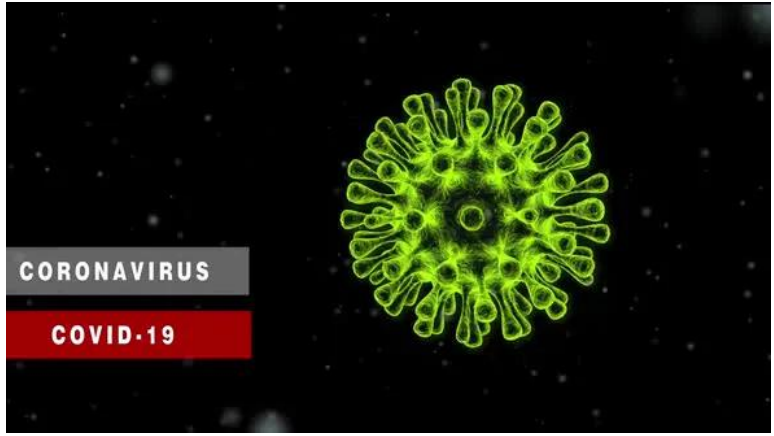
Meta-analysis of clinical trials of ivermectin to treat COVID-19 infection



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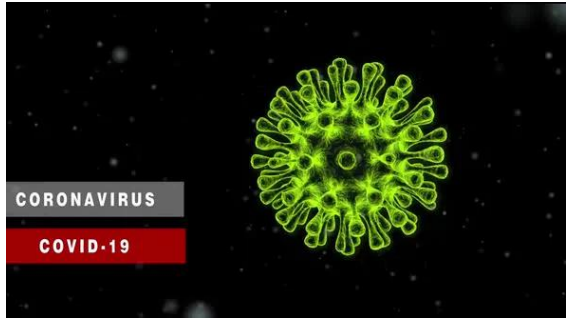
Introduction

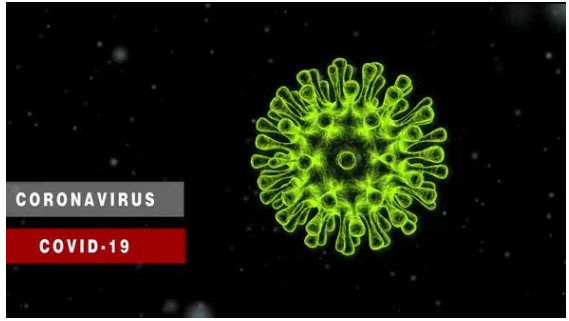


Ivermectin is a widely available, generic, re-purposed treatment for COVID-19, being evaluated in clinical trials worldwide

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

Research question



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

Endpoints:

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

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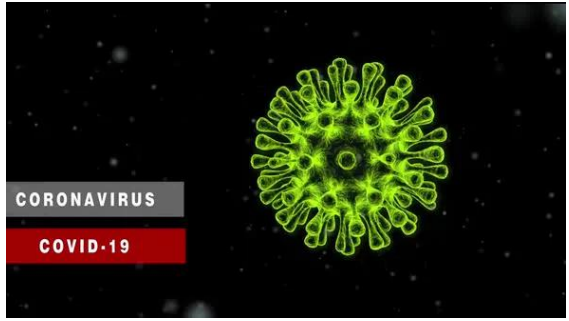
Search strategy



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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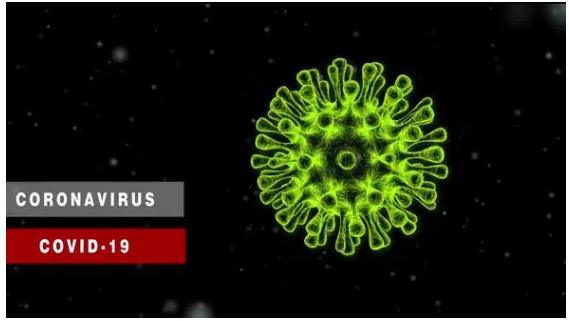
Randomised trials of Ivermectin, n=1452

