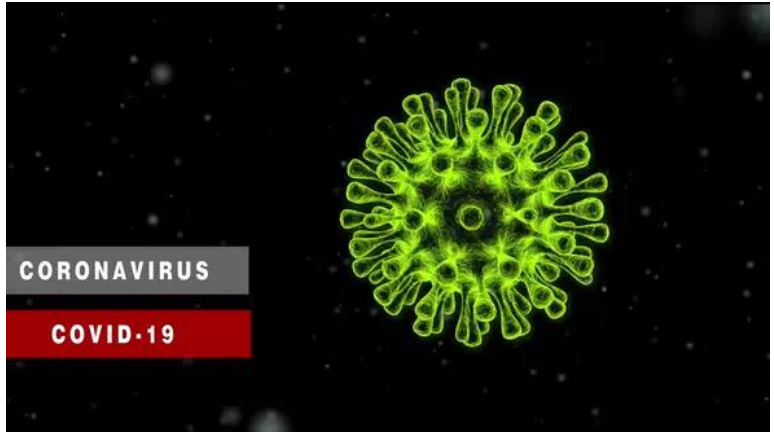
Meta-analysis of clinical trials of ivermectin to treat COVID-19 infection



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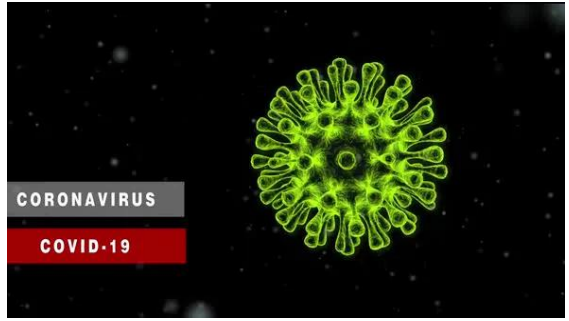
Introduction



Ivermectin is a widely available, generic treatment, being evaluated in 56 randomised clinical trials to treat COVID-19 worldwide, in over 7000 patients.

Mechanism of action likely to be anti-inflammatory (animal models).

No individual clinical trial is large enough to clearly establish efficacy
The combined data from all available clinical trials may be large enough to assess clinical efficacy reliably

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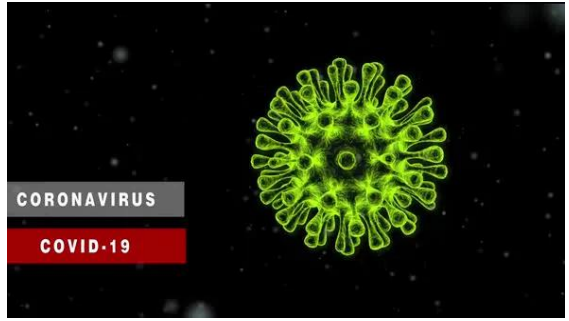
Research question



Is there enough clinical evidence to support the worldwide approval of ivermectin to treat COVID-19?

Endpoints:

Viral clearance (PCR)
Time to clinical recovery
Duration of Hospitalisation
Survival

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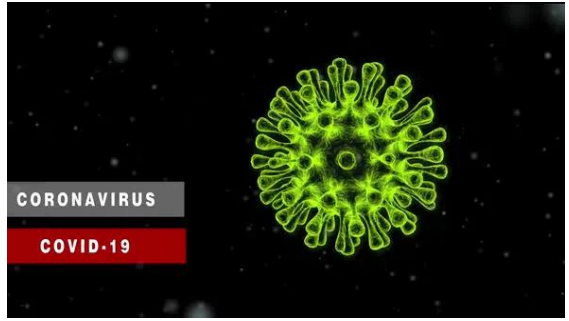
Search strategy



Systematic review of randomised trials of ivermectin to treat COVID-19 infection:

PUBMED
EMBASE
Archive pre-print databases (MEDRxiv, Research Square)
www.clinicaltrials.gov.
Coronavirus Antiviral Research Database (CoV-RDB)
WHO clinical trials website
Country-level clinical trials websites (Egypt, Iran, India, China)

