors indicate up to 5 day delay in real-world usage.** Authors note up to 11 days treatment delay with a remote clinical trial compared to up to 5 day for "real-world use" [695] @43:00, where the 5 days derives from testing and medical system delays. However, logical real-world use, as used in many locations, is to have the treatment on hand to take immediately.

López-Medina et al.

Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial

SEE ALSO
The Publication of Fraudulent Ivermectin Trials by the High Impact Medical ...
The Potemkin Argument, Part VI: The Ballad of Lopez-Medina
More Fraud Uncovered In The Lopez-Medina Ivermectin Trial Published In J...

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.

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

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 [1].

76 patients were excluded due to control patients receiving ivermectin. However, there was a similar percentage of adverse events like diarrhea, nausea, and

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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.

No pre-registered protocol documentation has been found, the same organization is associated with other COVID trials with extremely high financial conflicts of interest with this trial, and the official registration shows a different code to the paper (IVE-PA_CEIP vs. PI-CEP-1390) [709].

Ivermectin was widely used in the population and available OTC at the time of the study. The paper claims that patients were excluded if they used ivermectin within the last 5 days, however this conflicts with the trial registration which shows that use of ivermectin within the previous 2 days was an exclusion criterion. A post-hoc change to 5 days was made on December 16, 2020 [710,711], which is after enrollment ended (July 15 to November 30, 2020). Ivermectin may retain efficacy far beyond 2 or 5 days. Note that, with 75% of patients having symptoms for 4+ days at baseline, the trial registration allows patients to take ivermectin for a few days after symptoms and then join the placebo arm two days later [712].

The study reports 11.5% blurry vision with ivermectin, consistent with known side effects. However, the study also reports 11.6% blurry vision in the placebo group, which is not consistent with expected side effects of placebo. One possible explanation is that many placebo patients received ivermectin.

This study reportedly has an ethical issue whereby participants were told the study drug was "D11AX22" [713]. 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 [714-716].

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.

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 [440], 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.

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 [717].

For other confounding issues see [718] and additional issues can be found in the comments of the article [719]. Re-analysis of the raw data has been reported to show a significant positive effect [720].

Vallejos et al.

Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial

SEE ALSO
The Publication of Fraudulent Ivermectin Trials by the High Impact Medical ...

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. 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. 25+% of patients were hospitalized within 2/3 days for the placebo/treatment groups (Figure S2).

The companion prophylaxis study *IVERCOR PREP* has reported results in the press and an online presentation [721,722], however these results have not yet been formally published. The prophylaxis study results are very positive and statistically significant, and would be expected to receive priority publication due to the predicted impact on the pandemic and confirmation of previous prophylaxis studies. The lack of formal publication suggests a negative publication bias that may be due to politicization in the authors' location.

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 [450]). 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 [723]).

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 [440], 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.

For other issues see *trialsitenews.com (J)*.

Beltran Gonzalez et al.

Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients with Severe COVID-19: A Randomized Controlled Trial

Another study reports results on a larger group of patients in the same hospital, showing ivermectin mortality RR 0.81 [0.53-1.24] [725].

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 [726] (data from *gob.mx*).

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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%

Several other inconsistencies have been reported [181].

Although the data from this study is reported to be available and has been shared with an anti-treatment group, independent researchers have been unable to obtain the data for verification [181,728].

Popp et al. (version 1)

Ivermectin for preventing and treating COVID-19

SEE ALSO

The Publication of Fraudulent Ivermectin Meta-Analyses and Editorials by th...
The uses and abuses of systematic reviews: the case of ivermectin in Covid...
Rapid Response: Ivermectin in Covid-19

This meta analysis is designed to exclude most studies. Authors select a small subset of studies, with a majority of results based on only 1 or 2 studies. Authors split up studies which dilutes the effects and results in a lack of statistical significance for most outcomes. Authors perform 16+ meta analyses with very few studies in each analysis, and do not combine the evidence from all studies. However, we can consider the probability of the observed results across all outcomes.

Authors find positive results for 11 of 12 primary efficacy outcomes with events, or 16 of 18 including secondary outcomes. One of the primary outcomes and two of the secondary outcomes show statistically significant improvements in isolation. If we assume independence, the probability that 11+ of 12 primary efficacy outcomes were positive for an ineffective treatment is $p = 0.003$. For 16+ of 18 outcomes we get $p = 0.0007$. This simple analysis does not take into account the magnitude of positive effects, or the dependence due to some studies contributing multiple outcomes, however observation suggests that a full analysis of the combined evidence is likely to show efficacy.

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 (*Beltran Gonzalez* "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, which was shown to have no significant effect in *Butler (C)*. 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 [404].

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

Authors include *Beltran Gonzalez* as "moderate" COVID-19, however patients in this study were in severe condition (baseline SatO2 83).

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 [730-732]. 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."

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For discussion of issues added in the updated version see *Popp (B)*.

Popp et al. (version 2)

Ivermectin for preventing and treating COVID-19

SEE ALSO

The Cochrane Review on ivermectin violated its own inclusion criteria for 7...
The Publication of Fraudulent Ivermectin Meta-Analyses and Editorials by th...
The uses and abuses of systematic reviews: the case of ivermectin in Covid...
Rapid Response: Ivermectin in Covid-19

Highly biased meta analysis. Authors originally wrote a highly biased meta analysis that avoided statistical significance on individual outcomes with extreme exclusions[218], although efficacy was still seen when looking across all outcomes. Authors modified the protocol published a short time before, thereby performing a retrospective analysis, clearly designed to produce a desired outcome.

Authors indicated they would update the analysis but did not for a very long time. Authors would have been unable to maintain the lack of statistical significance with the protocol. In this new meta analysis, authors invented a new method to exclude most studies, thereby producing another retrospective analysis, again clearly designed to produce the desired outcome.

Authors included only 14 of 60 studies in the original analysis. For the update, they include even fewer studies, 11 of 87. A key method used was excluding studies without confirmation of prospective registration, however authors violate this to include the Together Trial[734], which accounts for 40% of the patients in the extreme subset selected.

In the companion article for the new exclusion methods, authors note that one indicator for exclusion is if the observed risk reduction is too large[735,736]. The trial resulting in Paxlovid approval would be excluded on this basis.

As just one example of extreme bias, authors classify the Together Trial as low risk of bias. This trial not only has very high risk of bias, but has very high actual known bias. The trial has refused to release data despite pledging to, has reported multiple impossible numbers, and had blinding failure and randomization failure, along with many other issues[161].

As another example of extreme bias, the authors avoid reporting on the 3 prophylaxis RCTs that all reported statistically significant improvement at the time (as of Jan 2023 there are 4, all showing statistically significant improvements), by simply deciding not to do so. Authors know that this shows statistically significant efficacy because they acknowledge reviewing our analysis. Notably, the paxlovid analysis from many of the same authors does not do this. The table shows the inclusion criteria for case results in their paxlovid vs. ivermectin analyses. Using the paxlovid criteria for ivermectin would show statistically significant reduction for both cases and clinical symptoms with ivermectin.

The analysis is also very out of date, including trials only up to April 2022, and including only trials with >1,000 patients since Dec 16, 2021 (yet another cherry-picking mechanism).

With regards to ivmmeta:

- authors claim ivmmeta "states the FLCCC and BIRD as its resources". This is false, there is no relationship with FLCCC or BIRD.

- author's discussion of pooled estimates is disingenuous. ivmmeta reports individual outcome results which are the first item discussed in the abstract. The advantages and disadvantages of pooled estimates are clearly discussed.

- authors statement that there is no prospective protocol is highly disingenuous. The ivmmeta protocol was published in November 2020, is unchanged from the same protocol published in October 2020 used for another medication, and the same protocol is used for 227 treatments. The ivmmeta analysis has been updated regularly with the same protocol. In contrast, authors have published their meta analysis only twice, both times changing the protocol creating a retrospective analysis. Further, authors have created a new unique protocol for this treatment.

- authors claim that "there is no assessment of the risk of bias or the certainty of evidence". This is false, studies are evaluated and 29 are excluded in exclusion analyses. Authors could note that ivmmeta focuses on actual bias as opposed to theoretical risk of bias. While authors assess risk of bias, their assessment is implausible, as shown with the example of the Together Trial above. Note that not only does the Together Trial have extreme actual bias, the theoretical risk of bias is also extremely high due to the conflicts of interest and trial design.

See[218] for many other issues.

Cochrane meta-analysis comparison—paxlovid vs. ivermectin

c19early.org

The Cochrane paxlovid and ivermectin meta-analyses have many shared authors, but a notable bias favoring the high-profit intervention.

	PAXLOVID[737] (2022-2023)	IVERMECTIN[218,219] (2021-2022)
Shared authors	Popp, Reis, Metzendorf, Kranke, Meybohm, Skoetz, Weibel	
Pre-exposure prophylaxis RCTs	Included in protocol	Not included (all 3 show significant efficacy)
Post-exposure prophylaxis RCTs	In protocol but not included[738] (no significant efficacy)	In protocol but not included[739] (96% lower cases with high viral load, p<0.001)
Inclusion criteria	Typical	Novel mechanisms to exclude studies never used before (selectively applied, e.g., *Reis et al.* does not qualify)
Protocol	Changes to include hospitalized patients and active comparator TCM (neither actually included)	Two very different protocols, both specified after all included results were known
Last update	November 2023	June 2022
Author changes	No changes	Gould removed and Reis, Schießer, Hausinger added in second version
Manufacturer revenue	~$25B+	$0 (chose patented molnupiravir)

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Revisions

Please submit updates and corrections at https://c19early.org/imeta.html.

10/20/2026: Updated media analysis.

8/31/2026: Updated media discussion.

8/27/2026: We added synergistic combinations in the preclinical discussion.

8/15/2026: We updated *Sarojvisut* to the full paper. Exclusion analyses now exclude this study due to many critical issues including missing primary outcome results, non-reproducible values, and protocol violations.

8/3/2026: Control group size correction for the viral decay rate [329], and updated computation and details for the gene E and gene N combination [294].

7/23/2026: Added missing median number of days to clinical recovery outcome [161].

5/25/2026: Discussion updates.

5/8/2026: We updated *Hashmi* to the journal version.

5/1/2026: We added *Mouawia*, corrected *Ravikirti (B)* to show late treatment, and excluded *Roy* for data integrity issues.

3/28/2026: We added *Zaher*.

2/8/2026: Updated discussion of treatment delay.

2/7/2026: Updated discussion of fed vs. fasting administration.

1/22/2026: TLDR updates.

1/19/2026: Preclinical updates. Summary of emergent results matching biological mechanisms.

1/13/2026: We added analysis of the efficacy gradient across stages.

1/6/2026: Updated discussion of administration.

11/14/2025: Updated study notes.

11/1/2025: Media coverage analysis and discussion updates.

9/16/2025: We added *Wagstaff (D)*.

6/20/2025: PRINCIPLE trial discussion updates.

4/26/2025: Preclinical updates.

3/20/2025: Preclinical updates.

12/7/2024: Discussion updates.

11/1/2024: We added *Bagheri-Far*.

7/22/2024: We added *Wijewickrema*.

6/13/2024: We added *Hashmi*.

5/3/2024: We added *Varnaseri*.

4/18/2024: We added *Shahin, Gao*.

3/30/2024: Updated discussion of pooled outcomes.

3/29/2024: We added *Siripongboonsitti*.

3/9/2024: Discussion updates.

2/29/2024: We added *Hayward*.

2/23/2024: RCT discussion updates.

2/12/2024: We added *Oranu*.

1/24/2024: We updated the introduction.

12/27/2023: We added *Mikamo*.

9/23/2023: Preclinical updates.

8/10/2023: Preclinical updates.

7/25/2023: We added *Osati*.

7/17/2023: We updated the introduction.

6/11/2023: We added *Llenas-García*.

6/6/2023: We added *Wada*.

4/21/2023: We added *Munir*.

4/18/2023: We updated *Desort-Henin* to the published version.

2/23/2023: We updated *Schilling* to the journal version.

2/2/2023: Scott Alexander response updates.

1/6/2023: We added *Sarojvisut, Desort-Henin*.

12/20/2022: We updated the discussion of heterogeneity and RCTs.

12/15/2022: We added the ACTIV-6 600μg/kg arm *Naggie (B)*.

12/9/2022: We updated *de la Rocha* to the journal version.

10/27/2022: We added *Ochoa-Jaramillo*.

10/21/2022: We updated the ACTIV-6 trial to the journal version.

9/23/2022: We added *Aref (B)*.

9/9/2022: We added *Qadeer*.

8/18/2022: We added *Bramante*.

7/26/2022: We added *Schilling*.

6/24/2022: We added *Mirahmadizadeh*.

6/16/2022: We updated the ACTIV-6 analysis.

6/16/2022: We added *Rezai, Rezai (B)*.

6/12/2022: We added *Naggie*.

6/1/2022: We updated the Together Trial analysis.

5/30/2022: We added *George*.

5/30/2022: We updated the Together Trial analysis.

5/27/2022: We added *de la Rocha*.

4/25/2022: SSC discussion updates.

4/17/2022: We added a section on preclinical research.

4/16/2022: We added discussion of the NIH recommendation.

4/9/2022: We updated the Together Trial analysis.

4/8/2022: We added *Ravikirti*.

4/5/2022: We added preprint discussion based on *Zeraatkar*, and updated the Together Trial analysis.

4/2/2022: We updated the Together Trial analysis.

3/30/2022: We updated *Reis* to the journal version.

3/21/2022: Strongyloides discussion updates.

3/3/2022: We updated *Beltran Gonzalez* to the journal version.

3/2/2022: We added *Soto*.

2/28/2022: We added *Efimenko*.

2/25/2022: We added *Thairu*.

2/23/2022: We updated *Mayer* to the journal version.

2/18/2022: We updated *Lim* to the journal version.

2/2/2022: We added *Manomaipiboon*.

1/28/2022: We added *de Jesús Ascencio-Montiel*.

1/21/2022: We added *Zubair*.

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1/17/2022: We added an explanation of why funnel plot analysis is not valid in this case.

1/16/2022: We added RCT viral clearance analysis and corrected missing symptomatic case results in the case analysis.

1/15/2022: We updated *Kerr* to the journal version.

1/15/2022: We corrected hospitalization group sizes in *Buonfrate*.

1/13/2022: We added *Abbas, Baguma*.

1/11/2022: We updated *Kerr* to the latest results, and added discussion of *Beltran Gonzalez*.

1/7/2022: We updated *Buonfrate* to the journal version, and we updated *Kerr* to the latest results.

12/31/2021: We added *Shimizu*.

12/29/2021: We added *Mustafa*.

12/26/2021: We updated *Kerr* to the revised version of the paper.

12/16/2021: We added *Jamir*.

12/11/2021: We added *Kerr*.

12/8/2021: We added analysis of the number of independent research groups reporting statistically significant positive results.

12/5/2021: We added *Ferreira*.

12/5/2021: We added *Rezk*.

12/3/2021: A note on Bernigaud: continuity correction uses the reciprocal of the contrasting arm *Sweeting*, as detailed in the appendix. We previously limited the size of the control group when showing the total number of patients, however this was confusing for people that did not read the details, as discussed below. The full group size has always been used when computing the RR.

12/1/2021: Strongyloides discussion updates.

11/30/2021: We corrected *Ghauri* to use the event counts.

11/24/2021: We added *Ozer*.

11/24/2021: SSC discussion updates.

11/21/2021: Strongyloides discussion updates.

11/20/2021: Strongyloides discussion updates.

11/19/2021: We added analysis by strongyloides prevalence, and updated it to match the revised classification used in the comparable analysis.

11/19/2021: We added additional exclusion analyses in the supplementary data.

11/18/2021: We incorrectly included *López-Medina* as a study not reporting use of steroids, however they report 6% usage in the control group.

11/18/2021: We added *Samajdar*.

11/17/2021: SSC response.

11/16/2021: Discussion updates.

11/12/2021: We now show the number of studies reporting statistically significant results for any outcome, primary outcomes, and the most serious outcome.

11/9/2021: Discussion updates.

11/5/2021: We added discussion of strongyloides, comparison with the recent molnupiravir approval, and notes on recruitment for remote outpatient delayed treatment trials.

11/3/2021: We added *Lim*.

11/3/2021: Discussion updates.

10/29/2021: Discussion updates including GMK vitamin D analysis.

10/28/2021: Discussion updates.

10/26/2021: We updated the GMK response.

10/24/2021: We added additional exclusion analyses for individual outcomes.

10/21/2021: We added *Borody*.

10/19/2021: Discussion updates.

10/18/2021: *Ghauri* was updated to the journal version.

10/16/2021: We added a summary plot for all results.

10/13/2021: 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.

10/11/2021: 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.