Study	Country	Daily dose	Duration	Sample Size	Patients	Comparator Arm
Elgazzar et al	Egypt	0.4 mg/kg	5 days (OL)	400	Mild to severe	Hydroxychloroquine
Mahmud et al	Bangladesh	12 mg	1 day (DB)	363	Mild/ moderate	Standard Care
Niaee et al	Iran	0.2 - 0.4 mg/kg	1-3 days (DB)	180	Mild / moderate	Standard Care Standard care + Placebo
Hashim et al	Iraq	0.2 mg/kg	2-3 days (SB)	140	Symptomatic	Standard Care
Chowdhury	Bangladesh	0.2 mg/kg	1 day (DB)	116	PCR positive	HCQ + Azithromycin
Ahmed et al	Bangladesh	0.2 mg/kg	5 days (DB)	72	Mild to moderate	Standard Care + Placebo
Podder et al	Bangladesh	0.2 mg/kg	1 day (OL)	62	Mild	Standard Care
Chachar et al	Bangladesh	0.2 mg/kg	7 days (OL)	50	Mild	Standard Care
Garrahan et al	Argentina	0.6 mg/kg	5 days	45	Outpatients	Standard Care
Saint	Spain	0.4 mg/kg	1 day	24	Moderate	Placebo

Meta-analysis - methods

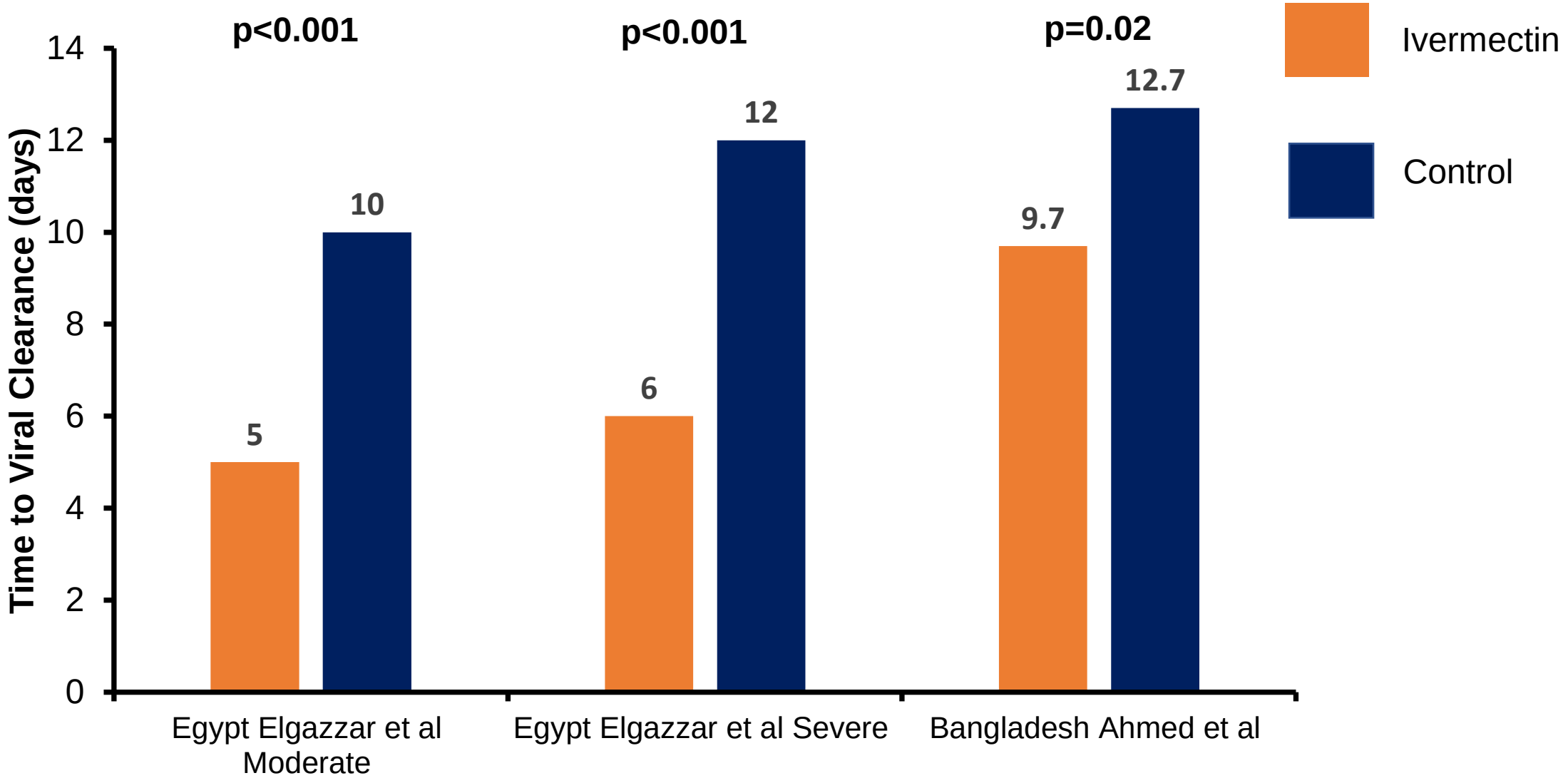


Only the randomised clinical trials were included: in WHO GRADE criteria, systematic review and meta-analysis of RCTs provides the highest level of evidence