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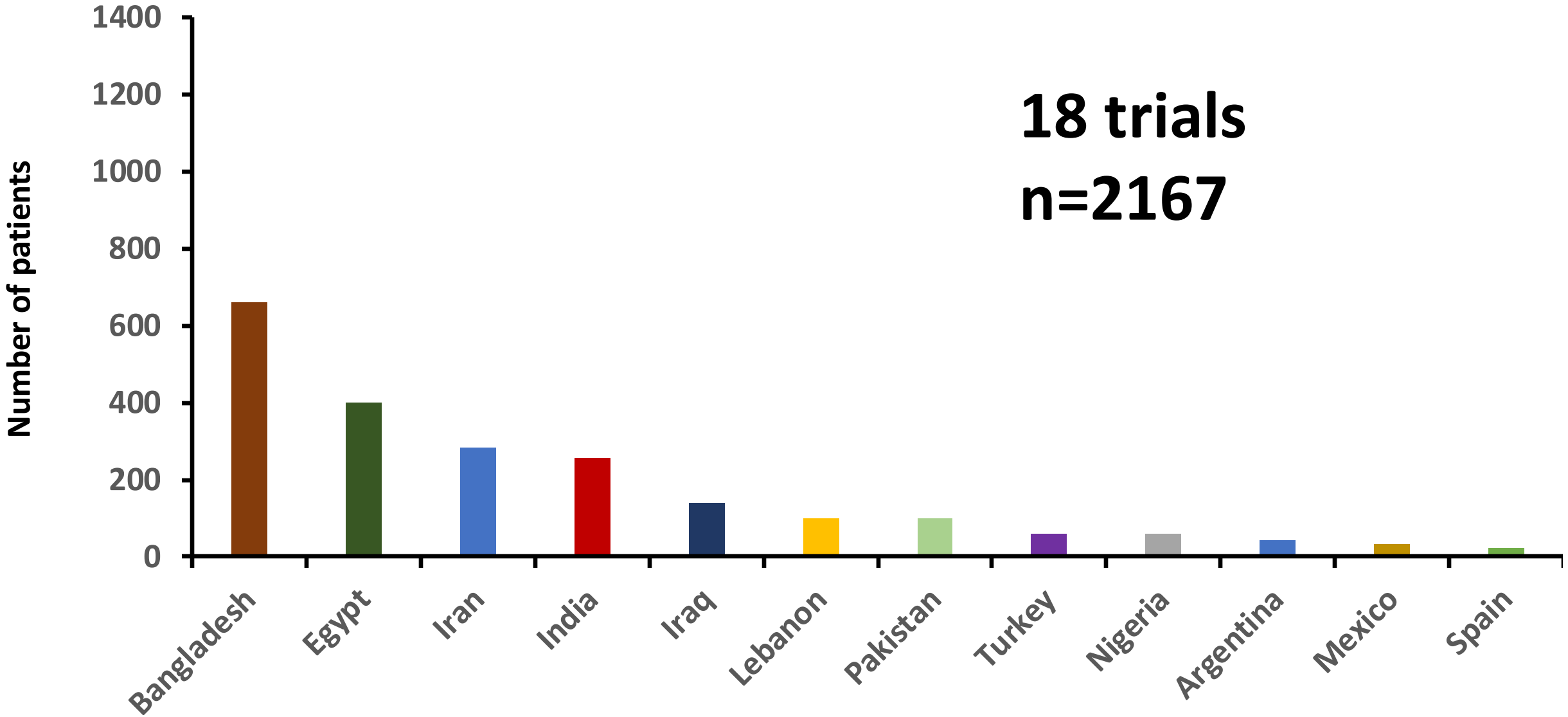
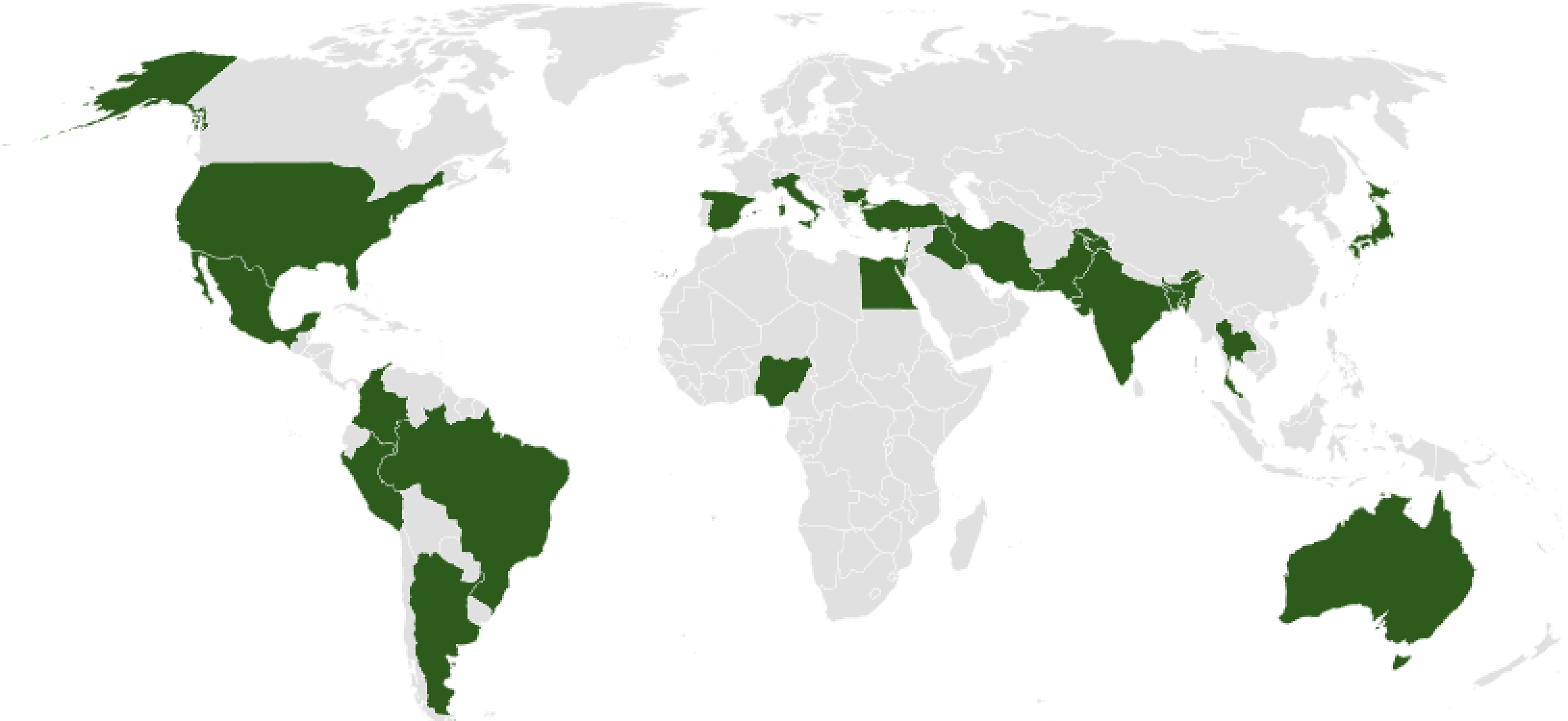
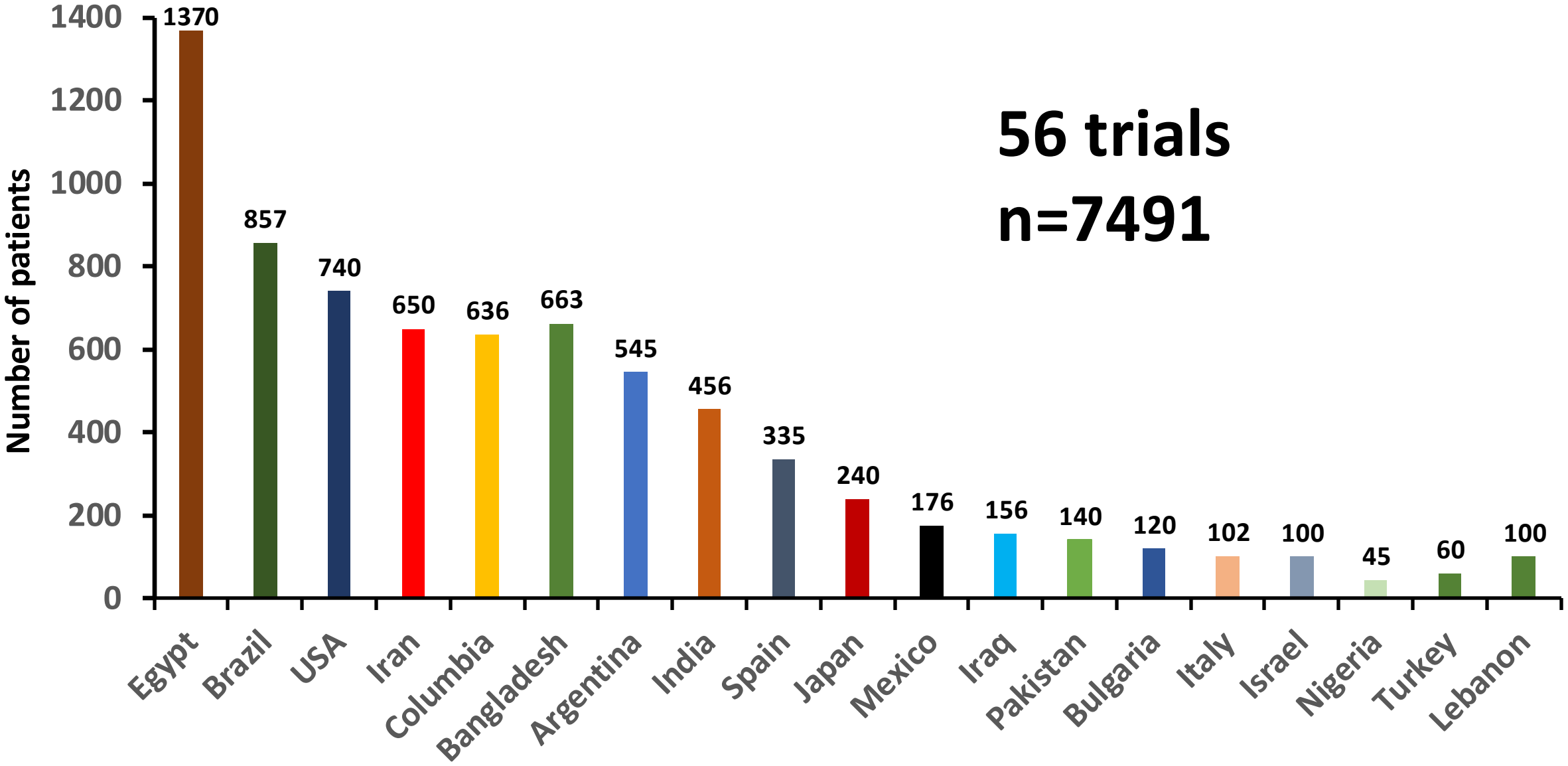
Randomised clinical trials of ivermectin in meta-analysis



Clinical trials of ivermectin in at least 21 countries worldwide



All randomised clinical trials of ivermectin



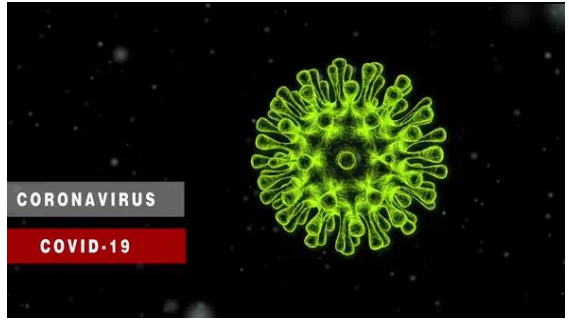
Ivermectin trials with dosing on Day 1 only, 9 randomized trials, n=1125

Study	Country	Daily dose	Duration	Sample Size	Patients	Intervention Arm	Comparator Arm
Spoorthi et al	India	0.2 mg/kg	1 day (DB)	100	Mild to moderate	Ivermectin + Doxycycline	Placebo
Raad et al	Lebanon	0.2 mg/kg	1 day (SB)	100	Mild	Ivermectin + SOC	Standard of Care
Asghar et al	Pakistan	0.2 mg/kg	1 day (OL)	100	Mild / moderate	Ivermectin + SOC	Standard of Care
Rezai et al	Iran	0.2 mg/kg	1 day (DB)	103	Moderate / severe	Ivermectin + SOC	Standard of Care
Mohan et al	India	0.2-0.4 mg/kg (elixir)	1 day (DB)	157	Mild / moderate	Ivermectin + SOC	Placebo + Standard of care
Mahmud et al	Bangladesh	12 mg	1 day (DB)	363	Mild/ moderate	Ivermectin + Doxycycline + SOC	Standard of Care
Chowdhury	Bangladesh	0.2 mg/kg	1 day (DB)	116	PCR positive	Ivermectin + Doxycycline	HCQ + Azithromycin
Podder et al	Bangladesh	0.2 mg/kg	1 day (OL)	62	Mild	Ivermectin + SOC	Standard of Care
Saint	Spain	0.4 mg/kg	1 day (DB)	24	Moderate	Ivermectin	Placebo