10/8/2021: Discussion updates.

10/7/2021: Samaha et al. has been reported as pending retraction and has been removed. There was no significant change in the results.

10/4/2021: Merck discussion updates.

9/29/2021: We corrected a display error causing a few points to be missing in Fig. 4.

9/27/2021: We added *Mayer*.

9/24/2021: We added a graph of variants over time for the Together Trial discussion and corrected outcome discussion for Popp et al.

9/22/2021: Discussion updates.

9/20/2021: Discussion updates.

9/18/2021: We added *Buonfrate*, and updated discussion of the Together Trial.

9/17/2021: We added study notes.

9/15/2021: Discussion updates.

9/14/2021: FDA discussion updates.

9/9/2021: We added sensitivity analysis to compute the minimum number of studies that need to be excluded in order to avoid showing efficacy. Discussion updates.

9/7/2021: Discussion updates.

9/6/2021: We corrected *Espitia-Hernandez* to use the reported recovery time and added missing recovery and viral clearance results.

9/3/2021: We updated discussion and excluded Carvallo et al. in the exclusion analysis.

8/27/2021: We updated *Morgenstern (B)* with the journal version of the article.

8/26/2021: We updated *Mohan* with the journal version of the article.

8/16/2021: We updated *Reis* with event counts.

8/15/2021: We updated discussion and made the abstract more concise.

8/12/2021: We added *Reis, Elavarasi*.

8/8/2021: We updated discussion in the responses.

8/6/2021: We updated *Behera (B)* with the journal version of the article.

8/5/2021: We added *Mondal*.

8/4/2021: We added discussion of the FDA recommendation.

8/3/2021: We added discussion in the responses section.

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8/2/2021: We added analysis restricted to serious outcomes and analysis restricted to recovery, and we added discussion in the responses section.

7/31/2021: We added discussion in the responses section related to *in vitro* evidence and therapeutic concentrations.

7/29/2021: We added discussion in the responses section.

7/20/2021: We updated *Hashim* with the journal version of the article.

7/16/2021: We updated *Ravikirti (B)* with the journal version of the article.

7/15/2021: Elgazzar et al. was withdrawn by the preprint server and has been removed.

7/9/2021: We added *Hazan (B)*.

7/8/2021: We updated *Cadegiani* to the journal version.

7/6/2021: 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.

7/3/2021: We added *Vallejos*.

7/2/2021: We updated Niaee et al. to the journal version.

6/21/2021: We added more information to the abstract.

6/19/2021: We updated *Bryant* to the journal version.

6/19/2021: *Beltran Gonzalez* was incorrectly included in the peer-reviewed analysis.

6/18/2021: We added *Krolewiecki*.

6/15/2021: We added *Aref*.

6/7/2021: We added *Hariyanto*.

6/5/2021: We added *Ahsan*.

6/2/2021: We added *Abd-Elsalam*.

5/31/2021: *Biber* was updated to the preprint.

5/26/2021: Samaha et al. was updated to the journal version.

5/18/2021: We added analysis of Merck's recommendation.

5/17/2021: We added *Szente Fonseca*.

5/15/2021: We updated the discussion of the WHO analysis.

5/13/2021: We updated *Mahmud* to the journal version.

5/10/2021: We added *Faisal*.

5/10/2021: We added additional information in the abstract.

5/8/2021: We added *Merino*.

5/7/2021: We updated *Shahbaznejad* to the journal version, which includes additional outcomes not reported earlier.

5/6/2021: We updated *Chahla* to the Research Square preprint.

5/6/2021: We added a comparison of CDC recommendations.

5/6/2021: We added mechanical ventilation and ICU admission analysis.

5/6/2021: We updated discussion based on peer review including discussion of heterogeneity, exclusion based sensitivity analysis, and search criteria.

5/5/2021: We updated *Okumuş* to the journal paper.

5/5/2021: 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.

5/4/2021: We added *Loue*.

4/30/2021: We added analysis of the WHO meta-analysis and updated *Kory* to the journal version.

4/28/2021: We added the WHO meta-analysis results for comparison.

4/27/2021: We added analysis restricted to hospitalization results and a comparison with the evidence base used in the approval of other COVID-19 treatments.

4/26/2021: We added notes on heterogeneity.

4/25/2021: We updated *Biber* to the latest results reported at the International Ivermectin for Covid Conference.

4/18/2021: We updated *Morgenstern* to the preprint.

4/16/2021: We added *Morgenstern*.

4/14/2021: We added *Seet*.

4/10/2021: We added *Kishoria*.

4/9/2021: We corrected a duplicate entry for *Bukhari*.

4/7/2021: We identified studies where minimal detail is currently available in the forest plots.

4/5/2021: We added *Mourya*.

4/4/2021: We added event counts to the forest plots.

3/31/2021: We updated *Chahla (B)* to the preprint.

3/30/2021: We added *Chahla*.

3/28/2021: We highlighted and added discussion for studies that use combined treatments.

3/26/2021: We added *Tanioka*.

3/25/2021: We added *Huvemek*.

3/17/2021: We added *Nardelli*.

3/12/2021: We added *Bryant, Roy*.

3/10/2021: We added *Pott-Junior*.

3/6/2021: We added *Chowdhury* and we identify studies that compare with another treatment.

3/5/2021: We added discussion of pooled effects (we show both pooled effects and individual outcome results).

3/4/2021: We added *López-Medina*, and we added more information in the abstract.

3/3/2021: 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.

3/2/2021: We updated *IVERCOR PREP* with the latest results *Vallejos (B)*.

2/27/2021: We added analysis restricted to peer reviewed studies.

2/24/2021: 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.

2/23/2021: We added *Beltran Gonzalez*.

2/18/2021: We updated *Babalola* to the journal version of the paper.

2/17/2021: We added *Elalfy*, and we added analysis restricted to viral clearance outcomes, and mortality results restricted to RCTs.

2/16/2021: We updated *Behera* to the journal version of the paper.

2/15/2021: We added *Behera (B)*.

2/14/2021: We added analysis restricted to COVID-19 case outcomes, and we added additional results in the abstract.

2/12/2021: We added *Biber*.

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2/11/2021: We added more details on the analysis of prospective vs. retrospective studies.

2/10/2021: We added *Lima-Morales*.

2/5/2021: We updated *Bukhari* to the preprint.

2/2/2021: We added *Mohan*.

1/26/2021: We updated *Shouman (B)* with the journal version of the article.

1/25/2021: We updated *IVERCOR PREP* with the recently released results.

1/19/2021: We added *Shahbaznejad* and Samaha et al. *Chaccour (B)* was updated to the journal version of the paper.

1/17/2021: We added *Bukhari*.

1/16/2021: We moved the analysis with exclusions to the main text, and added additional commentary.

1/15/2021: We added the effect measured for each study in the forest plots.

1/12/2021: We added *Okumuş*.

1/11/2021: We added *Chahla (B)*.

1/10/2021: We put all prophylaxis studies in a single group.

1/9/2021: We added *Ravikirti (B)*. 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.

1/7/2021: We added direct links to the study details in the chronological plots.

1/6/2021: We added *Babalola*.

1/5/2021: 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.

12/31/2020: We added additional details about the studies in the appendix.

12/29/2020: We added meta-analysis excluding late treatment.

12/27/2020: We added the total number of authors and patients.

12/26/2020: We added *IVERCOR PREP, Carvallo (B)*.

12/17/2020: We added *Alam*.

12/16/2020: We added *Ghauri*.

12/11/2020: We added *Soto-Becerra*.

12/7/2020: We added *Chaccour (B)*.

12/2/2020: We added *Ahmed*.

11/26/2020: Initial revision.

Appendix 1. Methods and Data

Search methods

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org, which regularly receives notification of studies upon publication. Search terms are ivermectin and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of 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. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. However for ivermectin certain high-profile studies that would normally be retracted currently remain published due to the politicization of this treatment—for transparency, and because inclusion does not affect the results, we currently include these studies.

Effect extraction

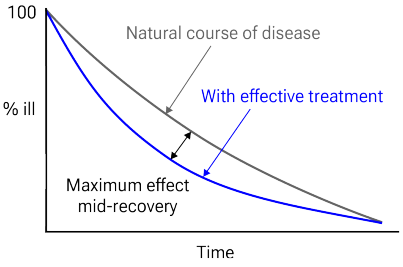

Fig. 42. Mid-recovery results can more accurately reflect efficacy when almost all patients recover. *Mateja et al.* confirm that intermediate viral load results more accurately reflect hospitalization/death.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome-specific analyses. For example, if effects for mortality and cases are reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral outcomes. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction [753]. 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.

Statistical methods

Forest plots are computed using PythonMeta [754] with the DerSimonian and Laird random-effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang (C) et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 [749]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.15.2) with scipy (1.18.1), pythonmeta (1.26), numpy (2.5.4), statsmodels (0.15.0), and plotly (6.9.0). Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. 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 be-

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low. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 is used to parse PDF documents.

For treatments that have multiple mechanisms of action relevant to all stages—blocking initial infection, minimizing viral replication, and mitigating secondary complications—we may find a gradient of efficacy across stages, with efficacy increasing as we go from late treatment → early treatment → prophylaxis. To evaluate this hypothesis we performed meta-regression with robust variance estimation. Stages were categorized into an ordinal scale with prophylaxis at 1, early treatment at 2, and late treatment at 3. The dependent variable was the natural logarithm of the Risk Ratio (ln(RR)) for each outcome, and the independent variable was the ordinal stage. We used the DerSimonian and Laird (DL) method-of-moments estimator to estimate residual heterogeneity (τ^2) around the meta-regression line, with weights assigned using the inverse-variance method ($w_i = 1 / (v_i + \tau^2)$). The meta-regression slope (β) represents the change in ln(RR) per unit increase in stage. A positive slope indicates that efficacy diminishes (the Risk Ratio increases) for later intervention.

When evaluating potential effect modification across groups, we use an interaction test as described by *Altman (C) et al.* We compared the log-transformed relative risks using a *z*-test, deriving the standard error of the difference from the 95% confidence intervals. A two-sided interaction *p*-value of < 0.05 was considered a statistically significant difference in treatment effect between the groups.

Quality evaluation

Cochrane RoB 2/ROBINS-I are often used to evaluate studies, and have the advantage of providing standardized rules that can be applied with minimal understanding of the domain and study. However, the rules do not account for many real-world issues, often overemphasize or underemphasize others, and studies show low inter-rater reliability[765]. Certain domains are more applicable for these tools, however the time-sensitive nature of a pandemic, with significant mortality for every day of delay in evidence assessment, and the characteristics of COVID-19 make them inappropriate for this domain. This can be demonstrated with examples where expert RoB 2/ROBINS-I ratings do not match reality for COVID-19. *Popp (B) et al.* use RoB 2 to classify *Reis et al.* as low risk of bias, however this is the opposite of reality—the trial not only has very high risk of bias, but has very high actual known bias, refusing to release data despite pledging to, reporting multiple impossible numbers, having blinding and randomization failure, and many other issues[161]. *Axfors et al.* use RoB 2 to classify *Horby et al.* as low risk of bias, however this is the opposite of reality—the very late treatment and excessive dosage used produces results with no relevance to recommended usage. HCQ shows poor results with late treatment and excessive dosage, and the combination shows harm[C]. *Hempenius et al.* use ROBINS-I to classify 33 studies for HCQ. The two rated as having the lowest risk of bias[763,764] are far from the most informative. Both involve very late treatment, providing no information on recommended usage, and ROBINS-I does a very poor job of accounting for the impact of confounding factors[D].

Our quality evaluation focuses on known issues and bias, and the potential impact on outcomes, rather than just the risk of bias. The estimated potential impact of each confounding factor, and the direction of the impact is considered. For example, consider a study that shows significantly lower risk, the value of the study varies significantly if confounding points to an underestimate or an overestimate of efficacy. In one case, the real effect may be null, while the other case provides stronger evidence of efficacy (which may be greater than the study shows). Analysis focusing on the risk of bias, while simpler, may penalize studies for theoretical or technical issues that have no or minimal impact on outcomes. Analysis also depends on the outcome, for example certain issues are less relevant for objective outcomes such as mortality. Inaccurate penalization, and inaccurate high-quality evaluation in the face of known major issues affecting outcomes, increases in significance during a pandemic when immediate recognition of new evidence is critical, and when considering all global studies, as required during a pandemic. Investigators in other countries may have different customs for design, analysis, and reporting, and different English language skills, however they may not be less diligent or have greater bias. Investigators in lower-pharmaceutical-profit countries may have lower bias towards profitable interventions.

Treatment time

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective[222,223].

Living analysis

This is a living analysis and is updated regularly. We received no funding, this research is done in our spare time. We have no affiliation with any pharmaceutical companies, supplement companies, governments, political parties, or advocacy organizations.

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://c19early.org/imeta.html.

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 pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Abbas, 12/31/2021, Double Blind Randomized Controlled Trial, placebo-controlled, China, peer-reviewed, 3 authors, study period May 2021 - August 2021, dosage 300µg/kg days 1-5, excluded in exclusion analyses: very minimal patient information, three different results for the recovery outcome, selective omission of the statistically significant recovery p-value, and other inconsistencies.	risk of death, 4.0% higher, RR 1.04, *p* = 1.00, treatment 1 of 99 (1.0%), control 1 of 103 (1.0%).
	deterioration of 2 or more points, 40.5% lower, RR 0.59, *p* = 0.54, treatment 4 of 99 (4.0%), control 7 of 103 (6.8%), NNT 36.
	escalation of care, 14.9% lower, RR 0.85, *p* = 0.82, treatment 9 of 99 (9.1%), control 11 of 103 (10.7%), NNT 63.
	fever during study, 17.9% lower, RR 0.82, *p* = 0.58, treatment 15 of 99 (15.2%), control 19 of 103 (18.4%), NNT 30.
	risk of no recovery, 35.6% lower, RR 0.64, *p* = 0.04, treatment 26 of 99 (26.3%), control 42 of 103 (40.8%), NNT 6.9, primary outcome.
	recovery time, 30.8% lower, relative time 0.69, *p* = 0.08, treatment 99, control 103, primary outcome.
Ahmed, 12/2/2020, Double Blind Randomized Controlled Trial, Bangladesh, peer-reviewed, mean age 42.0, 15	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%), NNT 6.3, relative risk is not 0 because of continuity correction due to zero