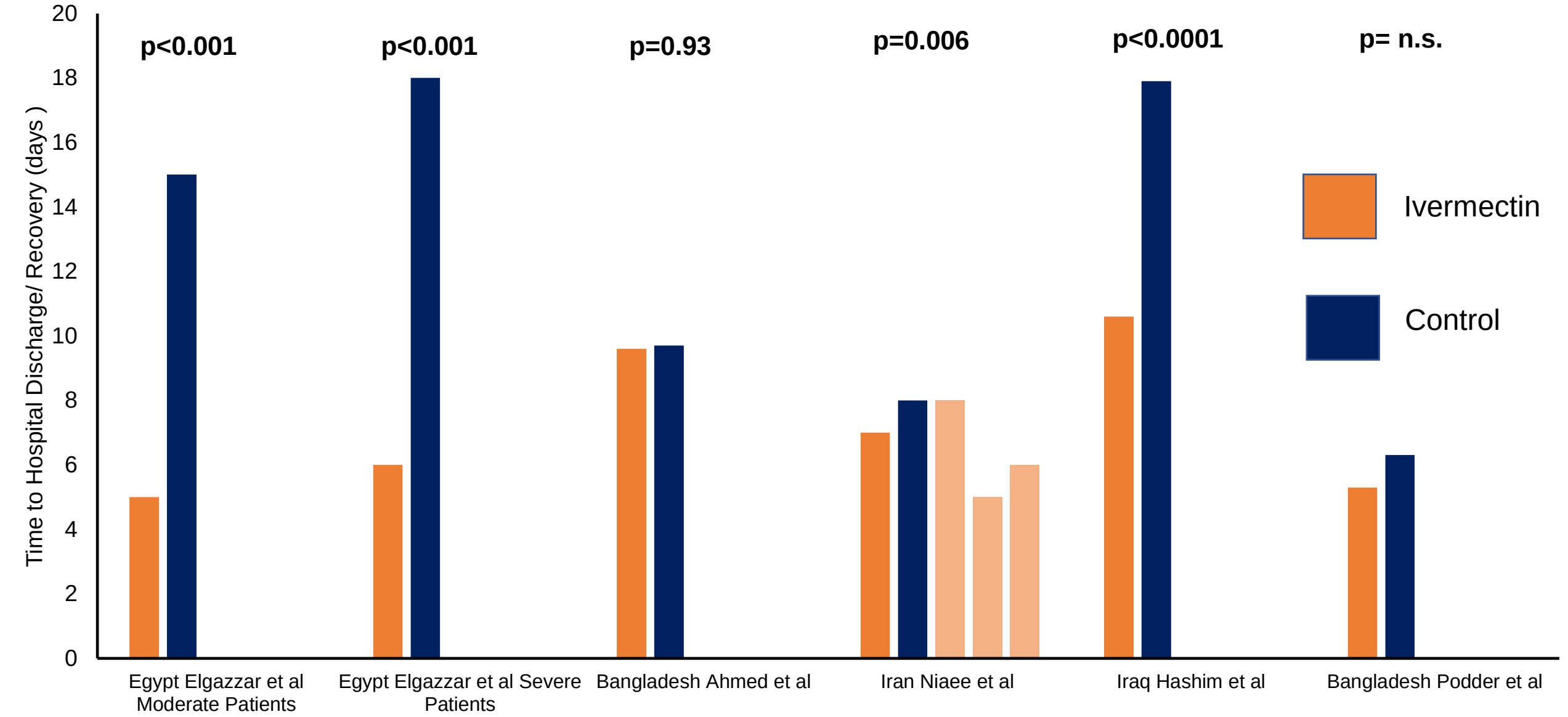
Cochran Mantel-Haenszel testing with inverse variance weighting and random effects modelling was used to compare outcomes between ivermectin with control treatment

Effects of ivermectin dose on response were investigated

Faster time to Viral Clearance



Faster time to hospital discharge or clinical recovery.