Ivermectin trials with multi-day dosing
9 randomized trials, n=1042

Study	Country	Daily dose	Duration	Sample size	Inclusion criteria	Intervention Arm	Comparator arm
Elgazzar et al	Egypt	0.4 mg/kg	5 days (OL)	400	Mild to severe	Ivermectin + SOC	HCQ + SOC
Niaee et al	Iran	0.2 - 0.4 mg/kg	1-3 days (DB)	180	Mild / moderate	Ivermectin + SOC	Standard of Care + Placebo
Hashim et al	Iraq	0.2 mg/kg	2-3 days (SB)	140	Symptomatic	Ivermectin + Doxycycline + SOC	Standard of Care
Ahmed et al	Bangladesh	0.2 mg/kg	5 days (DB)	72	Mild	Ivermectin + SOC	Standard of Care Placebo
Chachar et al	Pakistan	0.2 mg/kg	7 days (OL)	50	Mild	Ivermectin + SOC	Standard of Care
Garrahan et al	Argentina	0.6 mg/kg	5 days (OL)	45	Outpatients	Ivermectin + SOC	Standard of Care
Espitia et al	Mexico	0.2 mg/kg	5 days (OL)	35	Mild to moderate	Ivermectin + AZI + Cholecalciferol	Standard of Care
Okomus et al	Turkey	0.2 mg/kg	5 days (DB)	60	Severe	Ivermectin + SOC	FAVI/HQ/AZI (SOC)
Babaloa et al	Nigeria	0.1-0.2 mg/kg	2 / week (DB)	60	Mild	Ivermectin + SOC	Placebo + LPV/r (SOC)

Meta-analysis - methods



Only the randomised clinical trials were included: in WHO GRADE criteria, systematic review and meta-analysis of RCTs provides the highest level of evidence

Cochran Mantel-Haenszel testing with inverse variance weighting and random effects modelling was used to compare survival between ivermectin with control treatment. Other outcomes were summarised for each study individually

Effects of ivermectin dose on response were investigated

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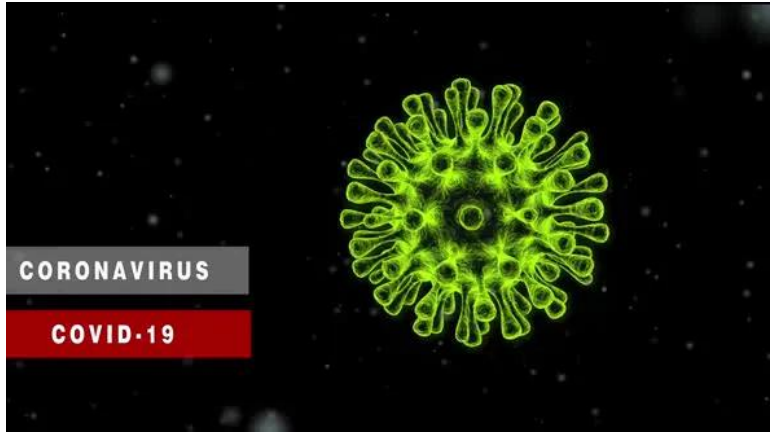

Effects on inflammatory markers

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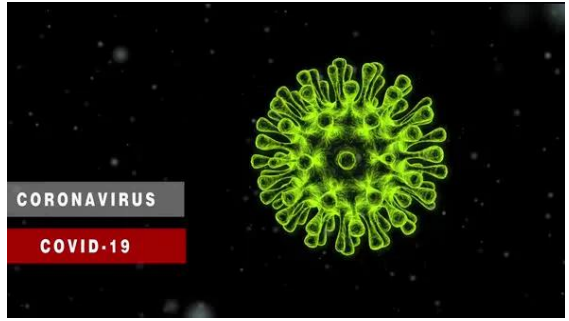
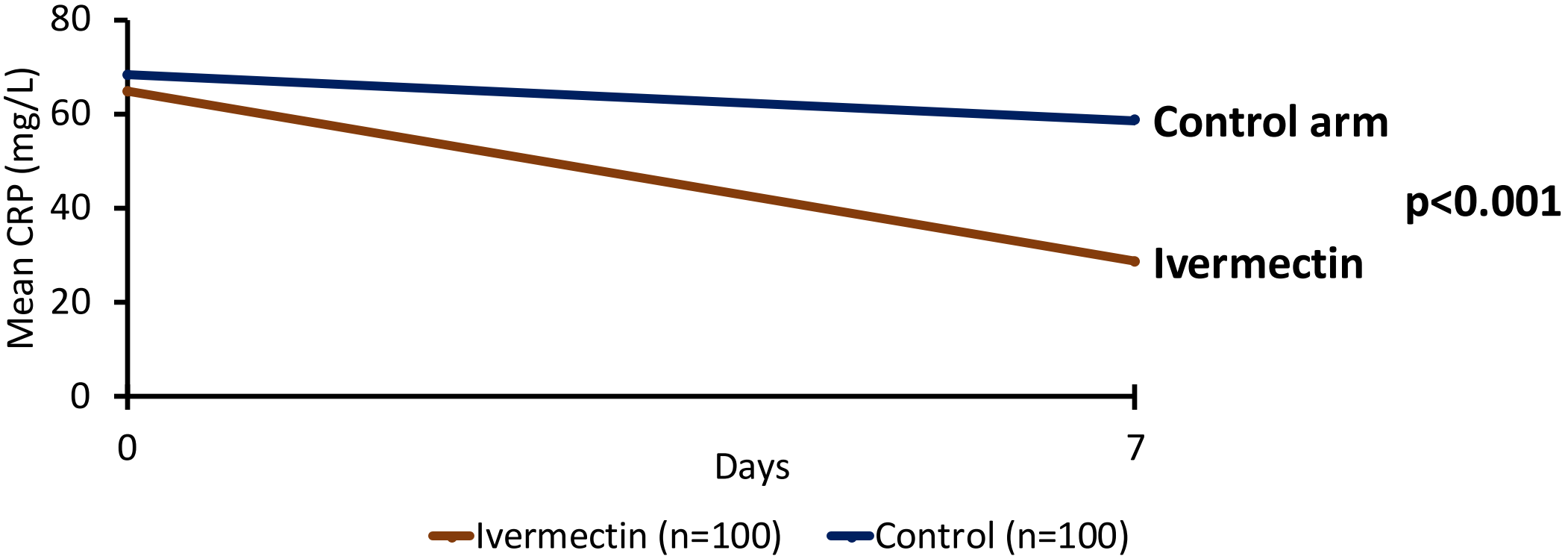
Elgazzar et al, Egypt

CRP- severe COVID-19





Reference: *https://www.researchsquare.com/article/rs-100956/v1*

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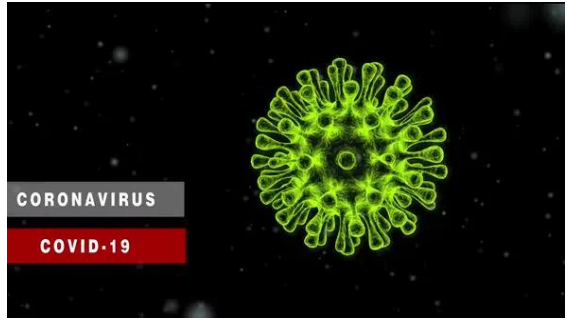
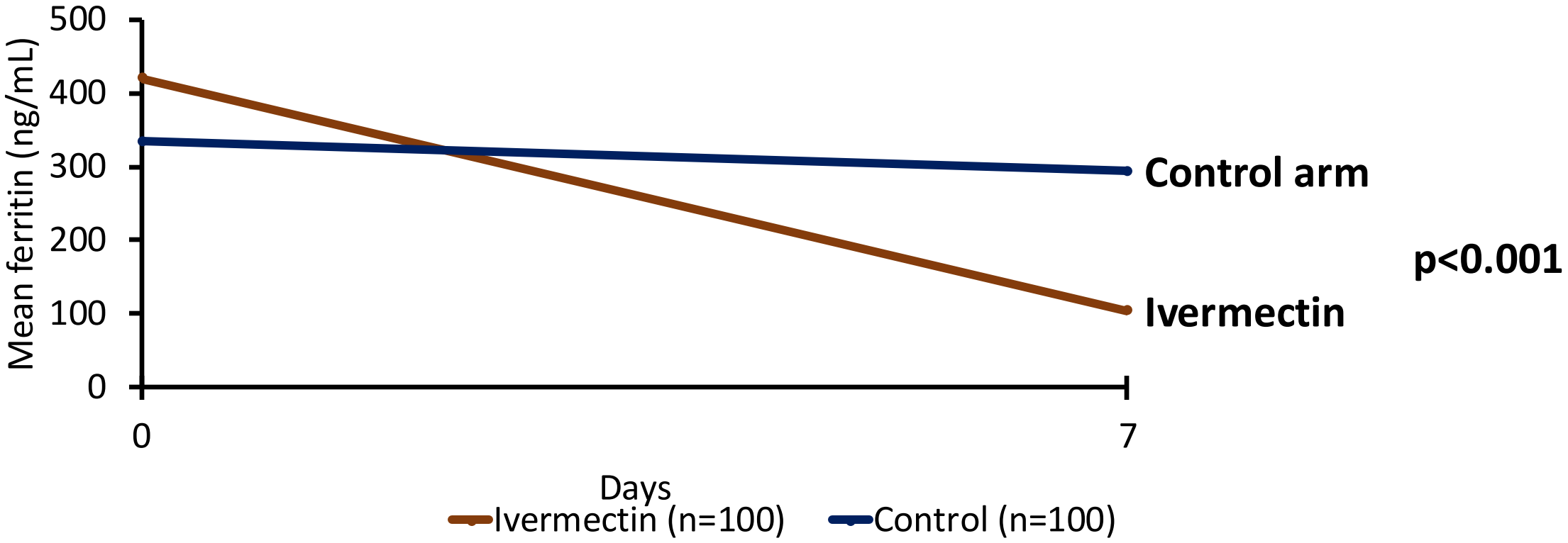
Elgazzar et al, Egypt