authors, average treatment delay 3.83 days, dosage 12mg days 1-5, the ivermectin + doxycycline group took only a single dose of ivermectin.	events (with reciprocal of the contrasting arm), day 7, fever, ivermectin (5 days), primary outcome.
	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%), NNT 10, day 7, fever, ivermectin (1 day) + doxycycline.
	risk of no viral clearance, 75.6% lower, HR 0.24, $p = 0.03$, treatment 11 of 22 (50.0%), control 20 of 23 (87.0%), NNT 2.7, adjusted per study, inverted to make HR<1 favor treatment, day 7, ivermectin (5 days).
	risk of no viral clearance, 56.5% lower, HR 0.43, $p = 0.22$, treatment 16 of 23 (69.6%), control 20 of 23 (87.0%), NNT 5.8, adjusted per study, inverted to make HR<1 favor treatment, day 7, ivermectin (1 day) + doxycycline.
	risk of no viral clearance, 63.0% lower, HR 0.37, $p = 0.02$, treatment 5 of 22 (22.7%), control 14 of 23 (60.9%), NNT 2.6, adjusted per study, inverted to make HR<1 favor treatment, day 14, ivermectin (5 days).
	risk of no viral clearance, 41.2% lower, HR 0.59, $p = 0.19$, treatment 9 of 23 (39.1%), control 14 of 23 (60.9%), NNT 4.6, adjusted per study, inverted to make HR<1 favor treatment, 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, peer-reviewed, 7 authors, study period February 2021 - March 2021, dosage not specified, trial NCT04716569 (history).	**relative duration of fever, 63.2% lower, relative time 0.37, $p < 0.001$**, treatment 57, control 57, primary outcome.
	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 viral clearance, 78.6% lower, RR 0.21, $p = 0.004$, treatment 3 of 57 (5.3%), control 14 of 57 (24.6%), NNT 5.2.
	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, peer-reviewed, baseline oxygen required 8.3%, 10 authors, study period May 2020 - November 2020, dosage 12mg or 6mg q84h for two weeks, this trial compares with another treatment - results may be better when compared to placebo.	**adjusted risk of viral+ at day 5, 63.9% lower, RR 0.36, $p = 0.11$**, treatment 40, control 20, adjusted per study, inverted to make RR<1 favor treatment.
	relative ΔSpO_2 (unadjusted), 41.5% better, RR 0.59, $p = 0.07$, treatment 38, control 18, figure 3.
	risk of no viral clearance, 58.0% lower, HR 0.42, $p = 0.01$, treatment 20, control 20, inverted to make HR<1 favor treatment, 12mg - Cox proportional hazard model.
	risk of no viral clearance, 40.5% lower, HR 0.60, $p = 0.12$, treatment 20, control 20, inverted to make HR<1 favor treatment, 6mg - Cox proportional hazard model.
	time to viral-, 49.2% lower, relative time 0.51, $p = 0.02$, treatment 20, control 20, 12mg, primary outcome.
	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, placebo-controlled, Israel, peer-reviewed, 10 authors, study period 12 May, 2020 - 31 October, 2020, average treatment delay 4.0 days, dosage 12mg days 1-3, 15mg for patients ≥70kg, trial NCT04429711 (history).	**risk of hospitalization, 70.2% lower, RR 0.30, $p = 0.34$**, treatment 1 of 47 (2.1%), control 3 of 42 (7.1%), NNT 20.
	risk of no viral clearance, 61.6% lower, RR 0.38, $p = 0.02$, treatment 8 of 47 (17.0%), control 17 of 42 (40.5%), NNT 4.3, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, Ct>30, multivariable, day 8.
	risk of no viral clearance, 39.0% lower, RR 0.61, $p = 0.09$, treatment 13 of 47 (27.7%), control 21 of 42 (50.0%), NNT 4.5, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, Ct>30, multivariable, day 6, primary outcome.
	risk of no viral clearance, 73.0% lower, RR 0.27, $p = 0.008$, treatment 3 of 23 (13.0%), control 14 of 29 (48.3%), NNT 2.8, culture viability.
	risk of no viral clearance, 70.2% lower, RR 0.30, $p = 0.14$, treatment 2 of 47 (4.3%), control 6 of 42 (14.3%), NNT 10.0, non-infectious samples (Ct>30 or non-viable culture), day 10.
	risk of no viral clearance, 82.1% lower, RR 0.18, $p = 0.01$, treatment 2 of 47 (4.3%), control 10 of 42 (23.8%), NNT 5.1, non-infectious samples (Ct>30 or non-viable culture), day 8.
	risk of no viral clearance, 75.6% lower, RR 0.24, $p = 0.02$, treatment 3 of 47 (6.4%), control 11 of 42 (26.2%), NNT 5.0, non-infectious samples (Ct>30 or non-viable culture), day 6.
	risk of no viral clearance, 65.1% lower, RR 0.35, $p = 0.05$, treatment 4 of 28 (14.3%), control 9 of 22 (40.9%), NNT 3.8, non-infectious samples (Ct>30 or non-viable culture), day 4.
	risk of no viral clearance, 51.9% lower, RR 0.48, $p = 0.08$, treatment 7 of 47 (14.9%), control 13 of 42 (31.0%), NNT 6.2, Ct>30, day 10.
	risk of no viral clearance, 57.9% lower, RR 0.42, $p = 0.02$, treatment 8 of 47 (17.0%), control 17 of 42 (40.5%), NNT 4.3, Ct>30, day 8.
	risk of no viral clearance, 44.7% lower, RR 0.55, $p = 0.049$, treatment 13 of 47 (27.7%), control 21 of 42 (50.0%), NNT 4.5, Ct>30, day 6.

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	risk of no viral clearance, 31.9% lower, RR 0.68, p = 0.16, treatment 13 of 28 (46.4%), control 15 of 22 (68.2%), NNT 4.6, Ct>30, day 4.
Borody, 10/19/2021, retrospective, Australia, preprint, 2 authors, study period 1 June, 2021 - 30 September, 2021, 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%), NNT 100, 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%), NNT 9.2, primary outcome.
Bramante, 8/18/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 37 authors, average treatment delay 4.6 days, dosage 430µg/kg days 1-3, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04510194 (history) (COVID-OUT).	risk of death, 197.1% higher, RR 2.97, p = 1.00, treatment 1 of 408 (0.2%), control 0 of 396 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 28.
	risk of death/hospitalization, 26.7% lower, RR 0.73, p = 0.66, treatment 4 of 406 (1.0%), control 5 of 394 (1.3%), NNT 352, odds ratio converted to relative risk.
	risk of progression, 36.8% higher, RR 1.37, p = 0.33, treatment 23 of 406 (5.7%), control 16 of 394 (4.1%), odds ratio converted to relative risk, combined ER, hospitalization, death, mismatch with symptom data.
	risk of progression, 3.7% higher, RR 1.04, p = 0.78, treatment 105 of 407 (25.8%), control 96 of 391 (24.6%), odds ratio converted to relative risk, combined hypoxemia, ER, hospitalization, death, primary outcome, authors note hypoxemia data unreliable.
	risk of hospitalization, 60.8% lower, RR 0.39, p = 0.28, treatment 2 of 206 (1.0%), control 5 of 202 (2.5%), NNT 66, IVM vs. placebo.
	risk of hospitalization, 74.6% lower, RR 0.25, p = 0.37, treatment 1 of 137 (0.7%), control 4 of 139 (2.9%), NNT 47, IVM vs. placebo, ≤5 days from onset.
	risk of hospitalization, 70.1% lower, RR 0.30, p = 0.12, treatment 3 of 406 (0.7%), control 5 of 202 (2.5%), NNT 58, IVM and IVM+MF vs. placebo.
	risk of hospitalization, 41.8% lower, RR 0.58, p = 0.50, treatment 3 of 406 (0.7%), control 5 of 394 (1.3%), NNT 189, IVM and IVM+MF vs. placebo and MF.
Bukhari, 1/16/2021, Randomized Controlled Trial, Pakistan, preprint, 10 authors, study period 15 March, 2020 - 15 June, 2020, dosage 12mg single dose, trial NCT04392713 (history).	risk of no viral clearance, 82.4% lower, RR 0.18, p < 0.001, treatment 4 of 41 (9.8%), control 25 of 45 (55.6%), NNT 2.2, day 7, primary outcome.
	risk of no viral clearance, 38.7% lower, RR 0.61, p < 0.001, treatment 24 of 41 (58.5%), control 43 of 45 (95.6%), NNT 2.7, day 3.
Buonfrate, 9/6/2021, Double Blind Randomized Controlled Trial, Italy, peer-reviewed, 18 authors, study period 31 July, 2020 - 8 June, 2021, average treatment delay 4.0 days, dosage 1200µg/kg days 1-5, arm B 600μg/kg, arm C 1200μg/kg, trial NCT04438850 (history) (COVER), excluded in exclusion analyses: significant unadjusted group differences, with 3 times as many patients in the ivermectin arms having the baseline visit in a hospital setting, and arm C having large differences in baseline gender, weight, cough, pyrexia, and anosmia, excessive dose for arm C.	risk of hospitalization, 92.3% lower, RR 0.08, p = 0.03, treatment 0 of 600 (0.0%), control 6 of 600 (1.0%), NNT 100, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 1.
	risk of hospitalization, 610.0% higher, RR 7.10, p = 0.11, treatment 3 of 30 (10.0%), control 0 of 31 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), arm C, very high dose, poorly tolerated with low compliance, poorly tolerated, low compliance.
	relative change in viral load, RR 0.80, p = 0.59, treatment mean 2.5 (±2.2) n=28, control mean 2.0 (±4.4) n=29, day 7, arm B, primary outcome.
	relative change in viral load, RR 0.69, p = 0.07, treatment mean 2.9 (±1.6) n=30, control mean 2.0 (±2.1) n=29, day 7, arm C, primary outcome.
Cadegiani, 11/4/2020, prospective, Brazil, peer-reviewed, 4 authors, average treatment delay 2.9 days, 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 group retrospectively obtained from untreated patients in the same population.	risk of death, 78.3% lower, RR 0.22, p = 0.50, treatment 0 of 110 (0.0%), control 2 of 137 (1.5%), NNT 68, 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%), NNT 15, relative risk is not 0 because of 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%), NNT 5.1, 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, 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.	risk of death, 85.4% lower, RR 0.15, p = 0.08, treatment 1 of 32 (3.1%), control 3 of 14 (21.4%), NNT 5.5, moderate/severe patients, the only treatment death was a patient already in the ICU before treatment, primary outcome.
Chaccour (B), 12/7/2020, Double Blind Randomized Controlled Trial, Spain, peer-reviewed, 24 authors, study period 31 July, 2020 - 11 September, 2020, average treatment delay 1.0 days, dosage 400µg/kg single dose, trial NCT04390022 (history) (SAINT).	risk of symptoms, 96.0% lower, OR 0.04, p < 0.05, treatment 12, control 12, logistic regression, chance of presenting any symptom, RR approximated with OR.
	viral load, 94.8% lower, relative load 0.05, p = 0.02, treatment 12, control 12, day 7 mid-recovery, relative viral load, geometric mean of gene E and gene N, p-value estimated with a Welch test assuming log-normal viral-load distributions and estimated log-scale standard deviations from the IQRs, Supplementary Table S1.

	risk of no viral clearance, 8.0% lower, RR 0.92, *p* = 1.00, treatment 12, control 12, primary outcome.
Chahla, 3/30/2021, Cluster Randomized Controlled Trial, Argentina, peer-reviewed, 9 authors, study period September 2020 - January 2021, dosage 24mg days 1, 8, 15, 22, trial NCT04784481 (history).	**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%), NNT 8.3, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, logistic regression, multivariable, primary outcome.
Chowdhury, 7/14/2020, Randomized Controlled Trial, Bangladesh, peer-reviewed, 6 authors, study period 2 May, 2020 - 5 June, 2020, dosage 200µg/kg single dose, this trial compares with another treatment - results may be better when compared to placebo, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary, trial NCT04434144 (history).	**risk of hospitalization, 80.6% lower, RR 0.19, *p* = 0.23**, treatment 0 of 60 (0.0%), control 2 of 56 (3.6%), NNT 28, 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%), NNT 2.6, mid-recovery day 5.
	recovery time, 15.2% lower, relative time 0.85, *p* = 0.07, treatment 60, control 56.
	risk of no viral clearance, 80.6% lower, RR 0.19, *p* = 0.23, treatment 0 of 60 (0.0%), control 2 of 56 (3.6%), NNT 28, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), primary outcome.
	time to viral-, 4.3% lower, relative time 0.96, *p* = 0.23, treatment 60, control 56.
de Jesús Ascencio-Montiel, 1/24/2022, retrospective, Mexico, peer-reviewed, 10 authors, dosage 6mg days 1-2, this trial uses multiple treatments in the treatment arm (combined with AZ, acetaminophen, aspirin) - results of individual treatments may vary.	**risk of death/hospitalization, 59.0% lower, RR 0.41, *p* < 0.001**, treatment 7,898, control 20,150, adjusted per study, multivariable, primary outcome.
	risk of death/hospitalization, 71.0% lower, RR 0.29, p < 0.001, treatment 5,557, control 12,526, adjusted per study, with phone call followup, multivariable.
	risk of death, 15.0% lower, RR 0.85, *p* = 0.16, treatment 101 of 7,898 (1.3%), control 303 of 20,150 (1.5%), NNT 445, unadjusted, excluded in exclusion analyses: unadjusted results with alternate outcome adjusted results showing significant changes with adjustments.
	risk of mechanical ventilation, 9.1% lower, RR 0.91, p = 0.51, treatment 77 of 7,898 (1.0%), control 216 of 20,150 (1.1%), NNT 1031, unadjusted, excluded in exclusion analyses: unadjusted results with alternate outcome adjusted results showing significant changes with adjustments.
	risk of hospitalization, 47.6% lower, RR 0.52, *p* < 0.001, treatment 485 of 7,898 (6.1%), control 2,360 of 20,150 (11.7%), NNT 18, unadjusted, excluded in exclusion analyses: unadjusted results with alternate outcome adjusted results showing significant changes with adjustments.
	risk of progression, 41.8% lower, RR 0.58, *p* < 0.001, treatment 435 of 7,898 (5.5%), control 1,906 of 20,150 (9.5%), NNT 25, unadjusted,

	ER, excluded in exclusion analyses: unadjusted results with alternate outcome adjusted results showing significant changes with adjustments.
de la Rocha, 5/23/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, peer-reviewed, 21 authors, study period 1 July, 2020 - 29 January, 2021, dosage 12mg days 1-3, trial NCT04407507 (history), excluded in exclusion analyses: data mismatch, no response from authors.	**risk of progression to serious adverse events, 186.7% higher, RR 2.87, *p* = 1.00**, treatment 1 of 30 (3.3%), control 0 of 26 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	viral load, 2.4% lower, relative load 0.98, *p* = 0.64, treatment mean 33.74 (±4.77) n=30, control mean 32.94 (±7.74) n=26, day 14.
	viral load, 7.8% lower, relative load 0.92, *p* = 0.04, treatment mean 30.64 (±3.74) n=30, control mean 28.25 (±4.21) n=26, mid-recovery, day 5.
Elalfy, 2/16/2021, retrospective, Egypt, 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 viral clearance, 86.9% lower, RR 0.13, *p* < 0.001**, treatment 7 of 62 (11.3%), control 44 of 51 (86.3%), NNT 1.3, day 15, primary outcome.
	risk of no viral clearance, 58.1% lower, RR 0.42, *p* < 0.001, treatment 26 of 62 (41.9%), control 51 of 51 (100.0%), NNT 1.7, day 7.
Espitia-Hernandez, 8/15/2020, retrospective, Mexico, 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%), NNT 1.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), primary outcome.
Faisal, 5/10/2021, Randomized Controlled Trial, Pakistan, peer-reviewed, 3 authors, study period 5 April, 2020 - 30 May, 2020, 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%), NNT 3.8, 6-8 days, mid-recovery, primary outcome.
	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%), NNT 5.6, 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%), NNT 8.3, 9-10 days.
Ghauri, 12/15/2020, retrospective, Pakistan, peer-reviewed, 6 authors, dosage 12mg days 1-6.	**risk of fever, 92.2% lower, RR 0.08, p = 0.04**, treatment 0 of 37 (0.0%), control 7 of 53 (13.2%), NNT 7.6, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of fever, 86.4% lower, RR 0.14, *p* < 0.001, treatment 2 of 37 (5.4%), control 21 of 53 (39.6%), NNT 2.9, day 10.
	risk of fever, 55.7% lower, RR 0.44, *p* < 0.001, treatment 13 of 37 (35.1%), control 42 of 53 (79.2%), NNT 2.3, day 7.

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	risk of fever, 42.2% lower, RR 0.58, $p < 0.001$, treatment 21 of 37 (56.8%), control 52 of 53 (98.1%), NNT 2.4, day 5.
Kamal, 9/1/2020, Randomized Controlled Trial, trial NCT04425707 (history).	Estimated 100 patient RCT with results unknown and over 6 years late.
Krolewiecki, 6/18/2021, Randomized Controlled Trial, Argentina, peer-reviewed, 23 authors, study period 18 May, 2020 - 9 September, 2020, average treatment delay 3.5 days, dosage 600µg/kg days 1-5, trial NCT004381884 (history).	risk of mechanical ventilation, 151.9% higher, RR 2.52, $p = 1.00$, treatment 1 of 27 (3.7%), control 0 of 14 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of 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, RR 0.34, $p = 0.09$, treatment 20, control 12, relative mean viral decay rate (corrigendum table 2, all treatment patients vs. all control patients), primary outcome.
Loue, 4/17/2021, retrospective quasi-randomized (patient choice), France, 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%), NNT 4.3.
	risk of severe case, 55.0% lower, RR 0.45, $p = 0.11$, treatment 3 of 10 (30.0%), control 10 of 15 (66.7%), NNT 2.7.
López-Medina, 3/4/2021, Double Blind Randomized Controlled Trial, Colombia, peer-reviewed, median age 37.0, 19 authors, study period 15 July, 2020 - 30 November, 2020, average treatment delay 5.0 days, 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%), NNT 198, 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%), NNT 33, 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%), NNT 97, 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%), NNT 65, odds ratio converted to relative risk, primary outcome.
	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%), NNT 38, 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%), NNT 31, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, Cox proportional-hazard model.
	lack of resolution of symptoms, 6.5% lower, HR 0.93, $p = 0.53$, treatment 200, control 198, inverted to make HR<1 favor treatment, post-hoc primary outcome.
Mahmud, 10/9/2020, Double Blind Randomized Controlled Trial, Bangladesh, peer-reviewed, 15 authors, study period 1 June, 2020 - 30 August, 2020, average treatment delay 4.0 days, dosage 12mg single dose, this trial uses multiple treatments in the treatment arm (combined with doxycycline) - results of individual treatments may vary, trial NCT04523831 (history).	risk of death, 85.7% lower, HR 0.14, $p = 0.25$, treatment 0 of 183 (0.0%), control 3 of 183 (1.6%), NNT 61, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of progression, 57.0% lower, HR 0.43, $p < 0.001$, treatment 16 of 183 (8.7%), control 32 of 180 (17.8%), NNT 11, adjusted per study, Cox regression.
	risk of no recovery, 94.0% lower, HR 0.06, $p < 0.001$, treatment 72 of 183 (39.3%), control 100 of 180 (55.6%), NNT 6.2, 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%), NNT 7.3, day 11.
	risk of no recovery, 96.0% lower, HR 0.04, $p < 0.001$, treatment 42 of 183 (23.0%), control 67 of 180 (37.2%), NNT 7.0, adjusted per study, day 12, Cox regression.
	time to recovery, 27.0% lower, HR 0.73, $p = 0.003$, treatment 183, control 180, Cox regression, primary outcome.
	risk of no viral clearance, 39.0% lower, HR 0.61, $p = 0.002$, treatment 14 of 183 (7.7%), control 36 of 180 (20.0%), NNT 8.1, adjusted per study, Cox regression.
Manomaipiboon, 2/2/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Thailand, peer-reviewed, mean age 48.6, 8 authors, study period 10 October, 2021 - 15 December, 2021, dosage 12mg days 1-5, trial NCT05076253 (history).	risk of no recovery, 43.5% lower, RR 0.57, $p = 0.26$, treatment 3 of 36 (8.3%), control 6 of 36 (16.7%), NNT 12, adjusted per study, odds ratio converted to relative risk, resolution of symptoms, Table S2, day 28.
	recovery time, 15.3% lower, RR 0.85, $p = 0.56$, treatment 36, control 36, inverted to make RR<1 favor treatment, time to resolution of symptoms.
	risk of no viral clearance, 5.0% lower, RR 0.95, $p = 1.00$, treatment 19 of 36 (52.8%), control 20 of 36 (55.6%), NNT 36, day 14, primary outcome.
	risk of no viral clearance, 3.3% lower, RR 0.97, $p = 1.00$, treatment 29 of 36 (80.6%), control 30 of 36 (83.3%), NNT 36, day 7.
Mayer, 9/23/2021, retrospective, Argentina, peer-reviewed, 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, Figure 3, multivariable.
	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, Figure 3, multivariable.
	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.