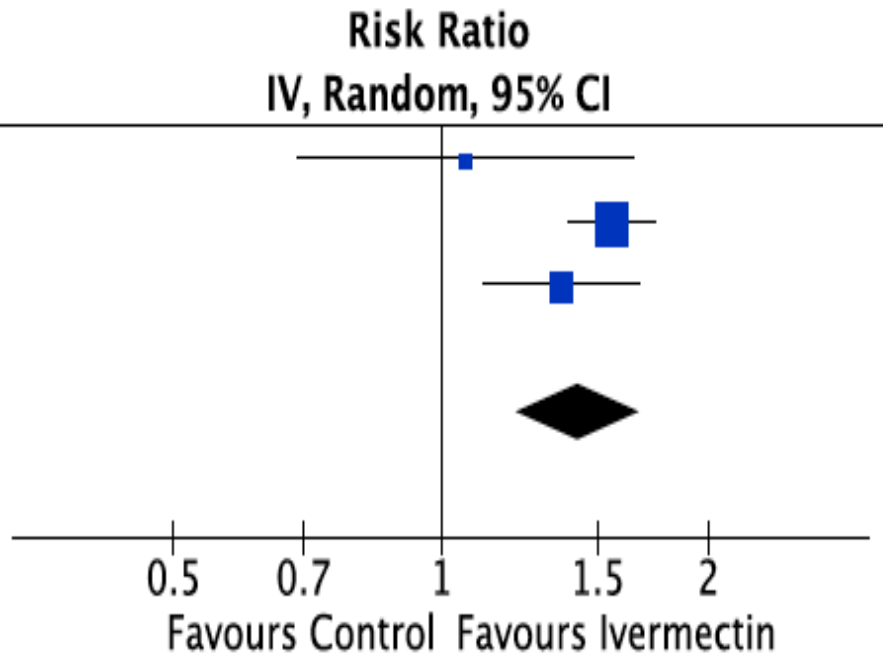
Meta-analysis for Clinical Recovery

Randomised Trials: 43% higher rates of clinical recovery (95% C.I. 21-67%) p<0.0001

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Bangladesh Chachar et al	16	25	15	25	11.4%	1.07 [0.69, 1.65]
Bangladesh Mahmud et al	193	200	124	200	54.4%	1.56 [1.39, 1.74]
Egypt Elgazzar et al	111	183	80	180	34.1%	1.36 [1.12, 1.67]
Total (95% CI)		**408**		**405**	**100.0%**	**1.43 [1.21, 1.67]**
Total events	320		219			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.59$, df = 2 (P = 0.17); $I^2 = 44\%$

Test for overall effect: Z = 4.35 (P < 0.0001)



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Survival benefits in Ivermectin Trials

83% improvement in survival in randomized trials of ivermectin in COVID-19 patients

Reduction in death rate = 83% (95% C.I. 65%-92%), p<0.0001

Trial	Ivermectin	Control
Mahmud (Bangladesh)	0/183	3/180
Elgazzar (Egypt)	2/200	24/200
Niaee (Iran)	4/120	11/60
Hashim (Iraq)	2/70	6/70
Total	**8/573 (5%)**	**44/510 (17%)**

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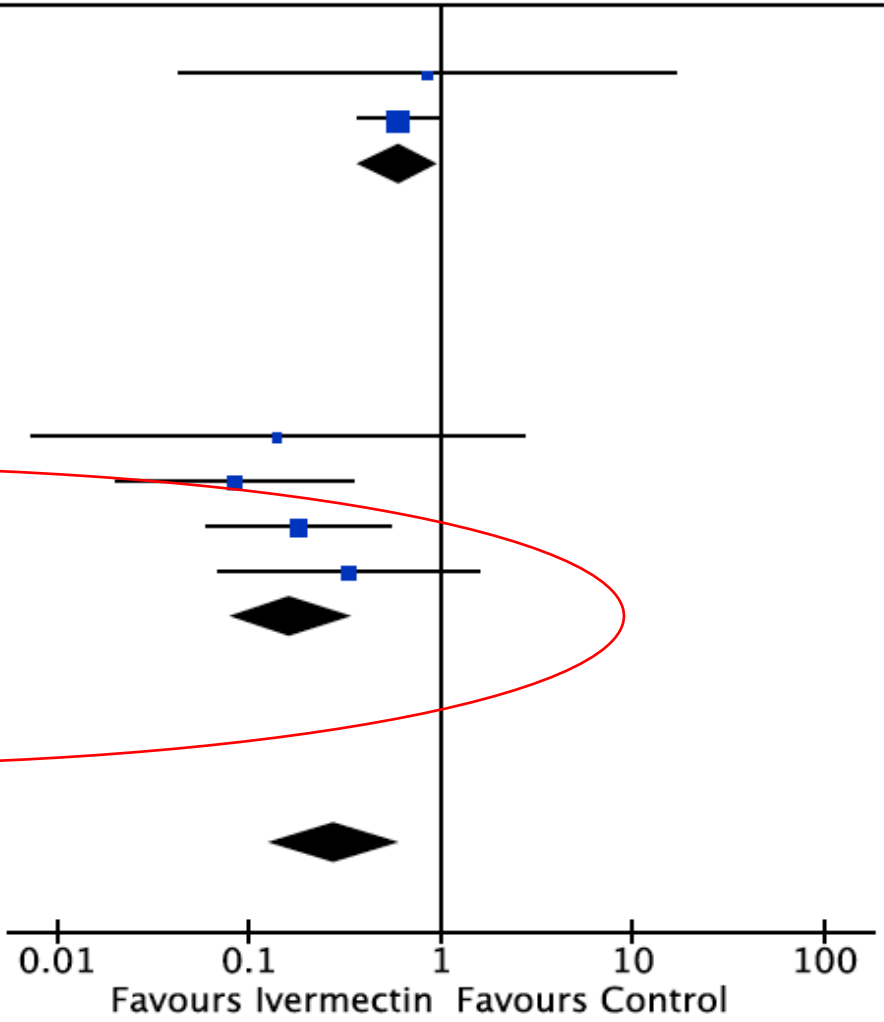
Meta-analysis for all-cause mortality