Ferritin- severe COVID-19





Reference: *https://www.researchsquare.com/article/rs-100956/v1*

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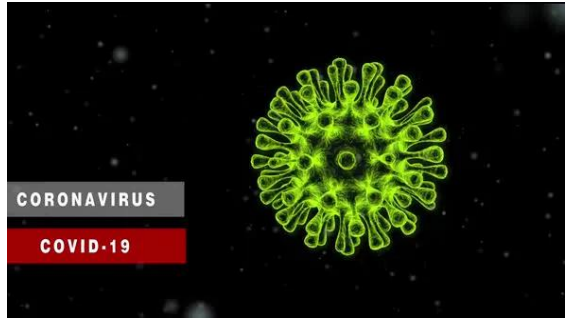
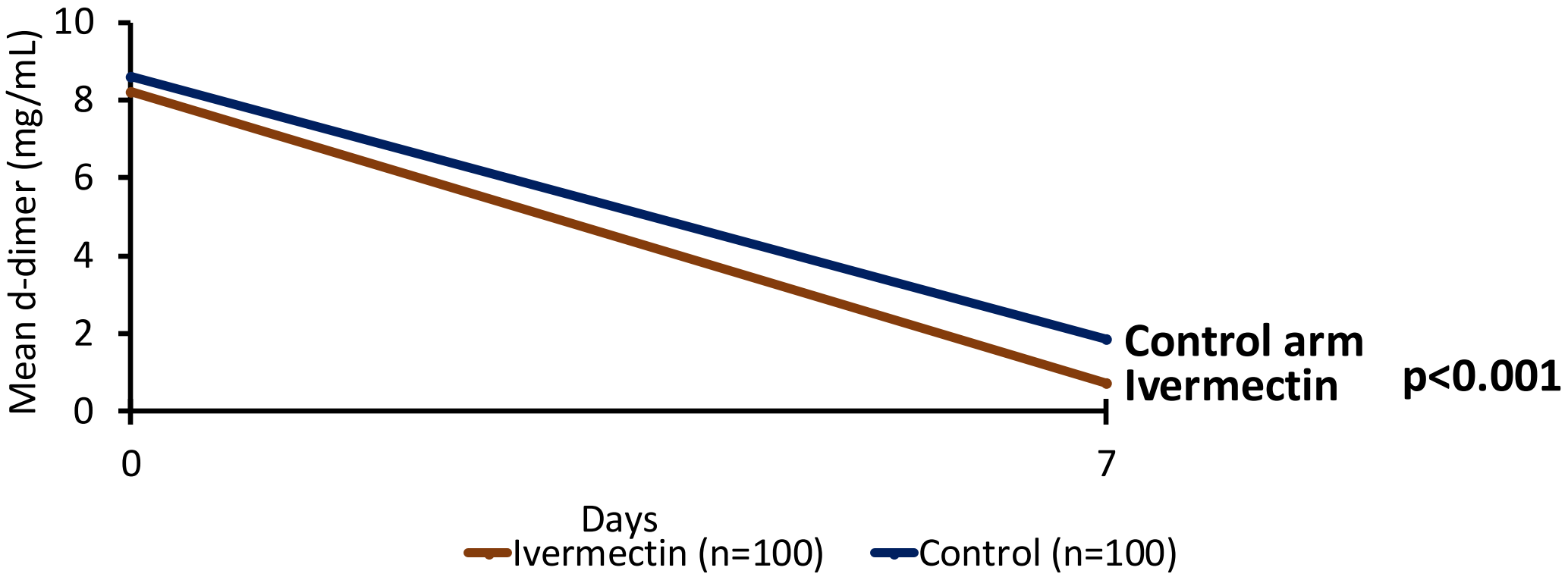
Elgazzar et al, Egypt

D-dimer- severe COVID-19





Reference: *https://www.researchsquare.com/article/rs-100956/v1*

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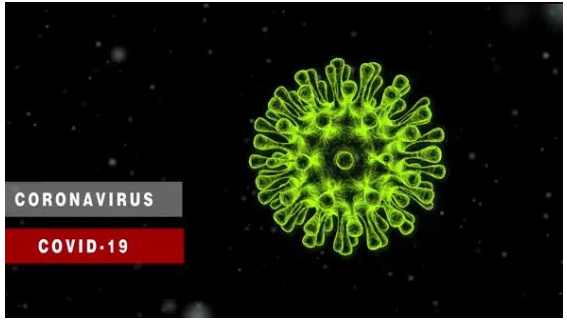
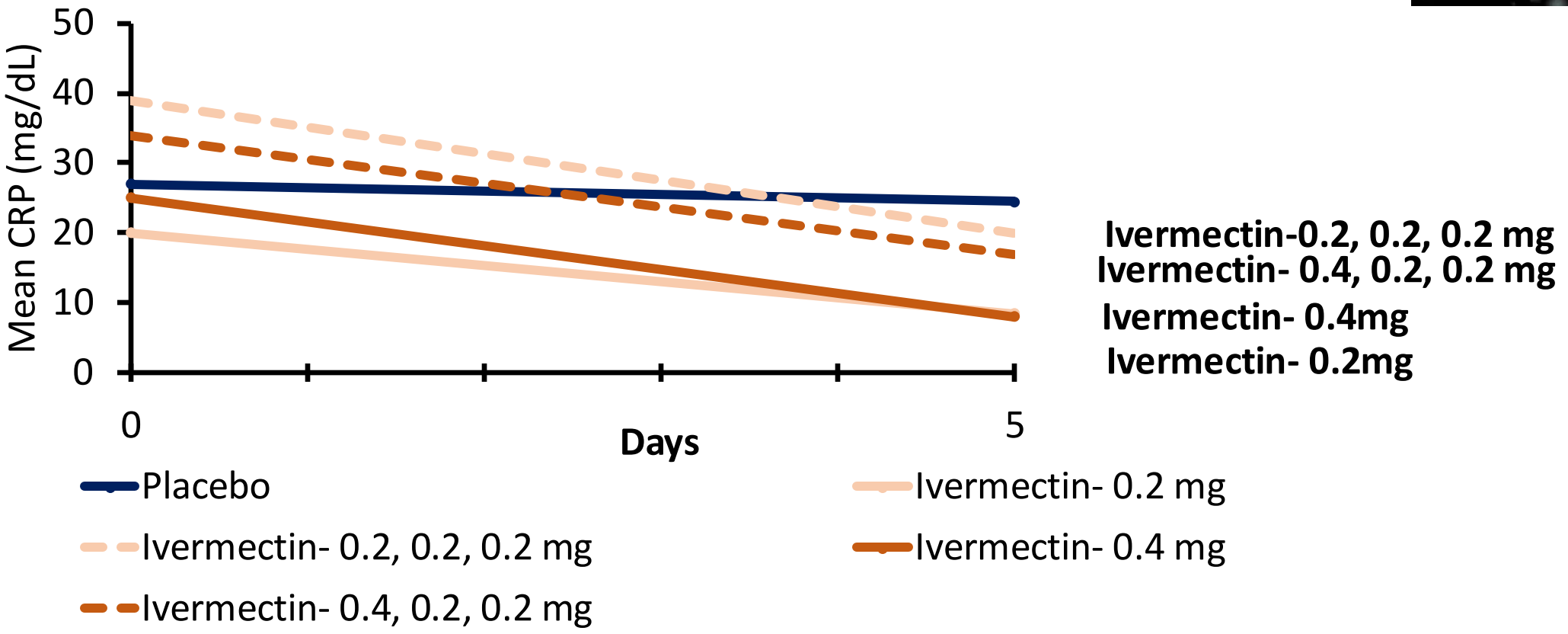
Niaee et al, Iran