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Merino, 5/3/2021, retrospective quasi-randomized (patients receiving kit), population-based cohort, Mexico, preprint, 7 authors, dosage 6mg bid days 1-2, censored, see notes.	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.
Mikamo, 9/26/2022, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, 19 authors, study period 12 November, 2021 - 7 August, 2022, average treatment delay 3.2 days, dosage 300µg/kg days 1-3, trial NCT05056883 (history) (IVERMILCO), excluded in exclusion analyses: very low risk group with almost no progression leaves little room for improvement, unbalanced baseline dyspnea and high symptom scores, design and post-hoc changes favor null result.	COVID-19 pneumonia, 205.0% higher, RR 3.05, $p = 0.49$, treatment 1 of 502 (0.2%), control 0 of 527 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), Table S8.
	use of therapeutic agents, oxygen, transfer, hospitalization, death, 214.9% higher, RR 3.15, $p = 0.36$, treatment 3 of 502 (0.6%), control 1 of 527 (0.2%).
	risk of no improvement, 4.0% higher, HR 1.04, $p = 0.62$, treatment 502, control 527, 168hr, improving trend, primary outcome.
	risk of no recovery, 4.0% lower, HR 0.96, $p = 0.72$, treatment 502, control 527, 168hr, clinical resolution, Figure S3.
	risk of no recovery, 4.0% lower, HR 0.96, $p = 0.64$, treatment 502, control 527, 240hr, clinical resolution, Figure S3.
Mirahmadizadeh, 6/23/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 12 authors, study period 9 April, 2021 - 20 May, 2021, dosage 24mg single dose, 12mg and 24mg arms.	risk of mechanical ventilation, 66.9% lower, RR 0.33, $p = 0.37$, treatment 1 of 131 (0.8%), control 3 of 130 (2.3%), NNT 65, 24mg.
	risk of mechanical ventilation, 33.3% lower, RR 0.67, $p = 1.00$, treatment 2 of 130 (1.5%), control 3 of 130 (2.3%), NNT 130, 12mg.
	risk of hospitalization, 45.9% lower, RR 0.54, $p = 0.22$, treatment 6 of 131 (4.6%), control 11 of 130 (8.5%), NNT 26, 24mg, primary outcome.
	risk of hospitalization, 27.3% lower, RR 0.73, $p = 0.63$, treatment 8 of 130 (6.2%), control 11 of 130 (8.5%), NNT 43, 12mg, primary outcome.
	risk of no recovery, 38.9% lower, RR 0.61, $p = 0.27$, treatment 8 of 131 (6.1%), control 13 of 130 (10.0%), NNT 26, day 28, 24mg.
	risk of no recovery, 30.8% lower, RR 0.69, $p = 0.50$, treatment 9 of 130 (6.9%), control 13 of 130 (10.0%), NNT 32, day 28, 12mg.
Mohan, 2/2/2021, Double Blind Randomized Controlled Trial, India, peer-reviewed, 27 authors, study period 28 July, 2020 - 29 September, 2020, average treatment delay 5.0 days, dosage 400µg/kg single dose, 200µg/kg also tested, trial CTRI/2020/06/026001 (RIVET-COV).	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%), NNT 12, 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%), NNT 28, 24mg.
	risk of no viral clearance, 23.8% lower, RR 0.76, $p = 0.18$, treatment 21 of 40 (52.5%), control 31 of 45 (68.9%), NNT 6.1, day 5, 24mg, primary outcome.
	risk of no viral clearance, 10.3% lower, RR 0.90, $p = 0.65$, treatment 20 of 36 (55.6%), control 26 of 42 (61.9%), NNT 16, day 7, 24mg.
Mouawia, 5/1/2026, Randomized Controlled Trial, Lebanon, peer-reviewed, mean age 40.1, 8 authors, study period November 2021 - December 2021, dosage 12mg single dose, <65kg - 9mg, 65-84kg - 12 mg, ≥85kg - 15 mg, trial ChiCTR2000033627.	risk of hospitalization, 55.6% lower, RR 0.44, $p = 0.24$, treatment 4 of 63 (6.3%), control 9 of 63 (14.3%), NNT 13, day 4.
	risk of no recovery, 30.9% lower, RR 0.69, $p = 0.007$, treatment 63, control 63, all symptoms combined.
	risk of no recovery, 81.2% lower, RR 0.19, $p = 0.002$, treatment 3 of 63 (4.8%), control 16 of 63 (25.4%), NNT 4.8, day 4, fever.
	risk of no recovery, 33.3% higher, RR 1.33, $p = 0.52$, treatment 16 of 63 (25.4%), control 12 of 63 (19.0%), day 4, cough.
	risk of no recovery, 60.0% lower, RR 0.40, $p = 0.44$, treatment 2 of 63 (3.2%), control 5 of 63 (7.9%), NNT 21, day 4, sore throat.
	risk of no recovery, 26.3% lower, RR 0.74, $p = 0.42$, treatment 14 of 63 (22.2%), control 19 of 63 (30.2%), NNT 13, day 4, dyspnea.
	risk of no recovery, 33.3% lower, RR 0.67, $p = 0.74$, treatment 4 of 63 (6.3%), control 6 of 63 (9.5%), NNT 32, day 4, pneumonia.
	risk of no recovery, 40.0% lower, RR 0.60, $p = 0.02$, treatment 21 of 63 (33.3%), control 35 of 63 (55.6%), NNT 4.5, day 4, headache.
	risk of no recovery, 46.2% higher, RR 1.46, $p = 0.31$, treatment 19 of 63 (30.2%), control 13 of 63 (20.6%), day 4, anosmia.
	risk of no recovery, 22.2% lower, RR 0.78, $p = 0.36$, treatment 21 of 63 (33.3%), control 27 of 63 (42.9%), NNT 10, day 4, myalgia.
	risk of no recovery, 48.0% lower, RR 0.52, $p = 0.03$, treatment 13 of 63 (20.6%), control 25 of 63 (39.7%), NNT 5.2, day 4, loss of taste.
	risk of no recovery, 46.7% lower, RR 0.53, $p = 0.02$, treatment 16 of 63 (25.4%), control 30 of 63 (47.6%), NNT 4.5, day 4, fatigue.
	risk of no recovery, 42.9% lower, RR 0.57, $p = 0.53$, treatment 4 of 63 (6.3%), control 7 of 63 (11.1%), NNT 21, day 4, dizziness.
	viral load, 61.9% lower, relative load 0.38, $p < 0.001$, treatment 8.38 [7.56-9.2] n=63, control 3.19 [2.36-4.02] n=63, relative ΔCt, day 4.
Mourya, 4/1/2021, retrospective, India, peer-reviewed, 5 authors, dosage 12mg days 1-7.	risk of no viral clearance, 89.4% lower, RR 0.11, $p < 0.001$, treatment 5 of 50 (10.0%), control 47 of 50 (94.0%), NNT 1.2, primary outcome.
Reis, 8/6/2021, Double Blind Randomized Controlled Trial, Brazil, peer-reviewed, 27 authors, study period 23 March, 2021 - 6 August, 2021, dosage 400µg/kg days 1-3, impossible data, see notes, trial NCT04727424 (history) (TOGETHER), excluded in exclusion analyses: multiple	risk of death, 12.0% lower, RR 0.88, $p = 0.68$, treatment 21 of 679 (3.1%), control 24 of 679 (3.5%), NNT 226.
	risk of mechanical ventilation, 23.0% lower, RR 0.77, $p = 0.38$, treatment 19 of 679 (2.8%), control 25 of 679 (3.7%), NNT 113.

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anomalies as per detailed analysis.	risk of hospitalization, 17.0% lower, RR 0.83, *p* = 0.19, treatment 79 of 679 (11.6%), control 95 of 679 (14.0%), NNT 42.
	extended ER observation or hospitalization, 10.0% lower, RR 0.90, *p* = 0.42, treatment 100 of 679 (14.7%), control 111 of 679 (16.3%), NNT 62, primary outcome.
	risk of no recovery, 4.8% lower, HR 0.95, *p* = 0.59, treatment 679, control 679, inverted to make HR<1 favor treatment.
	viral clearance, no change, RR 1.00, *p* = 1.00, treatment 106 of 142 (74.6%), control 123 of 165 (74.5%), day 7.
	viral clearance, 31.6% higher, RR 1.32, *p* = 0.46, treatment 148, control 170, inverted to make RR<1 favor treatment, day 3.
Rezai, 6/16/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, mean age 35.5, 29 authors, study period 19 February, 2021 - 30 August, 2021, dosage 400µg/kg days 1-3, trial IRCT20111224008507N4, excluded in exclusion analyses: multiple critical issues, see study page.	**risk of death, 4.9% higher, RR 1.05, *p* = 1.00**, treatment 1 of 268 (0.4%), control 1 of 281 (0.4%).
	risk of ICU admission, 9.0% higher, RR 1.09, *p* = 0.95, treatment 268, control 281.
	risk of hospitalization, 36.0% higher, RR 1.36, *p* = 0.41, treatment 268, control 281.
	risk of no recovery, 2.0% higher, RR 1.02, *p* = 0.49, treatment 268, control 281, inverted to make RR<1 favor treatment, post-hoc primary outcome.
	risk of no recovery, 13.2% lower, RR 0.87, *p* = 0.09, treatment mean 3.87 (±0.18) n=268, control mean 4.46 (±0.18) n=281, cough.
	risk of no recovery, 16.7% lower, RR 0.83, *p* = 0.81, treatment mean 2.5 (±0.51) n=268, control mean 3.0 (±0.92) n=281, tachypnea.
	risk of no viral clearance, 23.5% higher, RR 1.23, *p* = 0.16, treatment 268, control 281, inverted to make RR<1 favor treatment.
Schilling, 7/19/2022, Randomized Controlled Trial, Thailand, peer-reviewed, median age 27.0, 38 authors, study period 30 September, 2021 - 18 April, 2022, average treatment delay 2.0 days, dosage 600µg/kg days 1-7, trial NCT05041907 (history) (PLATCOV), excluded in exclusion analyses: post-hoc change to exclude patients treated before high viral load, population very low risk, recovering quickly without treatment, high baseline immunity, 2.2x greater baseline antibody negative for the treatment arm.	**risk of hospitalization, 66.7% lower, RR 0.33, *p* = 1.00**, treatment 0 of 45 (0.0%), control 1 of 45 (2.2%), NNT 45, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of progression, 85.7% lower, RR 0.14, *p* = 0.24, treatment 0 of 45 (0.0%), control 3 of 45 (6.7%), NNT 15, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), hospitalization or progression to COVID-19 rhabdomyolysis.
	relative clearance rate, 9.1% worse, RR 1.09, *p* = 0.36, treatment 45, control 45, primary outcome.
Siripongboonsitti, 3/29/2024, Randomized Controlled Trial, Thailand, peer-reviewed, 5 authors, study period 7 December, 2022 - 3 February, 2023, dosage 600µg/kg days 1-5, this trial uses multiple treatments in the treatment arm (combined with niclosamide) - results of individual treatments may vary, trial TCTR20230403007 (FINCOV), excluded in exclusion analyses: data consistency issues, very low risk patients/variants with almost no progression, all patients received known effective antiviral, baseline differences.	**risk of progression, 66.7% lower, RR 0.33, *p* = 1.00**, treatment 0 of 30 (0.0%), control 1 of 30 (3.3%), NNT 30, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), chest xray progression, day 3.
	risk of no recovery, 39.4% lower, RR 0.61, *p* = 0.19, treatment 30, control 30, combined symptoms.
	risk of no recovery, 70.0% lower, RR 0.30, *p* = 0.048, treatment 30, control 30, mid-recovery, day 3, cough.
	risk of no recovery, 14.3% lower, RR 0.86, *p* = 0.38, treatment 30, control 30, mid-recovery, day 3, sore throat.
	risk of no recovery, 66.7% lower, RR 0.33, *p* = 0.41, treatment 30, control 30, inverted to make RR<1 favor treatment, mid-recovery, day 3, runny nose.
	risk of no recovery, 50.0% lower, RR 0.50, *p* = 0.32, treatment 30, control 30, inverted to make RR<1 favor treatment, day 6, cough.
	relative Ct improvement, 6.1% better, RR 0.94, *p* = 0.75, treatment median 9.15 IQR 9.7 n=30, control median 8.59 IQR 8.24 n=30, E gene, mid-recovery, day 5, primary outcome.
Szente Fonseca, 10/31/2020, retrospective, Brazil, peer-reviewed, mean age 50.6, 10 authors, average treatment delay 4.6 days, 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, primary outcome.
Vallejos, 7/2/2021, Double Blind Randomized Controlled Trial, Argentina, peer-reviewed, 29 authors, study period 19 August, 2020 - 22 February, 2021, average treatment delay 4.0 days, 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%), NNT 36, odds ratio converted to relative risk, primary outcome.
	risk of no viral clearance, 5.0% higher, RR 1.05, *p* = 0.55, treatment 137 of 250 (54.8%), control 131 of 251 (52.2%), inverted to make RR<1 favor treatment, odds ratio converted to relative risk, day 3.
	risk of no viral clearance, 26.8% higher, RR 1.27, *p* = 0.29, treatment 38 of 250 (15.2%), control 30 of 251 (12.0%), inverted to make RR<1 favor treatment, odds ratio converted to relative risk, day 12.
Wijewickrema, 7/22/2024, Double Blind Randomized	**risk of death, 196.1% higher, RR 2.96, *p* = 1.00**, treatment 1 of 127 (0.8%), control 0 of 122

Controlled Trial, Sri Lanka, peer-reviewed, 11 authors, study period 29 July, 2021 - 17 March, 2022, dosage 24mg days 1-5, trial SLCTR/2021/020.	(0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	progression to moderate disease, 52.0% lower, RR 0.48, *p* = 0.62, treatment 1 of 127 (0.8%), control 2 of 122 (1.6%), NNT 117, progression to moderate disease.
	viral load, 51.2% lower, relative load 0.49, *p* = 0.03, treatment 80, control 81, relative viral load (copies/mL), day 10, primary outcome.