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	5.9%	0.85 [0.04, 16.84]
US ICON Study	26	173	27	107	33.8%	0.60 [0.37, 0.96]
Subtotal (95% CI)		**189**		**178**	**39.7%**	**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	6.0%	0.14 [0.01, 2.70]
Egypt Elgazzar et al	2	200	24	200	17.0%	0.08 [0.02, 0.35]
Iran Niaee et al	4	120	11	60	22.0%	0.18 [0.06, 0.55]
Iraq Hashim et al	2	70	6	70	15.3%	0.33 [0.07, 1.60]
Subtotal (95% CI)		**573**		**510**	**60.3%**	**0.17 [0.08, 0.35]**
Total events	8		44			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.69$, df = 3 (P = 0.64); $I^2 = 0\%$						
Test for overall effect: Z = 4.76 (P < 0.00001)						
Total (95% CI)		**762**		**688**	**100.0%**	**0.28 [0.13, 0.62]**
Total events	34		73			
Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 9.97$, df = 5 (P = 0.08); $I^2 = 50\%$						
Test for overall effect: Z = 3.16 (P = 0.002)						
Test for subgroup differences: $Chi^2 = 8.23$, df = 1 (P = 0.004), $I^2 = 87.8\%$						



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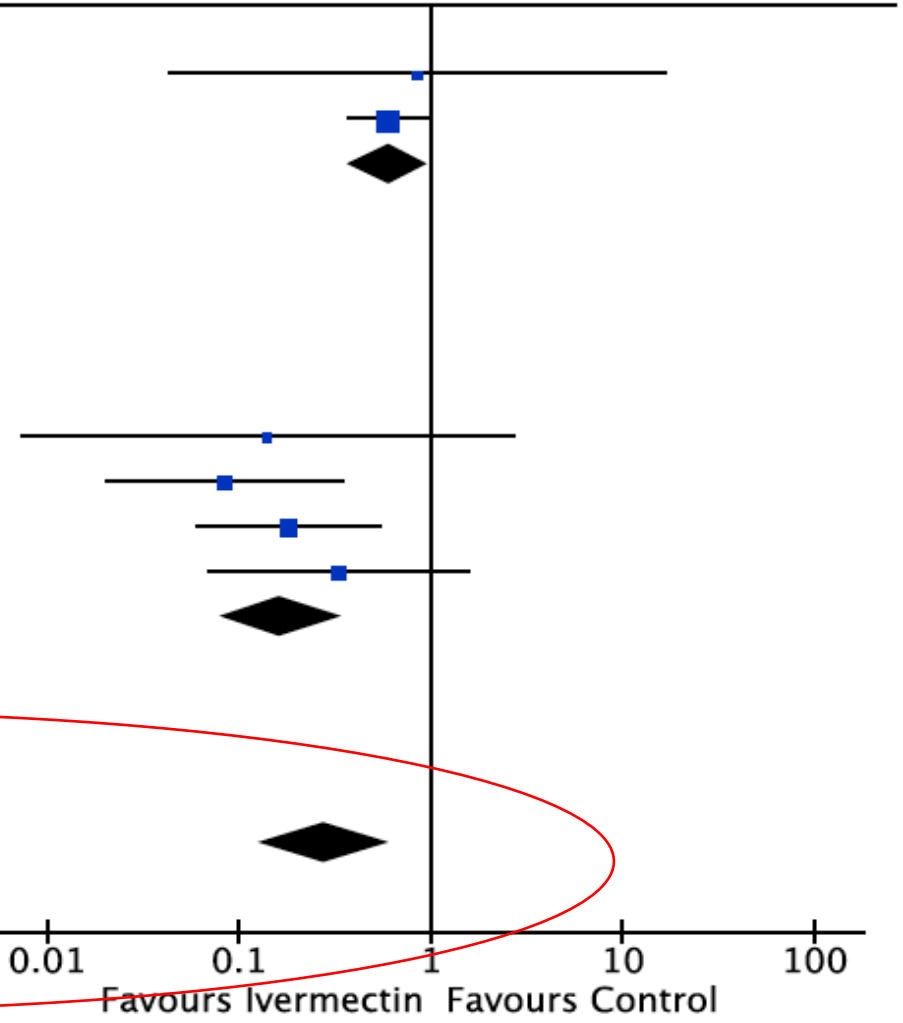
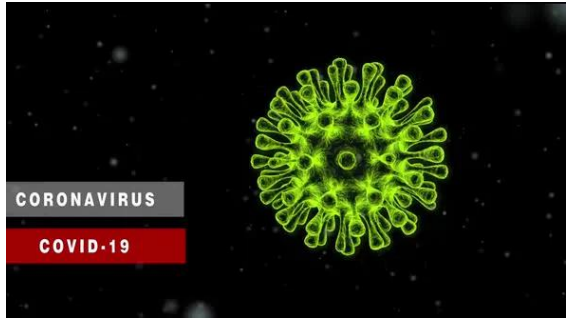