CRP



Ivermectin-0.2, 0.2, 0.2 mg
Ivermectin- 0.4, 0.2, 0.2 mg
Ivermectin- 0.4mg
Ivermectin- 0.2mg

p<0.001

Reference: *https://www.researchsquare.com/article/rs-109670/v1*

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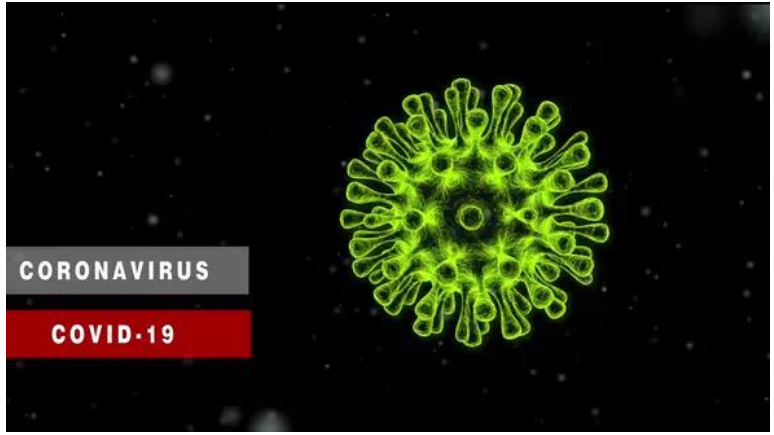
Inflammatory markers for 5 vs 1 day course of ivermectin (N=68)

Test	Ivermectin 5 days (n=22)			Ivermectin 1 days & Doxycycline (n=23)			Placebo (n=23)		
	Day 1	Day 7	*P-value*	Day 1	Day 7	*P-value*	Day 1	Day 7	*P-value*
C-reactive protein (mg/dl)	2.2 ± 3.6	0.3 ± 0.3	**0.02**	2.6 ± 4.7	1.1 ± 2.6	0.07	2.9 ± 4.9	1.4 ± 4.8	0.27
Ferritin(ng/ml)	268.5 ± 272.6	211.3 ± 201.0	0.06	258.7 ± 282.1	212.9 ± 207.8	0.17	222.4 ± 208.2	217.8 ± 203.6	0.85

Reference: *https://www.ijidonline.com/action/showPdf?pii=S1201-9712%2820%2932506-6*

Values mean ± SD



Effects on viral clearance

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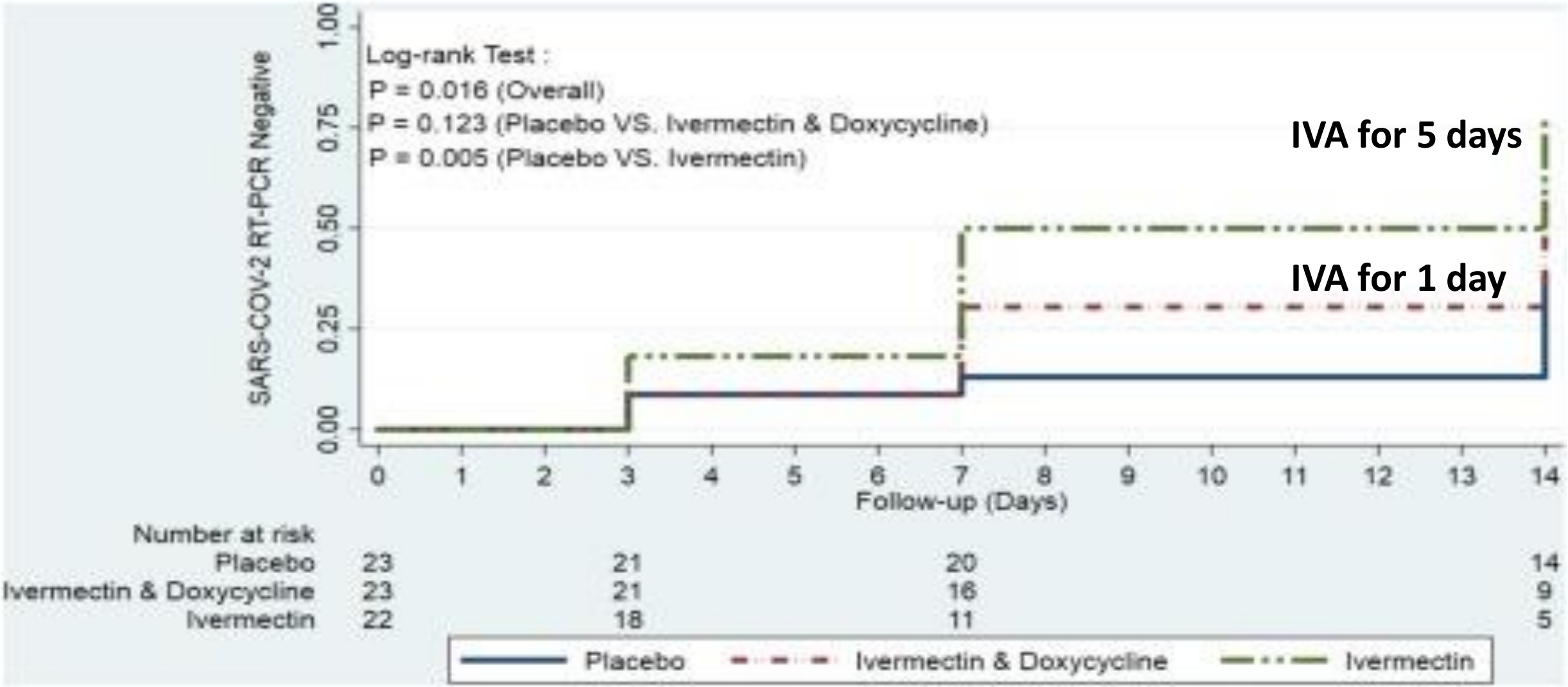
Effects of Ivermectin on viral clearance in randomized trials – dosing on Day 1 only

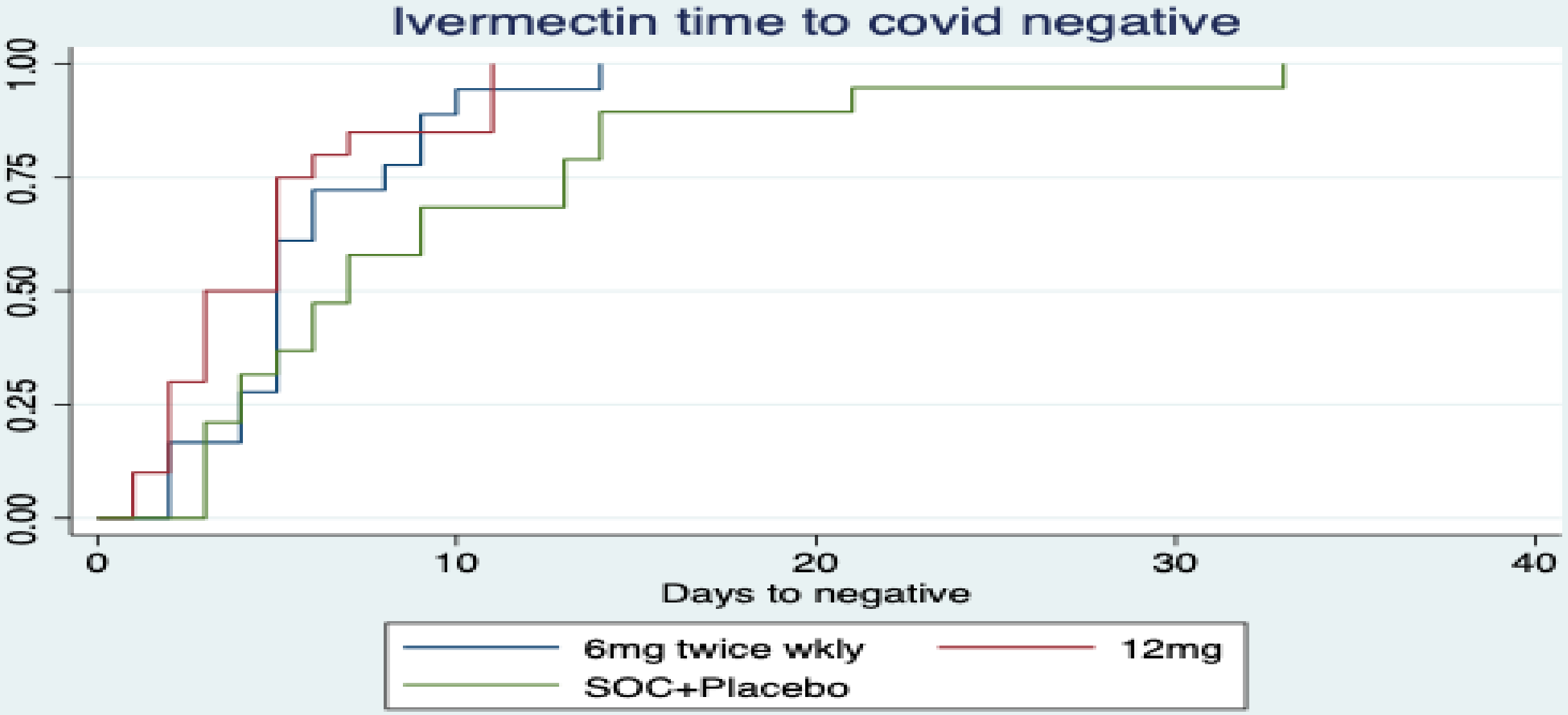
Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVA vs Control	P value
Mahmud et al	Bangladesh, n=363	12 mg	1 day (DB)	Detectable Day 14	8% vs 20%	p < 0.001
Asghar et al	Pakistan, n=103	0.2 mg/kg	1 day	Undetectable Day 7	90% vs 44%	p < 0.001
Chowdhury	Bangladesh, n=112	0.2 mg/kg	1 day (DB)	Time to PCR neg	9 vs 9.3 days	p = n.s.
Podder et al	Bangladesh, n=62	0.2 mg/kg	1 day (OL)	Day 10 PCR neg	90% vs 95%	p = n.s.
Raad et al	Lebanon, n=100	0.2 mg/kg	1 day	Day 3	Ct values	p = 0.01
Mohan et al	India, n=157	0.2 – 0.4mg/kg Elixir	1 day	Undetectable Day 5	48% vs 31%	p = n.s.