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 pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Abd-Elsalam, 6/2/2021, Randomized Controlled Trial, Egypt, peer-reviewed, 16 authors, study period March 2020 - October 2020, 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%), NNT 82, odds ratio converted to relative risk, logistic regression, primary outcome.
	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, 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%), NNT 6.5.
Aref (B), 9/19/2022, Randomized Controlled Trial, placebo-controlled, Egypt, peer-reviewed, 9 authors, study period 1 March, 2021 - 30 April, 2021, dosage 2 puffs of 70 µg/mL nasal ivermectin, trial NCT04951362 (history).	recovery time, 74.0% lower, relative time 0.26, *p* < 0.001, treatment 49, control 47, anosmia.
Baguma, 12/28/2021, retrospective, Uganda, preprint, 16 authors, study period March 2020 - October 2021, dosage not specified.	risk of death, 96.8% lower, RR 0.03, *p* = 0.31, treatment 7, control 474, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariable, control prevalance approximated with overall prevalence.
Beltran Gonzalez, 2/23/2021, Double Blind Randomized Controlled Trial, Mexico, peer-reviewed, mean age 53.8, 13 authors, average treatment delay 7.0 days, dosage 12mg single dose, 18mg for patients >80kg, excluded in exclusion analyses: major inconsistencies reported and the data is no longer available, although the authors state that it is available, and have shared it with an anti-treatment group.	risk of death, 14.4% lower, RR 0.86, *p* = 1.00, treatment 5 of 36 (13.9%), control 6 of 37 (16.2%), NNT 43.
	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%), NNT 48.
	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, primary outcome.
Budhiraja, 11/18/2020, retrospective, India, 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%), NNT 9.1, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), unadjusted, primary outcome.
Camprubí, 11/11/2020, retrospective, Spain, peer-reviewed, 9 authors, average treatment delay 12.0 days, 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%), NNT 6.5.
	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%), NNT 13, 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 viral clearance, 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, primary outcome.
Chachar, 9/30/2020, Randomized Controlled Trial, India, peer-reviewed, 6 authors, dosage 36mg, 12mg stat, 12mg after 12 hours, 12mg after 24 hours, trial NCT04739410 (history), excluded in exclusion analyses: multiple significant issues pending author response, see discussion.	risk of no recovery, 10.0% lower, RR 0.90, *p* = 0.50, treatment 9 of 25 (36.0%), control 10 of 25 (40.0%), NNT 25, day 7, primary outcome.
Efimenko, 2/28/2022, retrospective, propensity score matching, USA, peer-reviewed, 6 authors, study period 1 January, 2020 - 11 July, 2021, dosage not specified, this trial compares with another treatment - results may be better when compared to placebo, self-censored, see notes.	risk of death, 69.2% lower, OR 0.31, *p* < 0.001, treatment 1,072, control 40,536, propensity score matching, RR approximated with OR.
Elavarasi, 8/12/2021, retrospective, India, peer-reviewed, 31 authors, study period April 2021 - June 2021, 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%), NNT 24, unadjusted.
Ferreira, 11/26/2021, retrospective, Brazil, peer-reviewed, 5 authors, study period 12 March, 2020 - 8 July, 2020, average treatment delay 7.0 days, dosage not specified, excluded in exclusion	risk of death, 5.0% higher, RR 1.05, *p* = 0.94, treatment 3 of 21 (14.3%), control 11 of 81 (13.6%).
	risk of death/intubation, 54.3% higher, RR 1.54, *p* = 0.37, treatment 6 of 21 (28.6%), control 15 of 81 (18.5%).

analyses: unadjusted results with no group details; substantial unadjusted confounding by indication likely.	risk of death/intubation/ICU, 62.4% higher, RR 1.62, $p = 0.27$, treatment 8 of 21 (38.1%), control 19 of 81 (23.5%).
George, 5/27/2022, Randomized Controlled Trial, India, peer-reviewed, 15 authors, study period June 2020 - February 2021, dosage 24mg single dose, trial CTRI/2020/05/025068.	**risk of death, 30.4% lower, RR 0.70, $p = 0.55$**, treatment 5 of 35 (14.3%), control 8 of 39 (20.5%), NNT 16, 24mg.
	risk of death, 2.6% higher, RR 1.03, $p = 1.00$, treatment 8 of 38 (21.1%), control 8 of 39 (20.5%), 12mg.
	recovery time, 18.7% lower, relative time 0.81, $p = 0.37$, treatment mean 4.82 (±4.35) n=35, control mean 5.93 (±5.93) n=39, 24mg.
	recovery time, 6.2% lower, relative time 0.94, $p = 0.78$, treatment mean 5.56 (±5.42) n=38, control mean 5.93 (±5.93) n=39, 12mg.
	risk of progression, 33.1% lower, RR 0.67, $p = 0.41$, treatment 6 of 35 (17.1%), control 10 of 39 (25.6%), NNT 12, 24mg.
	risk of progression, 17.9% lower, RR 0.82, $p = 0.79$, treatment 8 of 38 (21.1%), control 10 of 39 (25.6%), NNT 22, 12mg.
Gorial, 7/8/2020, retrospective, Iraq, preprint, 9 authors, dosage 200µg/kg single dose, trial NCT04343092 (history).	**risk of death, 71.0% lower, RR 0.29, $p = 1.00$**, treatment 0 of 16 (0.0%), control 2 of 71 (2.8%), NNT 36, 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%), NNT 36, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), primary outcome.
Hashim, 10/26/2020, Single Blind Randomized Controlled Trial, Iraq, peer-reviewed, 7 authors, study period 1 July, 2020 - 14 October, 2020, 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, trial NCT04591600 (history).	**risk of death, 91.7% lower, RR 0.08, $p = 0.03$**, treatment 0 of 59 (0.0%), control 6 of 70 (8.6%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), excluding non-randomized critical patients, primary outcome.
	risk of death, 67.1% lower, RR 0.33, $p = 0.16$, treatment 2 of 70 (2.9%), control 6 of 70 (8.6%), NNT 18, odds ratio converted to relative risk, including critical patients that were always allocated to treatment.
	risk of progression, 83.1% lower, RR 0.17, $p = 0.07$, treatment 1 of 59 (1.7%), control 7 of 70 (10.0%), NNT 12, excluding non-randomized critical patients.
	risk of progression, 57.4% lower, RR 0.43, $p = 0.20$, treatment 3 of 70 (4.3%), control 7 of 70 (10.0%), NNT 18, 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.
Hashmi, 6/13/2024, Randomized Controlled Trial, Pakistan, peer-reviewed, 83 authors, study period 11 June, 2021 - 9 September, 2022, dosage 200µg/kg days 1-5, trial NCT02735707 (history) (REMAP-CAP), excluded in exclusion analyses: baseline severity favors control, post-hoc outcome and SAP changes, see discussion.	**risk of death, 25.6% lower, RR 0.74, $p = 0.40$**, treatment 81, control 69, adjusted per study, combined.
	risk of death, 26.5% lower, OR 0.74, $p = 0.57$, treatment 44, control 45, adjusted per study, inverted to make OR<1 favor treatment, concurrent, non-critical, day 90, Table S7, RR approximated with OR.
	risk of death, 24.8% lower, OR 0.75, $p = 0.55$, treatment 37, control 24, adjusted per study, inverted to make OR<1 favor treatment, concurrent, critical, day 90, Table S7, RR approximated with OR.
	risk of death, 14.9% lower, RR 0.85, $p = 0.64$, treatment 81, control 69, adjusted per study, combined.
	risk of death, 22.5% lower, OR 0.78, $p = 0.59$, treatment 44, control 45, adjusted per study, inverted to make OR<1 favor treatment, non-critical, day 90, RR approximated with OR.
	risk of death, 5.7% lower, OR 0.94, $p = 0.91$, treatment 37, control 24, adjusted per study, inverted to make OR<1 favor treatment, critical, day 90, RR approximated with OR.
	intubation, ECMO, death, 23.7% lower, OR 0.76, $p = 0.57$, treatment 44, control 45, adjusted per study, inverted to make OR<1 favor treatment, non-critical, RR approximated with OR.
	intubation, ECMO, death, 16.0% lower, OR 0.84, $p = 0.72$, treatment 37, control 24, adjusted per study, inverted to make OR<1 favor treatment, critical, RR approximated with OR.
	organ support-free days, 3.8% lower, OR 0.96, $p = 0.93$, treatment 44, control 45, inverted to make OR<1 favor treatment, non-critical, RR approximated with OR.
	organ support-free days, 6.4% higher, OR 1.06, $p = 0.89$, treatment 37, control 24, inverted to make OR<1 favor treatment, critical, RR approximated with OR.
Hayward, 2/29/2024, Randomized Controlled Trial, placebo-controlled, United Kingdom, peer-reviewed, 25 authors, study period 23 June, 2021 - 1 July, 2022, dosage 350µg/kg days 1-3, trial ISRCTN86534580 (PRINCIPLE).	**risk of death/hospitalization, 1.0% higher, HR 1.01, $p = 0.97$**, treatment 34 of 2,157 (1.6%), control 27 of 1,806 (1.5%), concurrent and eligible, primary outcome, details missing, mAb/AV confounding.
	risk of mechanical ventilation, 151.4% higher, RR 2.51, $p = 0.63$, treatment 3 of 2,149 (0.1%), control 1 of 1,801 (0.1%).
	risk of ICU admission, 319.0% higher, RR 4.19, $p = 0.23$, treatment 5 of 2,149 (0.2%), control 1 of 1,801 (0.1%).
	time to sustained recovery, 16.0% lower, HR 0.84, $p < 0.001$, treatment 2,157, control 1,806, inverted to make HR<1 favor treatment, concurrent and eligible.

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	early sustained recovery, 23.1% lower, HR 0.77, $p < 0.001$, treatment 2,154, control 1,805, inverted to make HR<1 favor treatment, concurrent and eligible.
	sustained alleviation, 17.4% lower, HR 0.83, $p < 0.001$, treatment 1,826, control 1,535, inverted to make HR<1 favor treatment, concurrent and eligible.
	alleviation of all symptoms, 16.0% lower, HR 0.84, $p < 0.001$, treatment 2,154, control 1,805, inverted to make HR<1 favor treatment, concurrent and eligible.
	first reported recovery, 13.0% lower, HR 0.87, $p < 0.001$, treatment 2,157, control 1,806, inverted to make HR<1 favor treatment, concurrent and eligible, primary outcome.
	no recovery at 3/6/12 months, 28.0% lower, HR 0.72, $p = 0.02$, treatment 94 of 1,941 (4.8%), control 109 of 1,624 (6.7%), NNT 54.
	risk of no recovery, 17.6% lower, RR 0.82, $p = 0.001$, treatment 417 of 1,848 (22.6%), control 420 of 1,533 (27.4%), NNT 21, day 365.
	risk of long COVID, 36.3% lower, RR 0.64, $p < 0.001$, treatment 1,886, control 1,567, all symptoms combined.
	risk of long COVID, 63.2% higher, RR 1.63, $p = 1.00$, treatment 2 of 1,507 (0.1%), control 1 of 1,230 (0.1%), ongoing/persistent, fever.
	risk of long COVID, 72.7% lower, RR 0.27, $p = 0.33$, treatment 1 of 1,819 (0.1%), control 3 of 1,489 (0.2%), NNT 683, ongoing/persistent, cough.
	risk of long COVID, 50.1% lower, RR 0.50, $p = 0.04$, treatment 15 of 1,886 (0.8%), control 25 of 1,567 (1.6%), NNT 125, ongoing/persistent, dyspnea.
	risk of long COVID, 35.3% higher, RR 1.35, $p = 0.74$, treatment 5 of 1,808 (0.3%), control 3 of 1,468 (0.2%), ongoing/persistent, chest pain.
	risk of long COVID, 25.2% lower, RR 0.75, $p = 0.36$, treatment 21 of 1,831 (1.1%), control 23 of 1,501 (1.5%), NNT 259, ongoing/persistent, smell.
	risk of long COVID, 58.7% lower, RR 0.41, $p = 0.42$, treatment 2 of 1,821 (0.1%), control 4 of 1,503 (0.3%), NNT 640, ongoing/persistent, diarrhoea.
	risk of long COVID, 70.2% lower, RR 0.30, $p < 0.001$, treatment 10 of 1,739 (0.6%), control 27 of 1,400 (1.9%), NNT 74, ongoing/persistent, headache.
	risk of long COVID, 29.8% lower, RR 0.70, $p = 0.25$, treatment 23 of 1,739 (1.3%), control 27 of 1,433 (1.9%), NNT 178, ongoing/persistent, muscle ache.
	risk of long COVID, 47.1% lower, RR 0.53, $p = 0.03$, treatment 19 of 1,724 (1.1%), control 30 of 1,441 (2.1%), NNT 102, ongoing/persistent, generally unwell.
	risk of long COVID, 20.1% lower, RR 0.80, $p = 0.19$, treatment 66 of 1,876 (3.5%), control 69 of 1,567 (4.4%), NNT 113, ongoing/persistent, fatigue.
	risk of long COVID, 42.9% lower, RR 0.57, $p < 0.001$, treatment 1,886, control 1,567, all symptoms combined.
	risk of long COVID, 63.2% higher, RR 1.63, $p = 1.00$, treatment 2 of 1,507 (0.1%), control 1 of 1,230 (0.1%), ongoing/persistent, fever.
	risk of long COVID, 72.7% lower, RR 0.27, $p = 0.33$, treatment 1 of 1,819 (0.1%), control 3 of 1,489 (0.2%), NNT 683, ongoing/persistent, cough.
	risk of long COVID, 50.1% lower, RR 0.50, $p = 0.04$, treatment 15 of 1,886 (0.8%), control 25 of 1,567 (1.6%), NNT 125, ongoing/persistent, dyspnea.
	risk of long COVID, 35.3% higher, RR 1.35, $p = 0.74$, treatment 5 of 1,808 (0.3%), control 3 of 1,468 (0.2%), ongoing/persistent, chest pain.
	risk of long COVID, 25.2% lower, RR 0.75, $p = 0.36$, treatment 21 of 1,831 (1.1%), control 23 of 1,501 (1.5%), NNT 259, ongoing/persistent, smell.
	risk of long COVID, 58.7% lower, RR 0.41, $p = 0.42$, treatment 2 of 1,821 (0.1%), control 4 of 1,503 (0.3%), NNT 640, ongoing/persistent, diarrhoea.
	risk of long COVID, 70.2% lower, RR 0.30, $p < 0.001$, treatment 10 of 1,739 (0.6%), control 27 of 1,400 (1.9%), NNT 74, ongoing/persistent, headache.
	risk of long COVID, 29.8% lower, RR 0.70, $p = 0.25$, treatment 23 of 1,739 (1.3%), control 27 of 1,433 (1.9%), NNT 178, ongoing/persistent, muscle ache.
	risk of long COVID, 47.1% lower, RR 0.53, $p = 0.03$, treatment 19 of 1,724 (1.1%), control 30 of 1,441 (2.1%), NNT 102, ongoing/persistent, excluding non-prespecified fatigue, generally unwell.
	risk of long COVID, 28.5% lower, RR 0.72, $p < 0.001$, treatment 1,513, control 1,238, adjusted per study, all symptoms combined.
	risk of long COVID, 39.9% lower, RR 0.60, $p = 0.01$, treatment 46 of 1,435 (3.2%), control 51 of 1,136 (4.5%), relatedness (yes + unsure) 9.1% (treatment) 11.2% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, cough.
	risk of long COVID, 41.6% lower, RR 0.58, $p < 0.001$, treatment 96 of 1,513 (6.3%), control

	106 of 1,238 (8.6%), relatedness (yes + unsure) 14.4% (treatment) 18.5% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, shortness of breath.
	risk of long COVID, 22.2% lower, RR 0.78, *p* = 0.27, treatment 39 of 1,426 (2.7%), control 36 of 1,117 (3.2%), relatedness (yes + unsure) 7.6% (treatment) 8.4% (control) , NNT 205, adjusted per study and for relatedness, moderate/major symptoms at 12 months, chest pain.
	risk of long COVID, 38.0% lower, RR 0.62, *p* = 0.02, treatment 46 of 1,427 (3.2%), control 44 of 1,140 (3.9%), relatedness (yes + unsure) 7.7% (treatment) 10.3% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, palpitations.
	risk of long COVID, 11.5% higher, RR 1.12, *p* = 0.52, treatment 77 of 1,403 (5.5%), control 57 of 1,131 (5.0%), relatedness (yes + unsure) 13.2% (treatment) 12.9% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, smell.
	risk of long COVID, 36.4% lower, RR 0.64, *p* = 0.02, treatment 51 of 1,375 (3.7%), control 51 of 1,116 (4.6%), relatedness (yes + unsure) 1.1% (treatment) 1.4% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, taste.
	risk of long COVID, 22.1% lower, RR 0.78, *p* = 0.37, treatment 26 of 1,290 (2.0%), control 25 of 1,057 (2.4%), relatedness (yes + unsure) 4.8% (treatment) 5.3% (control) , NNT 286, adjusted per study and for relatedness, moderate/major symptoms at 12 months, ear ache.
	risk of long COVID, 9.6% higher, RR 1.10, *p* = 0.73, treatment 37 of 1,325 (2.8%), control 25 of 1,089 (2.3%), relatedness (yes + unsure) 6.7% (treatment) 7.4% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, sore throat.
	risk of long COVID, 34.8% lower, RR 0.65, *p* = 0.12, treatment 24 of 1,308 (1.8%), control 27 of 1,077 (2.5%), relatedness (yes + unsure) 6.0% (treatment) 6.9% (control) , NNT 149, adjusted per study and for relatedness, moderate/major symptoms at 12 months, hoarse voice.
	risk of long COVID, 16.6% higher, RR 1.17, *p* = 0.42, treatment 60 of 1,341 (4.5%), control 46 of 1,082 (4.3%), relatedness (yes + unsure) 8.3% (treatment) 7.4% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, tinnitus.
	risk of long COVID, 34.7% lower, RR 0.65, *p* = 0.29, treatment 13 of 1,382 (0.9%), control 12 of 1,139 (1.1%), relatedness (yes + unsure) 2.2% (treatment) 3.0% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, vomiting.
	risk of long COVID, 46.5% higher, RR 1.46, *p* = 0.12, treatment 44 of 1,439 (3.1%), control 25 of 1,175 (2.1%), relatedness (yes + unsure)