Dose-response effects



Strongest treatment effects seen in Egyptian trial with 5 days of ivermectin, versus Iranian trial with 1 day of treatment

In Bangladesh, patients randomised to 1 or 5 days of ivermectin

In Argentina, PK/PD correlations analysed

Elgazzar et al, Egypt – 5 day treatment 0.4 mg/kg dose

	Ivermectin	Control	Ivermectin	Control	p value
	Mild/moderate		**Severe**		
Prognosis, n(%)					
Improved	99 (99%)	74 (74%)	94 (94%)	50 (50%)	<0.001
Progressed	1 (1%)	22 (22%)	4 (4%)	30 (30%)	
Died	0 (0%)	4 (4%)	2 (2%)	20 (20%)	
Hospital stay (days) , mean (SD)	5 (1)	15 (8)	6 (8)	18 (8)	<0.001
RT-PCR days, mean (SD)	5 (1)	10 (4)	6 (1)	12 (4)	<0.001

Link to publication: https://doi.org/10.21203/rs.3.rs-100956/v2

Niaee et al, Iran – 1-2 days of treatment 0.2 mg/kg dose

	Control Groups		Ivermectin Groups				P-value
	Standard Care	Placebo	Arm 1	Arm 2	Arm 3	Arm 4	
Duration of low O2sat	3 (2-5)	4 (2-6)	2 (1-2)	3 (2-5)	2 (1-4)	5 (3-6)	0.025
Duration of hospital stay	7 (7-9)	8 (6-11)	6 (5-7)	8 (6-9)	5 (4-7)	7 (6-10)	0.006
Mortality, n(%)	5 (17%)	6 (20%)	0 (0%)	3 (10%)	0 (0%)	1 (3.3%)	0.001

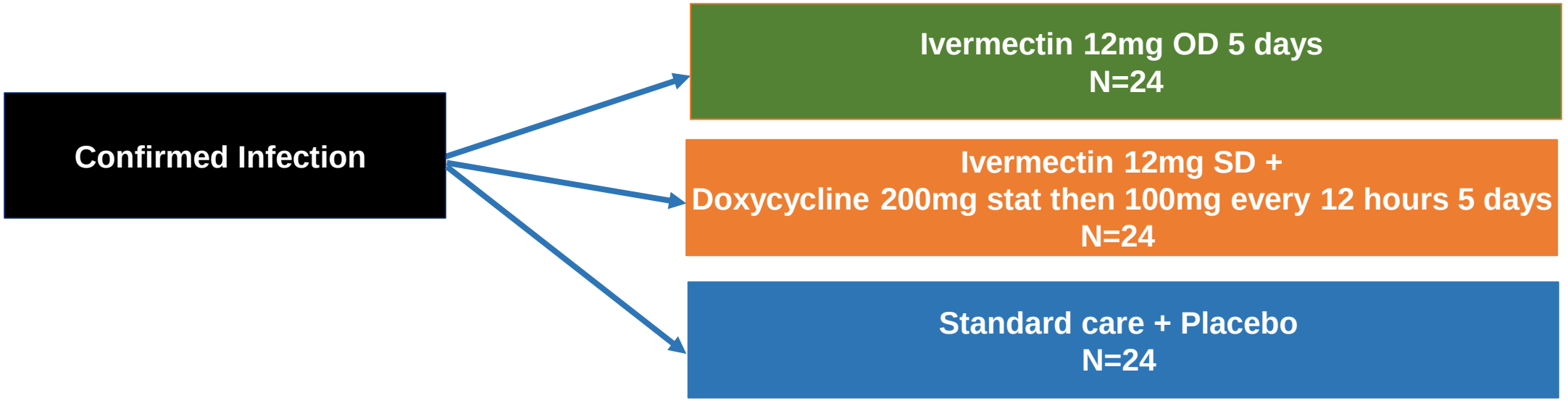
Link to publication: : https://doi.org/10.21203/rs.3.rs-109670/v1