Effects of dosing on viral clearance



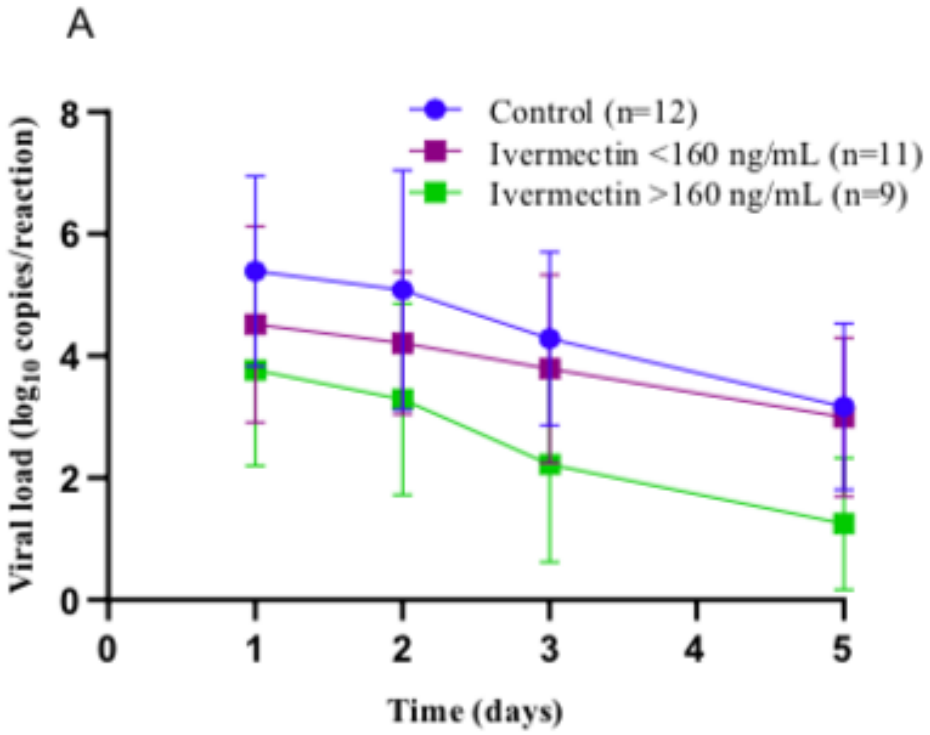
Link to publication: : https://doi.org/10.1016/j.ijid.2020.11.191

Nigeria – Viral clearance by dose

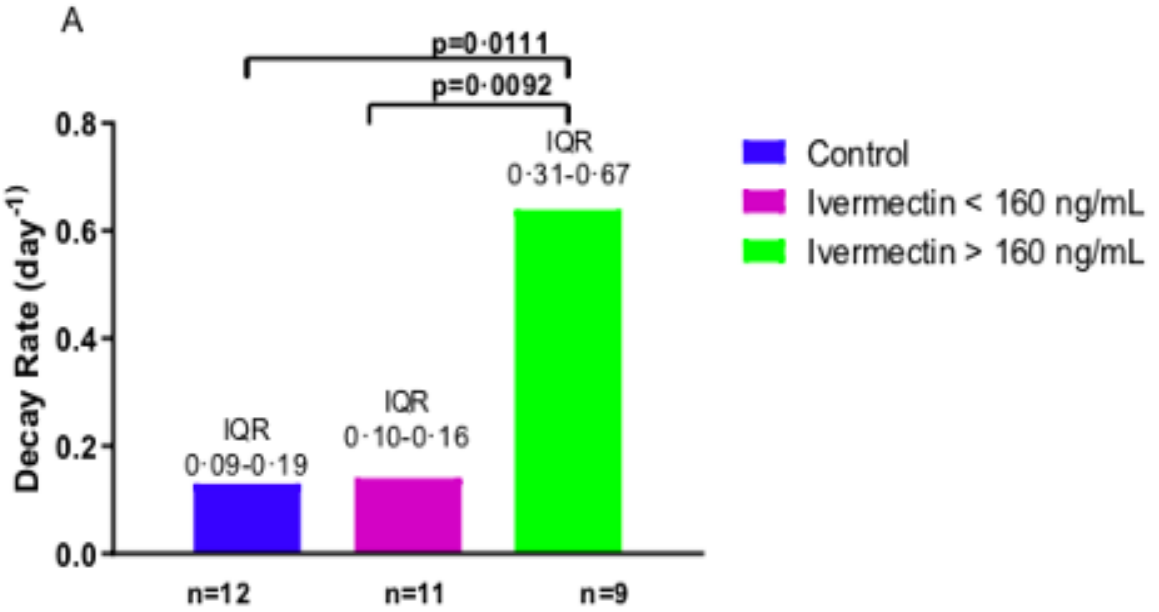


Argentina - Viral Load reduction by drug levels

Viral load by quantitative RT-PCR since treatment initiation (mean and SD) and viral load reduction between baseline and day-5 (median and IQR)



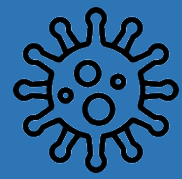
Viral load decay rates by quantitative RT-PCR in controls and IVM treated patients according to median plasma concentrations of IVM



**By the ratio between the area under the IVM plasma concentration curve and the area under the viral load curve (AUCivm/AUCvl)

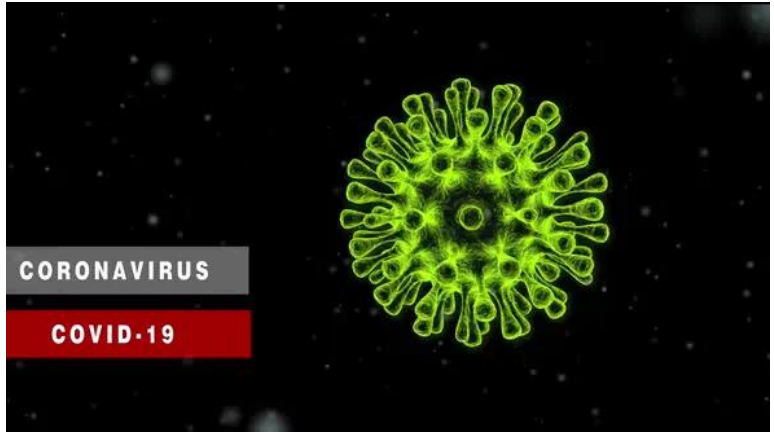
Publication: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3714649

Effects of Ivermectin on viral clearance in randomized trials – multi-day dosing



Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVA vs Control	P value
Elgazzar et al Mild / moderate	Egypt, n=200	0.4 mg/kg	5 days (OL)	Days detectable	5 vs 10 days	p < 0.001
Elgazzar et al Severe	Egypt, n=200	0.4 mg/kg	5 days (OL)	Days detectable	6 vs 12 days	p < 0.001
Okomus et al	Turkey, n=60	0.2 mg/kg	5 days (DB)	Day 10 PCR Neg	88% vs 38%	p = 0.01
Garrahan et al	Argentina, n=45	0.6 mg/kg	5 days	PK/PD	Dose-related	p = 0.02
Babaloa et al *	Nigeria, n=60	0.1-0.2 mg/kg	2 / week (DB)	Time to PCR neg	2 x faster clearance	p = 0.003
Ahmed et al *	Bangladesh, n=72	0.2 mg/kg	5 days (DB)	Time to PCR neg	7 vs 14 days	p = 0.005