	5.9% (treatment) 5.8% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, abdominal pain.
	risk of long COVID, 1.6% lower, RR 0.98, *p* = 0.95, treatment 33 of 1,416 (2.3%), control 24 of 1,167 (2.1%), relatedness (yes + unsure) 4.4% (treatment) 5.1% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, diarrhoea.
	risk of long COVID, 43.8% higher, RR 1.44, *p* = 0.23, treatment 30 of 1,417 (2.1%), control 17 of 1,160 (1.5%), relatedness (yes + unsure) 4.5% (treatment) 4.6% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, reduced appetite.
	risk of long COVID, 89.8% higher, RR 1.90, *p* = 0.27, treatment 11 of 1,375 (0.8%), control 4 of 1,129 (0.4%), relatedness (yes + unsure) 1.8% (treatment) 2.2% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, weight loss.
	risk of long COVID, 41.3% lower, RR 0.59, *p* < 0.001, treatment 89 of 1,287 (6.9%), control 94 of 973 (9.7%), relatedness (yes + unsure) 13.2% (treatment) 16.2% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, anxiety.
	risk of long COVID, 38.6% lower, RR 0.61, *p* < 0.001, treatment 95 of 1,298 (7.3%), control 92 of 992 (9.3%), relatedness (yes + unsure) 13.7% (treatment) 17.4% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, depression.
	risk of long COVID, 49.0% lower, RR 0.51, *p* < 0.001, treatment 129 of 1,376 (9.4%), control 143 of 1,105 (12.9%), relatedness (yes + unsure) 19.6% (treatment) 27.3% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, brain fog.
	risk of long COVID, 32.9% lower, RR 0.67, *p* = 0.08, treatment 37 of 1,187 (3.1%), control 33 of 874 (3.8%), relatedness (yes + unsure) 7.1% (treatment) 9.2% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, confusion.
	risk of long COVID, 41.9% lower, RR 0.58, *p* < 0.001, treatment 78 of 1,278 (6.1%), control 81 of 964 (8.4%), relatedness (yes + unsure) 12.5% (treatment) 15.7% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, headache.
	risk of long COVID, 45.4% lower, RR 0.55, *p* = 0.001, treatment 53 of 1,254 (4.2%), control 54 of 955 (5.7%), relatedness (yes + unsure) 11.5% (treatment) 15.8% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, dizziness.
	risk of long COVID, 73.5% lower, RR 0.27, *p* = 0.10, treatment 3 of 1,105 (0.3%), control 3 of 802 (0.4%), relatedness (yes + unsure) 0.4% (treatment) 1.1% (control) , adjusted per study

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	and for relatedness, moderate/major symptoms at 12 months, fainting.
	risk of long COVID, 38.7% lower, RR 0.61, p = 0.02, treatment 42 of 1,200 (3.5%), control 39 of 894 (4.4%), relatedness (yes + unsure) 7.9% (treatment) 10.7% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, numbness.
	risk of long COVID, 42.1% lower, RR 0.58, p < 0.001, treatment 123 of 1,288 (9.5%), control 121 of 982 (12.3%), relatedness (yes + unsure) 13.9% (treatment) 18.5% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, sleeping problems.
	risk of long COVID, 11.8% lower, RR 0.88, p = 0.37, treatment 99 of 1,180 (8.4%), control 88 of 967 (9.1%), relatedness (yes + unsure) 15.1% (treatment) 16.1% (control) , NNT 141, adjusted per study and for relatedness, moderate/major symptoms at 12 months, body pains.
	risk of long COVID, 32.2% lower, RR 0.68, p < 0.001, treatment 136 of 1,220 (11.1%), control 146 of 1,034 (14.1%), relatedness (yes + unsure) 16.1% (treatment) 19.0% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, joint pains.
	risk of long COVID, 30.2% lower, RR 0.70, p < 0.001, treatment 205 of 1,398 (14.7%), control 209 of 1,181 (17.7%), relatedness (yes + unsure) 24.1% (treatment) 28.3% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, fatigue.
	risk of long COVID, 31.9% lower, RR 0.68, p = 0.006, treatment 91 of 1,208 (7.5%), control 89 of 997 (8.9%), relatedness (yes + unsure) 14.5% (treatment) 18.1% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, weakness.
	risk of long COVID, 35.9% lower, RR 0.64, p < 0.001, treatment 99 of 1,211 (8.2%), control 107 of 1,002 (10.7%), relatedness (yes + unsure) 14.3% (treatment) 17.4% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, generally unwell.
	risk of long COVID, 9.2% lower, RR 0.91, p = 0.81, treatment 16 of 1,066 (1.5%), control 11 of 855 (1.3%), relatedness (yes + unsure) 3.0% (treatment) 3.8% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, fever.
	risk of long COVID, 42.4% lower, RR 0.58, p = 0.21, treatment 10 of 1,065 (0.9%), control 11 of 853 (1.3%), relatedness (yes + unsure) 3.0% (treatment) 3.7% (control) , adjusted per study and for relatedness, moderate/major symptoms at 12 months, rashes.
	risk of long COVID, 10.0% lower, RR 0.90, p = 0.62, treatment 47 of 1,090 (4.3%), control 41 of 873 (4.7%), NNT 260, adjusted per study,

	moderate/major symptoms at 12 months, other.
Hazan (B), 7/7/2021, retrospective, USA, 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, see notes, trial NCT04949230 (history), excluded in exclusion analyses: study uses a synthetic control arm.	risk of death, 86.2% lower, RR 0.14, p = 0.04, NNT 6.9, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 93.5% lower, RR 0.07, p = 0.001, NNT 3.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), primary outcome.
Huvemek, 3/25/2021, Double Blind Randomized Controlled Trial, Bulgaria, preprint, 1 author, average treatment delay 7.0 days, dosage 400µg/kg days 1-3, trial EudraCT2020-002091-12.	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%), NNT 8.3, patients with improvement on WHO scale, day 7.
	risk of no improvement, 31.8% lower, RR 0.68, p = 0.21, treatment 15 of 50 (30.0%), control 22 of 50 (44.0%), NNT 7.1, patients with improvement on WHO scale, day 6.
	risk of no improvement, 36.0% lower, RR 0.64, p = 0.10, treatment 16 of 50 (32.0%), control 25 of 50 (50.0%), NNT 5.6, patients with improvement on WHO scale, day 5.
	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%), NNT 5.0, patients with improvement on WHO scale, day 4.
Jamir, 12/13/2021, retrospective, India, peer-reviewed, 6 authors, study period June 2020 - October 2020, dosage not specified.	risk of death, 53.0% higher, RR 1.53, p = 0.13, treatment 32 of 76 (42.1%), control 69 of 190 (36.3%), adjusted per study, multivariable Cox regression.
Khan, 9/24/2020, retrospective, Bangladesh, peer-reviewed, 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%), NNT 17.
	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%), NNT 14.
	risk of progression, 83.5% lower, RR 0.17, p < 0.001, treatment 3 of 115 (2.6%), control 21 of 133 (15.8%), NNT 7.6.
	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%), NNT 17.
	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, peer-reviewed, 7 authors, dosage 12mg single dose, excluded in exclusion analyses:	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%).

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excessive unadjusted differences between groups.	risk of no viral clearance, 7.5% higher, RR 1.08, *p* = 1.00, treatment 11 of 19 (57.9%), control 7 of 13 (53.8%), day 3, primary outcome.
	risk of no viral clearance, 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.
Lim, 11/3/2021, Randomized Controlled Trial, Malaysia, peer-reviewed, 26 authors, study period 31 May, 2021 - 9 October, 2021, average treatment delay 5.1 days, dosage 400µg/kg days 1-5, trial NCT04920942 (history) (I-TECH).	**risk of death, 69.0% lower, RR 0.31, *p* = 0.09**, treatment 3 of 241 (1.2%), control 10 of 249 (4.0%), NNT 36, described as similar by authors.
	risk of death, 69.8% lower, RR 0.30, *p* = 0.09, treatment 3 of 247 (1.2%), control 10 of 249 (4.0%), NNT 36, ITT.
	risk of death, 75.2% lower, RR 0.25, *p* = 0.02, treatment 3 of 52 (5.8%), control 10 of 43 (23.3%), NNT 5.7, among patients progressing to severe cases (mostly before treatment ended).
	risk of mechanical ventilation, 59.0% lower, RR 0.41, *p* = 0.17, treatment 4 of 241 (1.7%), control 10 of 249 (4.0%), NNT 42.
	risk of mechanical ventilation, 59.7% lower, RR 0.40, *p* = 0.17, treatment 4 of 247 (1.6%), control 10 of 249 (4.0%), NNT 42, ITT.
	risk of ICU admission, 22.0% lower, RR 0.78, *p* = 0.79, treatment 6 of 241 (2.5%), control 8 of 249 (3.2%), NNT 138.
	risk of ICU admission, 24.4% lower, RR 0.76, *p* = 0.79, treatment 6 of 247 (2.4%), control 8 of 249 (3.2%), NNT 128, ITT.
	risk of progression, 31.1% lower, RR 0.69, *p* = 0.29, treatment 14 of 241 (5.8%), control 21 of 249 (8.4%), NNT 38, death/IMV/NIV/high flow (WHO severe cases).
	risk of progression, 25.0% higher, RR 1.25, *p* = 0.25, treatment 52 of 241 (21.6%), control 43 of 249 (17.3%), post-hoc primary outcome, post-hoc primary specific to this group.
	hospitalization time, 5.5% higher, relative time 1.05, *p* = 0.38, treatment 241, control 249.
	risk of no recovery, 2.5% higher, RR 1.02, *p* = 0.86, treatment 116 of 241 (48.1%), control 116 of 247 (47.0%), day 5.
Lima-Morales, 2/10/2021, prospective, Mexico, peer-reviewed, 10 authors, average treatment delay 7.2 days, 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%), NNT 6.7, 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%), NNT 50.
	risk of hospitalization, 67.4% lower, RR 0.33, *p* < 0.001, treatment 44 of 481 (9.1%), control 89 of 287 (31.0%), NNT 4.6, 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%), NNT 3.9, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, recovery at day 14 after symptoms, multivariate.
Llenas-García, 5/10/2023, retrospective, Spain, peer-reviewed, 11 authors, study period 23 February, 2020 - 14 March, 2021, average treatment delay 6.0 days, dosage 200µg/kg single dose.	**risk of death, 16.7% lower, RR 0.83, *p* = 0.82**, treatment 10 of 96 (10.4%), control 12 of 96 (12.5%), NNT 48.
	risk of oxygen therapy, 18.4% lower, RR 0.82, *p* = 0.37, treatment 31 of 96 (32.3%), control 38 of 96 (39.6%), NNT 14.
	risk of progression, 23.0% lower, OR 0.77, *p* = 0.52, treatment 96, control 96, adjusted per study, in-hospital mortality or respiratory support, multivariable, primary outcome, RR approximated with OR.
	risk of ICU admission, 4.0% higher, OR 1.04, *p* = 0.92, treatment 96, control 96, adjusted per study, multivariable, RR approximated with OR.
Munir, 4/21/2023, retrospective, Pakistan, peer-reviewed, 3 authors, study period March 2021 - March 2022, dosage not specified.	**risk of death, 48.2% lower, OR 0.52, *p* = 0.13**, treatment 92, control 908, adjusted per study, multivariable, RR approximated with OR.
Mustafa, 12/29/2021, retrospective, Pakistan, peer-reviewed, 7 authors, dosage varies, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 63.7% lower, RR 0.36, *p* = 0.09**, treatment 3 of 73 (4.1%), control 42 of 371 (11.3%), NNT 14.
Naggie, 6/12/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 28 authors, study period 23 June, 2021 - 4 February, 2022, average treatment delay 6.0 days, dosage 600µg/kg days 1-6, trial NCT04885530 (history) (ACTIV-6).	**risk of death, 202.3% higher, RR 3.02, *p* = 0.49**, treatment 1 of 708 (0.1%), control 0 of 724 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), 600*µ*g/kg, day 28.
	risk of death, 194.7% higher, RR 2.95, *p* = 1.00, treatment 1 of 817 (0.1%), control 0 of 774 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), 400*µ*g/kg, day 28.
	risk of death/hospitalization, 256.9% higher, RR 3.57, *p* = 0.11, treatment 7 of 708 (1.0%), control 2 of 722 (0.3%), 600*µ*g/kg, day 28.
	risk of hospitalization, 5.3% higher, RR 1.05, *p* = 1.00, treatment 10 of 817 (1.2%), control 9 of 774 (1.2%), 400*µ*g/kg, day 28.
	risk of progression, 68.4% lower, RR 0.32, *p* = 0.36, treatment 1 of 817 (0.1%), control 3 of 774 (0.4%), NNT 377, 400*µ*g/kg, aggravated C19 pneumonia, eTable 2.
	risk of progression, 3.0% lower, RR 0.97, *p* = 0.53, treatment 39 of 708 (5.5%), control 42 of 722 (5.8%), NNT 324, adjusted per study, urgent or emergency care visits, hospitalizations, or death, 600*µ*g/kg.