Bangladesh trial
1 versus 5 days of ivermectin (0.2 mg/kg)

Design: Randomised double-blind, placebo-controlled

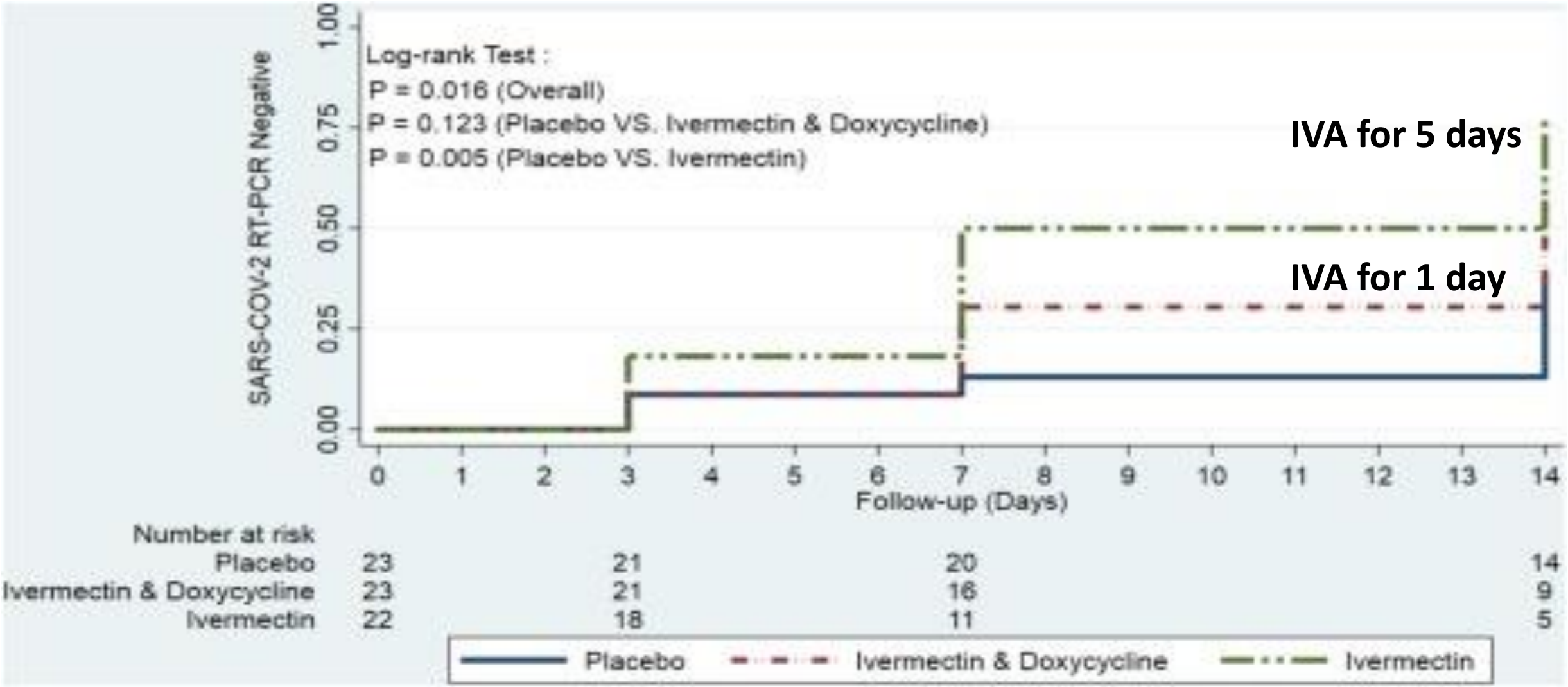
Inclusion Criteria: Age ≥ 18y; admitted to hospital in last 7 days; with either fever (≥37.5oC); cough or sore throat; and diagnosed positive for SARS-CoV-2 by PCR.
Exclusion Criteria: Allergy to ivermectin or doxycycline, chronic illness, received ivermectin or doxycycline in last 7 dyas; pregnant or breastfeeding.