* dose-response effects seen



Effects on clinical recovery and hospitalisation

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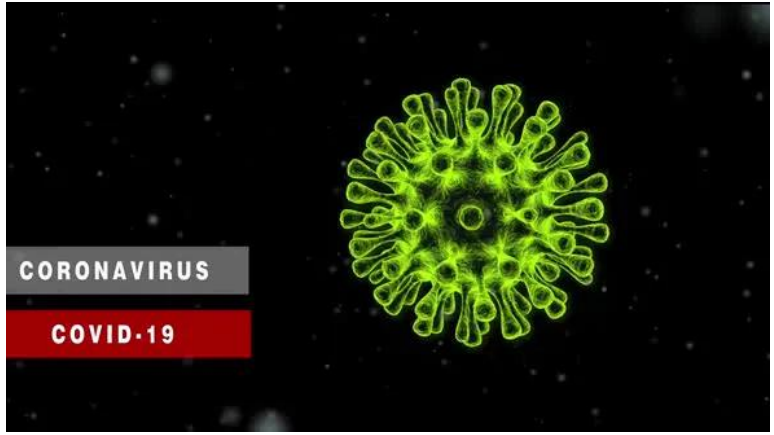
Effects of ivermectin on hospitalization or clinical recovery – dosing on Day 1 only

Study	Country	Daily dose	Duration	Endpoint	Results IVS vs control	P value
Mahmud	Bangladesh n=400	12 mg	1 day (DB)	Early clinical improvement	61% vs 44%	p = 0.013
Chowdhury	Bangladesh n=116	0.2 mg/kg	1 day (DB)	Time to clinical recovery	5.9 vs 6.9 days	p = 0.071
Podder	Bangladesh n=62	0.2 mg/kg	1 day (OL)	Time to clinical recovery	5.3 vs 6.3 days	p = n.s.
Rezai	Iran n=103	0.2 mg/kg	1 days (OL)	Time to clinical recovery	4.1 vs 5.2 days	p = 0.01
Rezai	Iran n=103	0.2 mg/kg	1 days (OL)	Days in hospital	6.9 vs 8.4 days	p = 0.01
Raad	Lebanon n=100	0.2 mg/kg	1 day (OL)	Hospitalisation	0% vs 3%	p = n.s.
Spoorthi	India n=100	0.2 mg/kg	1 day (SB)	Time to clinical recovery	3.7 vs 4.7 days	p=0.03
Spoorthi	India n=100	0.2 mg/kg	1 day (SB)	Time in hospital	6.7 vs 7.9 days	p=0.01
Mohan	India n=157	0.2 – 0.4 mg/kg Elixir	1 day (SB)	Time to clinical recovery	4.3 vs 4.6 days	p = n.s.

Effects of ivermectin on hospitalization or clinical recovery – multi-day dosing

Study	Country	Daily dose	Duration	Endpoint	Results IVA vs control	P value
Elgazzar Mild/moderate	Egypt n=200	0.4 mg/kg	5 days (OL)	Days in hospital	5 vs 15 days	p < 0.001
Elgazzar Severe	Egypt n=200	0.4 mg/kg	5 days (OL)	Days in hospital	6 vs 18 days	p < 0.001
Chachar	Pakistan n=50	0.2 mg/kg	7 days (OL)	Day 7 Clinical recovery	64% vs 60%	p = n.s.
Okomus	Turkey n=60	0.2 mg/kg	5 days (DB)	Day 10 Clinical improvement	73% vs 53%	p = 0.10
Niaee	Iran n=165	0.2 - 0.4 mg/kg	1-3 days (DB)	Days in hospital	6.5 vs 7.5 days	p = 0.006
Hashim	Iraq n=140	0.2 mg/kg	2-3 days (SB)	Time to clinical recovery	10.6 vs 17.9 days	p < 0.001



Effects on survival

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Survival benefits in ivermectin Trials

Reduction in death rate = 75% (95% C.I. 42%-89%), p=0.001

Trial	Dosing	Ivermectin	Control
Hashim (Iraq)	0.2-0.4 mg/kg 2-3 days	2/70	6/70
Elgazzar (Egypt)	0.4 mg/kg 5 days	2/200	24/200
Mahmud (Bangladesh)	0.2 mg/kg, 1 day	0/183	3/180
Niaee (Iran)	0.2 mg/kg 1-3 days	4/120	11/60
Okomus (Turkey)	0.2 mg/kg, 5 days	6/30	9/30
Total		**14/603 (2.3%)**	**53/540 (10%)**

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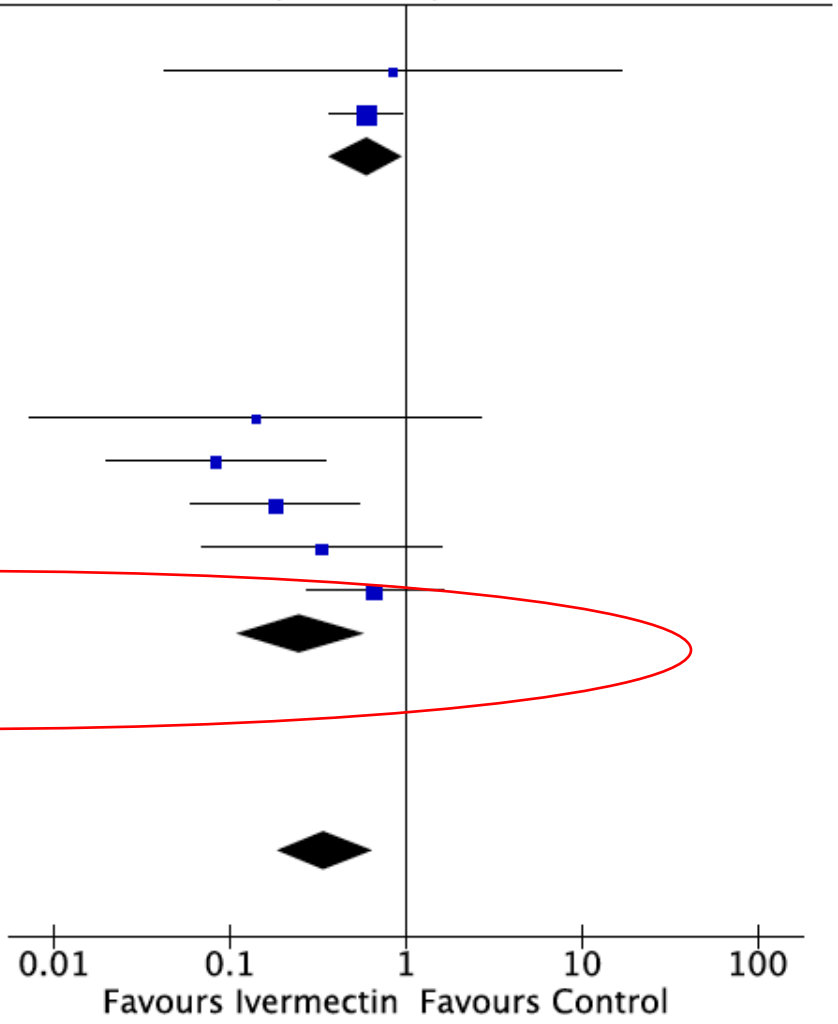
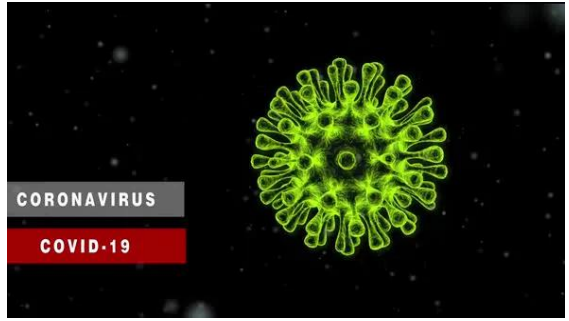
Meta-analysis for All-cause mortality

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Observational Studies						
Iraq Gorial et al	0	16	2	71	3.9%	0.85 [0.04, 16.84]
US ICON Study	26	173	27	107	30.4%	0.60 [0.37, 0.96]
Subtotal (95% CI)		**189**		**178**	**34.2%**	**0.60 [0.37, 0.97]**
Total events	26		29			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$						
Test for overall effect: Z = 2.10 (P = 0.04)						
1.1.2 Randomised Trials						
Bangladesh Mahmud et al	0	183	3	180	4.0%	0.14 [0.01, 2.70]
Egypt Elgazzar et al	2	200	24	200	12.6%	0.08 [0.02, 0.35]
Iran Niaee et al	4	120	11	60	17.2%	0.18 [0.06, 0.55]
Iraq Hashim et al	2	70	6	70	11.1%	0.33 [0.07, 1.60]
Turkey Okumus et al	6	30	9	30	20.9%	0.67 [0.27, 1.64]
Subtotal (95% CI)		**603**		**540**	**65.8%**	**0.25 [0.11, 0.58]**
Total events	14		53			
Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 7.16$, df = 4 (P = 0.13); $I^2 = 44\%$						
Test for overall effect: Z = 3.27 (P = 0.001)						
Total (95% CI)		**792**		**718**	**100.0%**	**0.35 [0.19, 0.65]**
Total events	40		82			
Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 10.89$, df = 6 (P = 0.09); $I^2 = 45\%$						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Test for subgroup differences: $Chi^2 = 3.17$, df = 1 (P = 0.08), $I^2 = 68.4\%$						



Limitations



Current results are from 18 randomised trials in 2167 patients, another 37 clinical trials registered (total 7491 patients)

Potential for publication bias – are there trials with unpublished results?