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	risk of progression, 20.0% higher, RR 1.20, p = 0.32, treatment 32 of 817 (3.9%), control 28 of 774 (3.6%), adjusted per study, urgent or emergency care visits, hospitalizations, or death, 400μg/kg.
	clinical progression, 29.0% higher, OR 1.29, p = 0.39, treatment 708, control 724, mid-recovery, 600μg/kg, day 7, RR approximated with OR.
	clinical progression, 150.0% higher, OR 2.50, p = 0.08, treatment 708, control 724, 600μg/kg, day 14, RR approximated with OR.
	clinical progression, 150.0% higher, OR 2.50, p = 0.09, treatment 708, control 724, 600μg/kg, day 28, RR approximated with OR.
	clinical progression, 24.0% lower, OR 0.76, p = 0.07, treatment 817, control 774, mid-recovery, 400μg/kg, day 7, RR approximated with OR.
	clinical progression, 27.0% lower, OR 0.73, p = 0.05, treatment 817, control 774, 400μg/kg, day 14, RR approximated with OR.
	clinical progression, 10.0% lower, OR 0.90, p = 0.62, treatment 817, control 774, 400μg/kg, day 28, RR approximated with OR.
	time to recovery, 2.0% lower, HR 0.98, p = 0.71, treatment 708, control 724, inverted to make HR<1 favor treatment, 600μg/kg, post-hoc primary outcome.
	risk of limited activity, 30.5% lower, RR 0.70, p = 0.14, treatment 30 of 805 (3.7%), control 41 of 765 (5.4%), NNT 61, eFigure 2, 400μg/kg, day 14.
	time to recovery, 6.5% lower, HR 0.93, p = 0.22, treatment 817, control 774, inverted to make HR<1 favor treatment, 400μg/kg, post-hoc primary outcome.
	time to recovery, 46.2% lower, HR 0.54, p = 0.02, treatment 39, control 51, inverted to make HR<1 favor treatment, 400μg/kg, severe, recovery.
Ochoa-Jaramillo, 10/21/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Colombia, peer-reviewed, 8 authors, study period 10 December, 2020 - 9 December, 2021, average treatment delay 8.8 days, dosage 400µg/kg single dose, trial NCT04602507 (history).	**risk of death, 57.0% lower, HR 0.43, p = 0.35**, treatment 2 of 37 (5.4%), control 4 of 38 (10.5%), NNT 20, Cox proportional hazards.
	risk of mechanical ventilation, 34.0% higher, HR 1.34, p = 0.62, treatment 7 of 37 (18.9%), control 5 of 38 (13.2%), Cox proportional hazards.
	risk of ICU admission, 37.0% higher, HR 1.37, p = 0.52, treatment 8 of 37 (21.6%), control 6 of 38 (15.8%), Cox proportional hazards, primary outcome.
Okumuş, 1/12/2021, Double Blind Randomized Controlled Trial, Turkey, peer-reviewed, 15 authors, study period May 2020 - September 2020, dosage 200µg/kg days 1-5, 36-50kg - 9mg, 51-65kg - 12mg, 66-79kg - 15mg, >80kg 200µg/kg, trial NCT04646109 (history).	**risk of death, 33.3% lower, RR 0.67, p = 0.55**, treatment 6 of 30 (20.0%), control 9 of 30 (30.0%), NNT 10.
	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%), NNT 5.0.
	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%), NNT 10, primary outcome.
	risk of no viral clearance, 80.0% lower, RR 0.20, p = 0.02, treatment 2 of 16 (12.5%), control 5 of 8 (62.5%), NNT 2.0, day 10.
Osati, 7/16/2023, retrospective, Tanzania, preprint, median age 60.0, 22 authors, study period 26 March, 2021 - 30 July, 2022, dosage not specified.	**risk of death, 31.5% lower, OR 0.68, p = 0.02**, treatment 448, control 849, adjusted per study, inverted to make OR<1 favor treatment, multivariable, RR approximated with OR.
Ozer, 11/23/2021, prospective, USA, peer-reviewed, 12 authors, dosage 200µg/kg days 1, 3.	**risk of death, 75.0% lower, RR 0.25, p = 0.09**, treatment 2 of 60 (3.3%), control 8 of 60 (13.3%), NNT 10.0, PSM.
	risk of mechanical ventilation, 12.6% lower, RR 0.87, p = 0.20, treatment 3 of 60 (5.0%), control 2 of 60 (3.3%), adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable.
	ventilation time, 83.3% lower, relative time 0.17, p = 0.002, treatment 60, control 60.
	risk of ICU admission, 48.7% lower, RR 0.51, p = 0.42, treatment 6 of 60 (10.0%), control 3 of 60 (5.0%), adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable.
	ICU time, 70.6% lower, relative time 0.29, p < 0.001, treatment 60, control 60.
	hospitalization time, 9.0% higher, relative time 1.09, p = 0.09, treatment 60, control 60, adjusted per study, propensity score matching, multivariable.
Podder, 9/3/2020, Randomized Controlled Trial, Bangladesh, peer-reviewed, 4 authors, study period 1 May, 2020 - 31 July, 2020, average treatment delay 7.0 days, 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, peer-reviewed, 10 authors, study period 1 July, 2020 - 1 December, 2020, average treatment delay 8.0 days, dosage 200µg/kg single dose, dose varies in three arms 100, 200, 400µg/kg, censored, see notes, trial NCT04431466 (history).	**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%), NNT 4.7.
	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%), NNT 4.7.
	relative improvement in Ct value, 0.8% better, RR 0.99, p = 1.00, treatment 27, control 3.
	risk of no viral clearance, 11.1% higher, RR 1.11, p = 1.00, treatment 10 of 27 (37.0%), control 1 of 3 (33.3%), primary outcome.
Qadeer, 8/31/2022, prospective, Pakistan, peer-reviewed, median age 55.4, 6 authors, study period 1 November, 2020 - 30 May, 2021, dosage	**risk of no viral clearance, 58.3% lower, RR 0.42, p < 0.001**, treatment 35 of 105 (33.3%), control 84 of 105 (80.0%), NNT 2.1, mid-recovery, day 10.

12mg days 1-5, excluded in exclusion analyses: minimal baseline details provided.	risk of no viral clearance, 20.0% lower, RR 0.80, $p < 0.001$, treatment 84 of 105 (80.0%), control 105 of 105 (100.0%), NNT 5.0, day 7.
	risk of no viral clearance, 98.6% lower, RR 0.01, $p < 0.001$, treatment 0 of 105 (0.0%), control 35 of 105 (33.3%), NNT 3.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
Rajter, 10/13/2020, retrospective, propensity score matching, USA, peer-reviewed, 6 authors, dosage 200µg/kg single dose.	risk of death, 46.0% lower, RR 0.54, $p = 0.045$, treatment 13 of 98 (13.3%), control 24 of 98 (24.5%), NNT 8.9, 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%), NNT 9.8, adjusted per study, odds ratio converted to relative risk, multivariate, primary outcome.
	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%), NNT 14, matched cohort excluding intubated at baseline.
Ravikirti, 4/6/2022, retrospective, India, preprint, 7 authors, study period 1 April, 2021 - 15 May, 2021, dosage varies, excluded in exclusion analyses: exclusion of patients in less severe condition, data/analysis concerns.	risk of death, 2.8% lower, RR 0.97, $p = 0.82$, treatment 53 of 171 (31.0%), control 254 of 794 (32.0%), NNT 100, odds ratio converted to relative risk.
Ravikirti (B), 1/9/2021, Double Blind Randomized Controlled Trial, India, peer-reviewed, 11 authors, study period 1 August, 2020 - 31 October, 2020, average treatment delay 6.1 days, 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%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 79.3% lower, RR 0.21, $p = 0.10$, treatment 1 of 55 (1.8%), control 5 of 57 (8.8%), NNT 14.
	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%), NNT 70.
	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%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no viral clearance, 11.6% higher, RR 1.12, $p = 0.35$, treatment 42 of 55 (76.4%), control 39 of 57 (68.4%).
Rezai (B), 6/16/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, mean age 53.8, 29 authors, study period 19 February, 2021 - 14 August, 2021, average treatment delay 7.18 days, dosage 400µg/kg days 1-3, trial IRCT20111224008507N5, excluded in exclusion analyses:	risk of death, 30.8% lower, RR 0.69, $p = 0.36$, treatment 13 of 311 (4.2%), control 18 of 298 (6.0%), NNT 54.
	risk of mechanical ventilation, 50.0% lower, RR 0.50, $p = 0.07$, treatment 311, control 298.
	risk of ICU admission, 16.0% lower, RR 0.84, $p = 0.47$, treatment 311, control 298.
multiple critical issues, see study page.	hospitalization time, 11.5% higher, relative time 1.11, $p = 0.009$, treatment mean 7.98 (±4.4) n=311, control mean 7.16 (±3.2) n=298.
	deterioration, 12.7% higher, RR 1.13, $p = 0.74$, treatment 20 of 311 (6.4%), control 17 of 298 (5.7%).
	risk of no recovery, 24.2% lower, RR 0.76, $p = 0.02$, treatment 311, control 298, inverted to make RR<1 favor treatment, post-hoc primary outcome.
	risk of no recovery, 64.0% lower, RR 0.36, $p = 0.06$, treatment 5 of 145 (3.4%), control 10 of 105 (9.5%), NNT 16, day 7, cough.
	risk of no recovery, 76.0% lower, RR 0.24, $p = 0.38$, day 7, tachypnea.
Rezk, 10/30/2021, prospective, Egypt, peer-reviewed, 4 authors, dosage 36mg days 1, 3, 6.	risk of death, 80.0% lower, RR 0.20, $p = 0.50$, treatment 0 of 160 (0.0%), control 2 of 160 (1.2%), NNT 80, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of progression, 55.6% lower, RR 0.44, $p = 0.06$, treatment 8 of 160 (5.0%), control 18 of 160 (11.2%), NNT 16, 2 weeks, including deaths.
	risk of no recovery, 33.4% lower, RR 0.67, $p = 0.27$, treatment 14 of 145 (9.7%), control 20 of 138 (14.5%), NNT 21, 4 weeks, more patients were lost to followup in the control group.
	time to viral-, 27.3% lower, relative time 0.73, $p = 0.01$, treatment 160, control 160.
Sarojvisut, 12/12/2022, Randomized Controlled Trial, Thailand, peer-reviewed, 8 authors, study period 1 October, 2021 - 31 May, 2022, dosage 400µg/kg days 1-5, trial TCTR20220427005, excluded in exclusion analyses: many critical issues including missing primary outcome results, non-reproducible values, and protocol violations.	risk of death, 1.9% higher, RR 1.02, $p = 1.00$, treatment 1 of 157 (0.6%), control 1 of 160 (0.6%), all-cause in-hospital mortality.
	risk of ICU admission, 103.8% higher, RR 2.04, $p = 0.62$, treatment 2 of 157 (1.3%), control 1 of 160 (0.6%).
	risk of no improvement, 103.8% higher, RR 2.04, $p = 0.62$, treatment 2 of 157 (1.3%), control 1 of 160 (0.6%), failure to improve ≥2 points on WHO ordinal scale.
	recovery time, 3.8% lower, relative time 0.96, $p = 0.63$, treatment 157, control 160.
Shahbaznejad, 1/19/2021, Double Blind Randomized Controlled Trial, Iran, peer-reviewed, 8 authors, average treatment delay 6.29 days, dosage 200µg/kg single dose, trial IRCT20111224008507N3.	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, $p = 0.048$, treatment 35, control 34, duration of dsypnea.

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	recovery time, 19.2% lower, relative time 0.81, $p = 0.02$, treatment 35, control 34, duration of all symptoms, primary outcome.
	hospitalization time, 15.5% lower, relative time 0.85, $p = 0.02$, treatment 35, control 34.
Shimizu, 12/31/2021, retrospective, Japan, peer-reviewed, 11 authors, study period December 2020 - May 2021, dosage 200µg/kg days 1, 14.	risk of death, 99.9% lower, HR 0.001, $p < 0.001$, treatment 0 of 39 (0.0%), control 8 of 49 (16.3%), NNT 6.1, adjusted per study, Cox proportional hazard regression.
	ventilator free days, 47.9% lower, OR 0.52, $p = 0.03$, treatment 39, control 49, adjusted per study, inverted to make OR<1 favor treatment, proportional odds logistic regression, primary outcome, RR approximated with OR.
	ventilation time, 38.5% lower, relative time 0.62, $p < 0.001$, treatment 39, control 49.
	ICU free days, 42.8% lower, OR 0.57, $p = 0.06$, treatment 39, control 49, adjusted per study, inverted to make OR<1 favor treatment, proportional odds logistic regression, RR approximated with OR.
	ICU time, 37.5% lower, relative time 0.62, $p < 0.001$, treatment 39, control 49.
	GI complications while ventilated, 77.9% lower, RR 0.22, $p = 0.03$, treatment 39, control 49, adjusted per study, Cox proportional hazard regression.
Soto, 3/2/2022, retrospective, Peru, peer-reviewed, median age 58.0, 10 authors, study period April 2020 - August 2020, dosage not specified, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; substantial confounding by time possible due to significant changes in SOC and treatment propensity near the start of the pandemic.	risk of death, 41.0% higher, HR 1.41, $p = 0.001$, treatment 280 of 484 (57.9%), control 374 of 934 (40.0%), adjusted per study, multivariable.
Soto-Becerra, 10/8/2020, retrospective, database analysis, Peru, preprint, median age 59.4, 4 authors, study period 1 April, 2020 - 19 July, 2020, 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, HR 0.83, $p = 0.01$, treatment 92 of 203 (45.3%), control 1,438 of 2,630 (54.7%), NNT 11, IVM vs. control day 43 (last day available) weighted KM from figure 3, per the pre-specified rules the last available day results have priority, day 43.
	risk of death, 39.0% higher, HR 1.39, $p = 0.16$, treatment 47 of 203 (23.2%), control 401 of 2,630 (15.2%), adjusted per study, Table 2, IVM wHR, day 30, primary outcome.
Spoorthi, 11/14/2020, prospective, India, 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.
Thairu, 2/25/2022, retrospective, Nigeria, peer-reviewed, mean age 41.7, 6 authors, study period April 2021 - November 2021, dosage 200µg/kg days 1-5, excluded in exclusion analyses: significant confounding by time possible due to separation of groups in different time periods.	risk of death, 87.9% lower, RR 0.12, $p = 0.12$, treatment 0 of 21 (0.0%), control 4 of 26 (15.4%), NNT 6.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), propensity score matching.
	risk of death, 93.0% lower, RR 0.07, $p = 0.007$, treatment 0 of 61 (0.0%), control 4 of 26 (15.4%), NNT 6.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), all patients.
	time to discharge, 54.6% lower, relative time 0.45, $p < 0.001$, treatment 61, control 26, propensity score matching.
	risk of no viral clearance, 94.8% lower, RR 0.05, $p = 0.001$, treatment 0 of 21 (0.0%), control 10 of 26 (38.5%), NNT 2.6, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), propensity score matching, day 21.
	risk of no viral clearance, 95.2% lower, RR 0.05, $p < 0.001$, treatment 1 of 21 (4.8%), control 26 of 26 (100.0%), NNT 1.1, propensity score matching, day 14.
	risk of no viral clearance, 28.6% lower, RR 0.71, $p = 0.005$, treatment 15 of 21 (71.4%), control 26 of 26 (100.0%), NNT 3.5, propensity score matching, day 5.
Varnaseri, 4/30/2024, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 14 authors, study period July 2020 - June 2021, dosage 14mg bid days 1-3.	risk of mechanical ventilation, 81.8% lower, RR 0.18, $p = 0.02$, treatment 2 of 55 (3.6%), control 11 of 55 (20.0%), NNT 6.1.
	risk of ICU admission, 83.3% lower, RR 0.17, $p < 0.001$, treatment 3 of 55 (5.5%), control 18 of 55 (32.7%), NNT 3.7.
	hospitalization time, 33.3% lower, relative time 0.67, $p < 0.001$, treatment 55, control 55.
	recovery time, 28.4% lower, relative time 0.72, $p < 0.001$, treatment 55, control 55, all symptoms combined.
	recovery time, 25.0% lower, relative time 0.75, $p < 0.001$, treatment 55, control 55, dyspnea.
	recovery time, 25.0% lower, relative time 0.75, $p < 0.001$, treatment 55, control 55, fever.
	recovery time, 25.0% lower, relative time 0.75, $p < 0.001$, treatment 55, control 55, shivering.
	recovery time, 40.0% lower, relative time 0.60, $p < 0.001$, treatment 55, control 55, cough.
	recovery time, 37.5% lower, relative time 0.62, $p = 0.09$, treatment 55, control 55, sore throat.
	recovery time, 25.0% lower, relative time 0.75, $p = 0.01$, treatment 55, control 55, nausea.
	recovery time, 37.5% lower, relative time 0.62, $p = 0.005$, treatment 55, control 55, diarrhea.

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	recovery time, 40.0% lower, relative time 0.60, $p < 0.001$, treatment 55, control 55, myalgia.
Wada, 5/22/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Japan, peer-reviewed, 26 authors, study period August 2020 - October 2021, average treatment delay 6.6 days, dosage 200µg/kg single dose, trial NCT04703205 (history).	risk of progression, 19.0% lower, RR 0.81, $p = 0.46$, treatment 19 of 106 (17.9%), control 23 of 106 (21.7%), NNT 26, adjusted per study, odds ratio converted to relative risk.
	risk of progression, 27.1% lower, RR 0.73, $p = 0.47$, treatment 7 of 28 (25.0%), control 9 of 29 (31.0%), NNT 17, adjusted per study, odds ratio converted to relative risk, pneumonia for patients w/o pneumonia at baseline.
	risk of oxygen therapy, 14.3% higher, RR 1.14, $p = 0.46$, treatment 22 of 106 (20.8%), control 19 of 106 (17.9%), adjusted per study, odds ratio converted to relative risk.
	improvement, 23.5% worse, OR 1.23, $p = 0.61$, treatment 106, control 106, adjusted per study, inverted to make OR<1 favor treatment, RR approximated with OR.
	risk of no recovery, 60.0% lower, RR 0.40, $p = 0.17$, treatment 4 of 107 (3.7%), control 10 of 107 (9.3%), NNT 18, day 15, dyspnea.
	risk of no recovery, 20.0% lower, RR 0.80, $p = 1.00$, treatment 4 of 107 (3.7%), control 5 of 107 (4.7%), NNT 107, day 15, headache.
	risk of no recovery, no change, RR 1.00, $p = 1.00$, treatment 7 of 107 (6.5%), control 7 of 107 (6.5%), day 15, sore throat.
	risk of no recovery, 18.2% lower, RR 0.82, $p = 0.81$, treatment 9 of 107 (8.4%), control 11 of 107 (10.3%), NNT 53, day 15, nasal discharge.
	risk of no recovery, 3.8% higher, RR 1.04, $p = 1.00$, treatment 27 of 107 (25.2%), control 26 of 107 (24.3%), day 15, cough.
	risk of no recovery, no change, RR 1.00, $p = 1.00$, treatment 18 of 107 (16.8%), control 18 of 107 (16.8%), day 15, sputum.
	risk of no recovery, 20.0% lower, RR 0.80, $p = 1.00$, treatment 4 of 107 (3.7%), control 5 of 107 (4.7%), NNT 107, day 15, diarhhea.
	risk of no recovery, 66.7% higher, RR 1.67, $p = 0.72$, treatment 5 of 107 (4.7%), control 3 of 107 (2.8%), day 15, myalgia.
	risk of no recovery, 1000.0% higher, RR 11.00, $p = 0.06$, treatment 5 of 107 (4.7%), control 0 of 107 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 15, arthralgia.
	risk of no viral clearance, 4.2% higher, HR 1.04, $p = 0.79$, treatment 106, control 106, inverted to make HR<1 favor treatment, Kaplan-Meier, primary outcome.
Zubair, 1/18/2022, retrospective, Pakistan, peer-reviewed, 8 authors, study period October 2020 - February 2021,	risk of death, 9.0% higher, RR 1.09, $p = 1.00$, treatment 5 of 90 (5.6%), control 5 of 98 (5.1%), unadjusted.
dosage 12mg single dose, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; unadjusted results with no group details.	hospitalization time, 8.0% higher, relative time 1.08, $p = 0.40$, treatment 90, control 98, unadjusted, Table 3, mean number of days.