Individual trials can have limited statistical power

Several trials were open-label – potential for investigator bias

Range of doses and durations. Endpoints differ between trials

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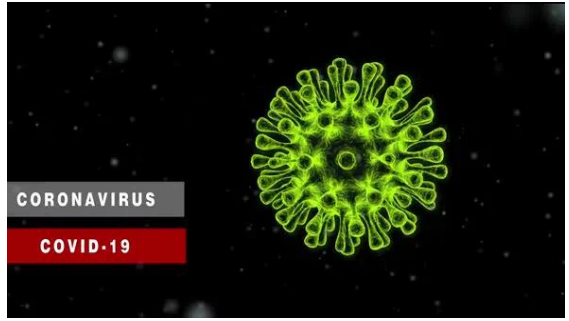
Implications: treatment as prevention



A 5-day course of ivermectin is associated with significantly faster clearance of SARS-CoV-2 versus control treatment

This treatment effect is consistent across five randomised trials

If undetectable viral load lowers the risk of onward transmission, a “test and treat” approach could significantly lower the risk of patients transmitting the virus.

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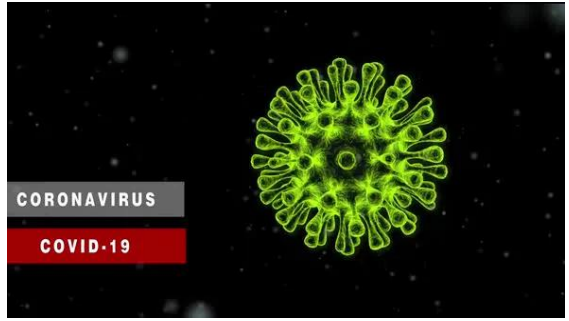
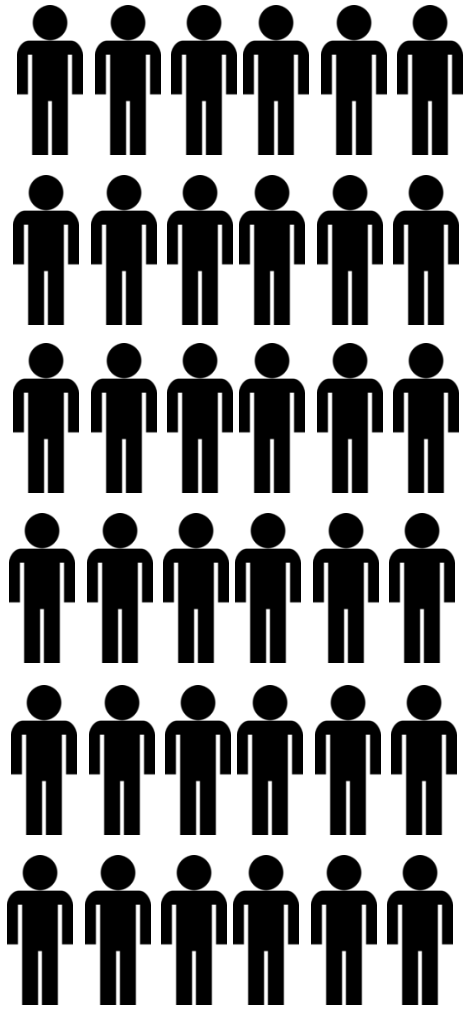
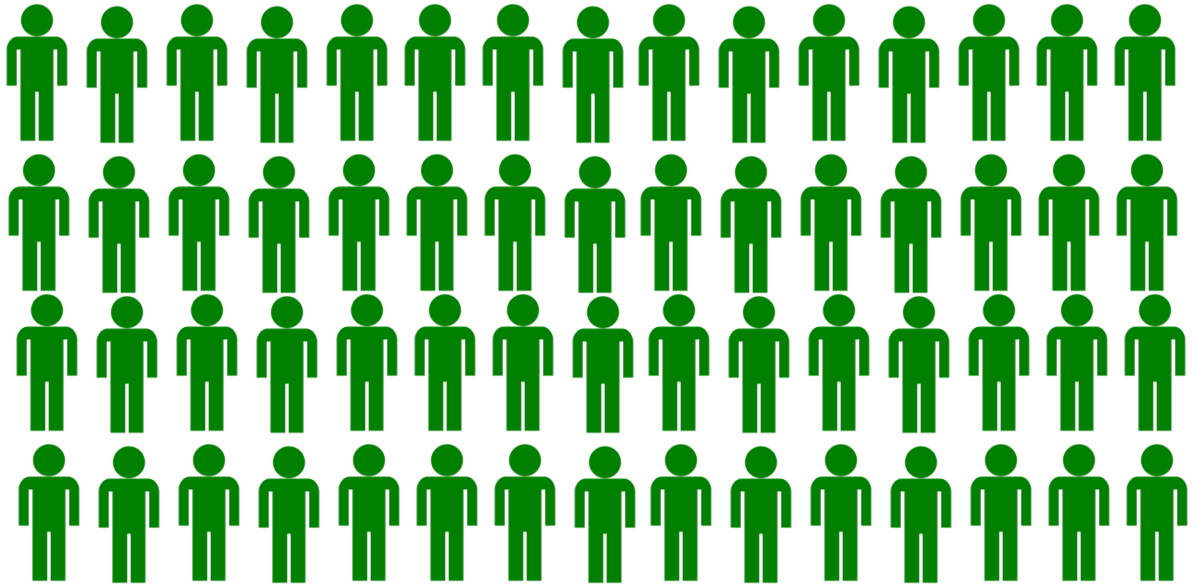
Same day “Test and Treat” strategy



Rapid viral load test



Negative: Vaccination



Positive: Treatment with ivermectin

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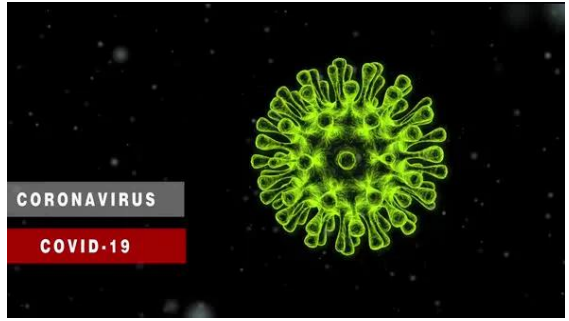
New trial data emerging



Bulgaria (n=120) – Dr Petkov – January 4th

Brazil (n=176) – Dr Exman - Jan 8th

Columbia (n=450) – Dr Lopez - Jan 22nd

Argentina (n=500) – Dr Zoni – Feb 5th

Mexico (n=3000) – dose-ranging - Dr Hernandez – Feb 5th

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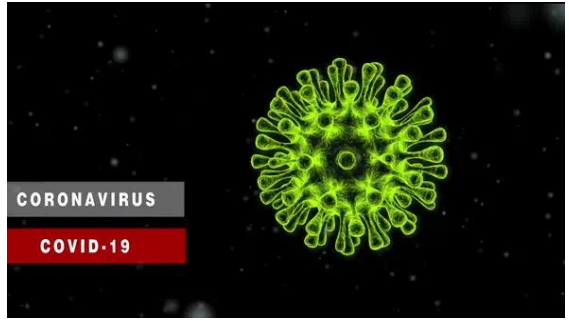
Conclusions



In this meta-analysis of 18 randomised trials in 2167 patients

Ivermectin treatment was associated with:

Faster time to viral clearance
Shorter duration of hospitalisation
Higher rates of clinical recovery
75% improvement in survival rates (95% C.I. 42-89%)

Dosing for 5 days provides the strongest virological and clinical benefits

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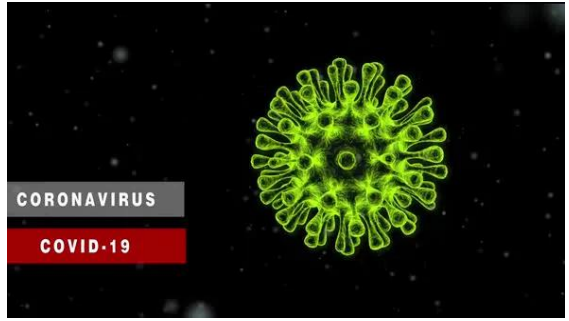
Next Steps: review on Feb 5th?



Detailed assessment of data quality from each trial (Cochrane handbook, evaluation of bias – questions to trials needed)

Integrate results from key emerging trials

Decisions on integrating ivermectin into new randomised studies:

Mild infection: lower risk of hospitalisation, faster viral clearance
Moderate/severe infection: faster clinical recovery, improved survival

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