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 pooled analysis, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Alam, 12/15/2020, prospective, Bangladesh, peer-reviewed, 13 authors, dosage 12mg monthly.	risk of case, 90.6% lower, RR 0.09, $p < 0.001$, treatment 4 of 58 (6.9%), control 44 of 60 (73.3%), NNT 1.5.
Behera (B), 2/15/2021, prospective, India, peer-reviewed, 14 authors, dosage 300µg/kg days 1, 4.	risk of case, 83.0% lower, RR 0.17, $p < 0.001$, treatment 45 of 2,199 (2.0%), control 133 of 1,147 (11.6%), NNT 10, two doses, primary outcome.
Behera, 11/3/2020, retrospective, India, peer-reviewed, 13 authors, dosage 300µg/kg days 1, 4.	risk of case, 53.8% lower, RR 0.46, $p < 0.001$, treatment 41 of 117 (35.0%), control 145 of 255 (56.9%), NNT 4.6, adjusted per study, odds ratio converted to relative risk, model 2 2+ doses conditional logistic regression.
Bernigaud, 11/28/2020, retrospective, France, 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%), NNT 20, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of case, 55.1% lower, RR 0.45, $p = 0.01$, treatment 7 of 69 (10.1%), control 692 of 3,062 (22.6%), NNT 8.0.
Carvallo, 11/17/2020, prospective, Argentina, 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, see notes, excluded in exclusion analyses: concern about potential data issues.	risk of case, 99.9% lower, RR 0.001, $p < 0.001$, treatment 0 of 788 (0.0%), control 237 of 407 (58.2%), NNT 1.7, 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, 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, see notes, trial NCT04425850 (history), excluded in exclusion analyses: concern about potential data issues.	risk of case, 96.3% lower, RR 0.04, $p < 0.001$, treatment 0 of 131 (0.0%), control 11 of 98 (11.2%), NNT 8.9, 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 Controlled Trial, Ar-	risk of moderate/severe case, 95.2% lower, RR 0.05, $p = 0.002$, treatment 0 of 117 (0.0%),

gentina, peer-reviewed, 11 authors, study period 15 October, 2020 - 31 December, 2020, dosage 12mg weekly, this trial uses multiple treatments in the treatment arm (combined with iota-carrageenan) - results of individual treatments may vary, trial NCT04701710 (history).	control 10 of 117 (8.5%), NNT 12, 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 case, 84.0% lower, RR 0.16, p = 0.004, treatment 4 of 117 (3.4%), control 25 of 117 (21.4%), NNT 5.6, adjusted per study, odds ratio converted to relative risk, all cases, primary outcome.
Desort-Henin, 1/5/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Bulgaria, preprint, 5 authors, study period March 2022 - October 2022, dosage 200µg/kg day 1, 100µg/kg days 2-28, trial NCT05305560 (history) (SAIVE).	**risk of high viral load, 96.0% lower, RR 0.04, p < 0.001**, treatment 4 of 200 (2.0%), control 99 of 199 (49.7%), NNT 2.1.
	risk of case, 71.6% lower, RR 0.28, p < 0.001, treatment 30 of 200 (15.0%), control 105 of 199 (52.8%), NNT 2.6, primary outcome.
Hellwig, 11/28/2020, retrospective, ecological study, multiple countries, 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 case, 78.0% lower, RR 0.22, p < 0.02**, African countries, PCTI vs. no PCT, relative cases per capita.
IVERCOR PREP, 12/20/2020, retrospective, Argentina, preprint, 1 author, dosage 12mg weekly, excluded in exclusion analyses: minimal details provided.	**risk of case, 73.4% lower, RR 0.27, p < 0.001**, treatment 13 of 389 (3.3%), control 61 of 486 (12.6%), NNT 11.
Kerr, 12/11/2021, retrospective, propensity score matching, Brazil, peer-reviewed, 9 authors, study period July 2020 - December 2020, dosage 200µg/kg days 1, 2, 16, 17, 0.2mg/kg/day for 2 days every 15 days.	**risk of death, 70.0% lower, RR 0.30, p < 0.001**, treatment 25 of 3,034 (0.8%), control 79 of 3,034 (2.6%), NNT 56, adjusted per study, multivariate linear regression, propensity score matching.
	risk of hospitalization, 67.0% lower, RR 0.33, p < 0.001, treatment 44 of 3,034 (1.5%), control 99 of 3,034 (3.3%), adjusted per study, multivariate linear regression, propensity score matching.
	risk of case, 44.5% lower, RR 0.56, p < 0.001, treatment 4,197 of 113,845 (3.7%), control 3,034 of 45,716 (6.6%), NNT 34.
Mondal, 5/31/2021, retrospective, India, 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, adjusted per study, odds ratio converted to relative risk, control prevalence approximated with overall prevalence, multivariable, primary outcome.
Moraes, 4/30/2021, Randomized Controlled Trial, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04384458 (history).	Estimated 400 patient RCT with results unknown and over 5 years late.
Morgenstern, 4/16/2021, retrospective, propensity score matching, Dominican Republic, peer-reviewed, 16 authors, dosage 200µg/kg weekly, trial NCT04832945 (history).	**risk of hospitalization, 80.0% lower, RR 0.20, p = 0.50**, treatment 0 of 271 (0.0%), control 2 of 271 (0.7%), NNT 136, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), PSM.
	risk of case, 74.0% lower, RR 0.26, p = 0.008, treatment 5 of 271 (1.8%), control 18 of 271 (6.6%), NNT 21, adjusted per study, PSM, multivariate Cox regression, primary outcome.
PREVENT-COVID, 6/24/2023, Double Blind Randomized Controlled Trial, placebo-controlled, trial NCT05060666 (history) (PREVENT-COVID).	Estimated 412 patient RCT with results unknown and over 4 years late.
Samajdar, 11/17/2021, retrospective, India, peer-reviewed, 9 authors, study period 1 September, 2020 - 31 December, 2020, dosage not specified, excluded in exclusion analyses: minimal details provided; unadjusted results with no group details; results may be significantly affected by survey bias.	**risk of case, 79.8% lower, RR 0.20, p < 0.001**, treatment 12 of 164 (7.3%), control 29 of 81 (35.8%), NNT 3.5, odds ratio converted to relative risk, physician survey.
	risk of case, 48.6% lower, RR 0.51, p = 0.03, treatment 11 of 109 (10.1%), control 39 of 200 (19.5%), NNT 11, odds ratio converted to relative risk, combined ivermectin or HCQ in community.
Seet, 4/14/2021, Cluster Randomized Controlled Trial, Singapore, peer-reviewed, 15 authors, study period 13 May, 2020 - 31 August, 2020, dosage 12mg single dose, 200µg/kg, maximum 12mg, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04446104 (history).	**risk of symptomatic case, 49.8% lower, RR 0.50, p < 0.001**, treatment 32 of 617 (5.2%), control 64 of 619 (10.3%), NNT 19.
	risk of case, 5.8% lower, RR 0.94, p = 0.61, treatment 398 of 617 (64.5%), control 433 of 619 (70.0%), NNT 18, adjusted per study, odds ratio converted to relative risk, model 6, primary outcome.
Shouman (B), 8/28/2020, Randomized Controlled Trial, Egypt, peer-reviewed, 8 authors, study period 1 June, 2020 - 28 July, 2020, dosage 18mg days 1, 3, dose varies depending on weight - 40-60kg: 15mg, 60-80kg: 18mg, >80kg: 24mg, trial NCT04422561 (history).	**risk of symptomatic case, 91.3% lower, RR 0.09, p < 0.001**, treatment 15 of 203 (7.4%), control 59 of 101 (58.4%), NNT 2.0, adjusted per study, inverted to make RR<1 favor treatment, multivariate, primary outcome.
	risk of severe case, 92.9% lower, RR 0.07, p = 0.002, treatment 1 of 203 (0.5%), control 7 of 101 (6.9%), NNT 16, unadjusted.
Tanioka, 3/26/2021, retrospective, ecological study, multiple countries, 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.
Wagstaff (D), 9/16/2025, Double Blind Randomized Controlled Trial, placebo-controlled, Australia, peer-reviewed, median age 50.0, 9	**DAFS, 54.5% lower, OR 0.45, p = 0.04**, treatment 36, control 32, adjusted per study, inverted to make OR<1 favor treatment, DAFS 1-14, multivariable, RR approximated with OR.

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authors, study period 22 November, 2021 - 31 May, 2024, trial ACTRN12621001535864.	DAFS, 33.3% lower, OR 0.67, p = 0.35, treatment 36, control 32, adjusted per study, inverted to make OR<1 favor treatment, DAFS 1-28, multivariable, RR approximated with OR.
	viral+ time, 47.4% lower, relative time 0.53, p = 0.03, treatment 36, control 32, adjusted per study, inverted to make RR<1 favor treatment, relative mean time to positive PCR/RAT.
	risk of case, 11.1% lower, RR 0.89, p = 0.80, treatment 11 of 36 (30.6%), control 11 of 32 (34.4%), NNT 26.

Evaluation Notes

Analyzing the data from first principles is always important, and may be especially important for COVID-19. Bias in the design, analysis, and reporting of clinical studies has long been reported, and may be increased for COVID-19 due to politicization. For example, Scott Alexander noted that *"if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele."* [210] Social pressure to report politically acceptable results was very strong. There may therefore be unusually strong bias in design, analysis, and reporting. For example, Prof. Greenland reports that *Hayward et al.* applied an unjustified and undisclosed extremely tight, null-centered Bayesian prior that biases towards more politically acceptable results [771]. While the politicization focused on certain treatments, it was not limited to them. For example, media coverage was highly biased against positive results for low-cost treatments [772] across the 227 treatments we cover. Studies should be evaluated from first principles, incorporating the treatment delay, treatment regimen, patient population, and other confounding factors. For COVID-19, there is no significant difference in the results of RCTs compared to observational studies, RR 0.97 [0.91-1.03] [157]—in both cases bias varies from minimal to extreme, and all studies must be evaluated individually.

US authorities claim only three high-profit drugs from companies with strong US lobbying are beneficial for early treatment (2 repurposed drugs - remdesivir and molnupiravir, and one novel drug - nirmatrelvir) [E]. COVID-19 involves the interplay of many viral and host proteins and factors, providing over 500 therapeutic targets [253]. Given the 12,000+ proposed treatments [46], existing results for many treatments with overlapping secondary complications and therapeutic targets, and the combination of known safety and pharmocokinetics for certain treatments along with strong mechanistic evidence, the probability of only 3 high-profit drugs from top lobbying companies being beneficial is extremely low. This likely reflects a bias toward evaluation of drugs with strong financial resources and efforts devoted to passing the US approval process, and very limited or non-existing evaluation of low-cost treatments. Indeed, official recommendations varied widely between countries [773]. Some countries evaluated limited low-cost treatments early and 26 low-cost treatments were approved in one or more countries [773].

Note that RCTs widely cited in a negative light report results far more positive than claimed, despite very poor design and major issues. The Oxford PRINCIPLE RCT shows 36% lower ongoing persistent COVID-19 specific symptoms, p<0.0001 [164]. The primary outcome shows superiority of ivermectin with significantly faster recovery and a probability of superiority > 0.999, consistent across multiple variants of the recovery outcome. The other arms of this trial confirm that the efficacy is not due to the open-label design. The co-principal investigator of the TOGETHER trial stated that *"There is a clear signal that IVM works in COVID patients.. that would be significant if more patients were added.."* [161]. The ACTIV-6-400 trial reported 99%, 98%, 97% superiority for time unwell, and progression @14,7 days. Authors changed these results and have not been able to provide a reason, however this efficacy can be seen in the preprint [428] and presentation [429]. The COVID-OUT RCT shows 61% lower hospitalization for ivermectin vs. placebo (unreported in the paper but available in the data). Authors detail why the hypoxemia results are unusable, however analysis of the data shows that the ER results are similarly uninformative and do not appear to be related to symptoms [163]. The I-TECH RCT shows 69% lower mortality, narrowly missing the significance threshold. Prof. Fenton shows that Bayesian analysis results in significantly lower mortality (97% probability that ivermectin reduces mortality [774]).

Contrary to claims found online, we analyze both all studies and higher-quality studies (with evaluation focusing on known issues and bias, and the potential impact on outcomes, rather than just the risk of bias), we analyze specific outcomes and pooled outcomes (with extensive analysis and validation of pooled outcomes), and we do not include preclinical studies or retracted studies such as *Elgazzar et al.* in meta-analysis. Pooled outcomes can detect efficacy earlier but do not bias towards efficacy—the inclusion of less appropriate designs such as very late treatment may hide efficacy for appopriate use. Our analysis includes some low-quality negative studies with major flaws such as the TOGETHER trial, which includes multiple impossible numbers, broke blinding, had randomization failure, refuses to release data, and had many protocol violations [161]. These trials would normally be retracted, however retraction of studies claiming negative results is likely to be delayed until a new generation of editors take over, due to the politicization. We include these studies for transparency because they remain in the literature. They do not affect the results—significant efficacy is seen even when they are included.

Supplementary Data

Supplementary Data

Footnotes

a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

b. Smoking was known to cause lung cancer since at least 1939, but this was not widely recognized in the US until 1964, 25 years later. Surgeon general Leroy Burney tried publicizing the danger starting in 1957, with limited success. Surgeon general Luther Terry, appointed in 1961, prompted by President Kennedy in 1962 amid pressure from health advocates, finally got recognition in 1964. The 1964 report reviewed 7,000+ studies, but these could (and should) have been reviewed and acted upon in real-time as they were published. Historians attribute the 25 year delay to an industry campaign to manufacture doubt and controversy, through tactics like funding biased and fraudulent research from "independent" organizations, attacking scientists, and political lobbying. The success of the industry campaign is only possible because officials did not analyze the research in detail. Fraudulent industry research supported prior failures, but would have been called out as fraudulent by officials that analyzed and understood the research in real-time.

c. When administered late in infection, HCQ may enhance viral egress by further increasing lysosomal pH beyond the effect of ORF3a's water channel activity, thereby promoting lysosomal exocytosis, inactivating degradative enzymes, and facilitating the release of SARS-CoV-2 particles into the extracellular environment [759,760]. Research also suggests potential cardioprotective effects at lower doses, but cardiotoxicity with excessive dosage [761]. *Bobrowski et al.* also indicate negative effects if HCQ and remdesivir are combined.

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d. *Peters (B) et al.* is subject to confounding by calendar-time (SOC evolved rapidly early in the pandemic, the linear covariate does not reflect non-linear SOC changes and hospital specific effects), hospital type (non-treatment hospitals were tertiary university centers), confounding by indication (4/7 hospitals initiated treatment on deterioration), immortal-time bias for as-treated (exposure assigned after baseline), significant differences for other experimental treatments, potential overadjustment from collider bias (steroid use and indication bias), limited baseline severity information, differences in hospice referral propensity across hospitals, unadjusted difference in time from onset to admission, difference in PCR positivity, and other factors. *Mahévas et al.* is subject to confounding by hospital (treatment highly dependent on the hospital, different SOC/ICU transfer practices, not included in PS), immortal time (only partly addressed in sensitivity analysis), co-treatment differences, calendar-time (SOC evolved rapidly early in the pandemic), binary coding for age (age ≥65 despite steep age-risk gradient), residual imbalance (variables dropped from PS), a composite outcome dependent on hospital triage/capacity, and other factors.

e. Monoclonal antibodies were previously included. Other treatments such as dexamethasone, tocilizumab, and baricitinib were recommended for late stage hospitalized patients.

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