Primary endpoint: The primary endpoints were the time required for virological clearance (a negative RT-PCR result on nasopharyngeal swab); remission of fever (≥37.5C) and cough within 7 days



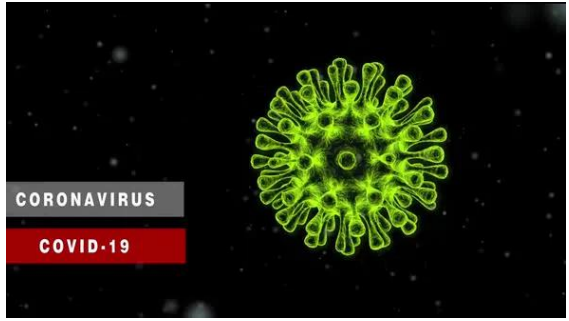
Link to publication: : https://doi.org/10.1016/j.ijid.2020.11.191

PCR negativity: effects of dose



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

Limitations



Current results from 11 randomised trials in 1456 patients

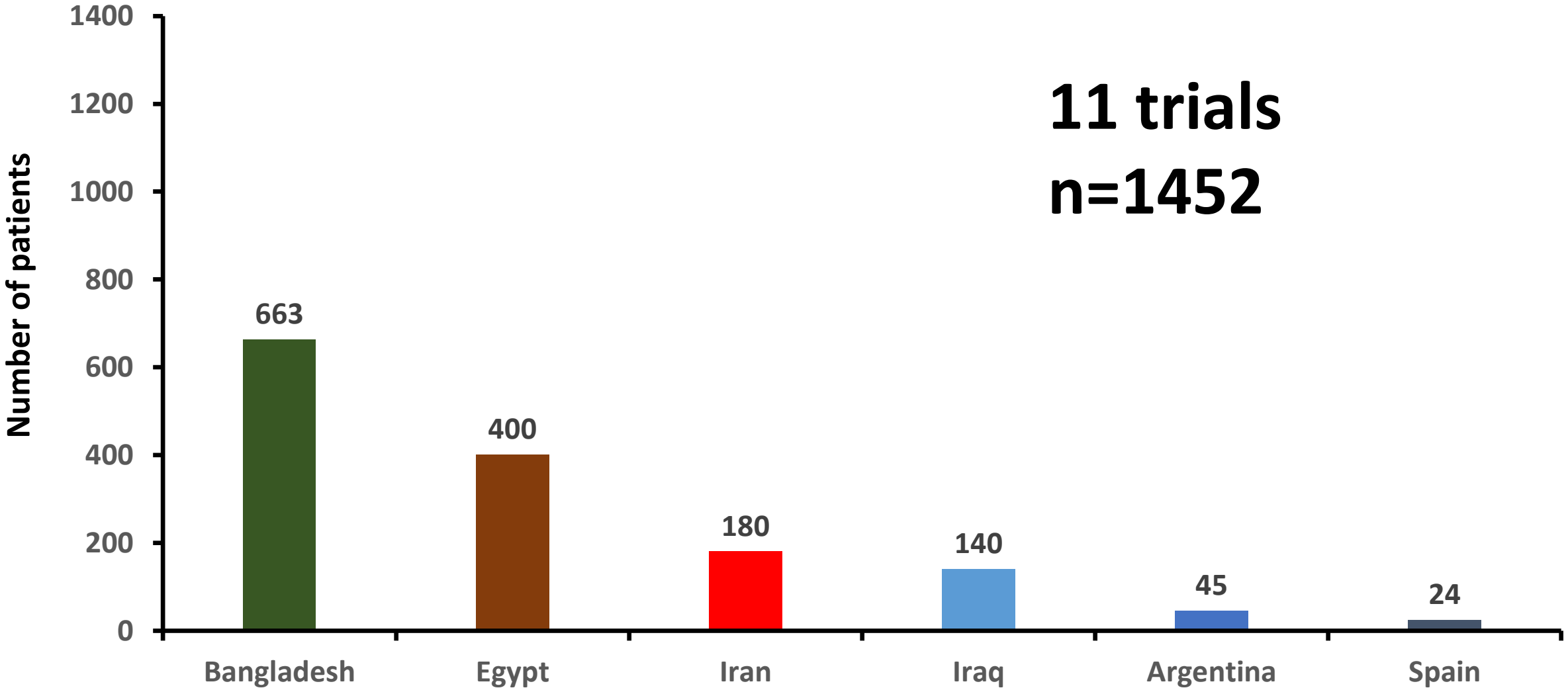
Another 45 clinical trials in progress (total 7100 patients)

Potential for publication bias – are there other unpublished trials?

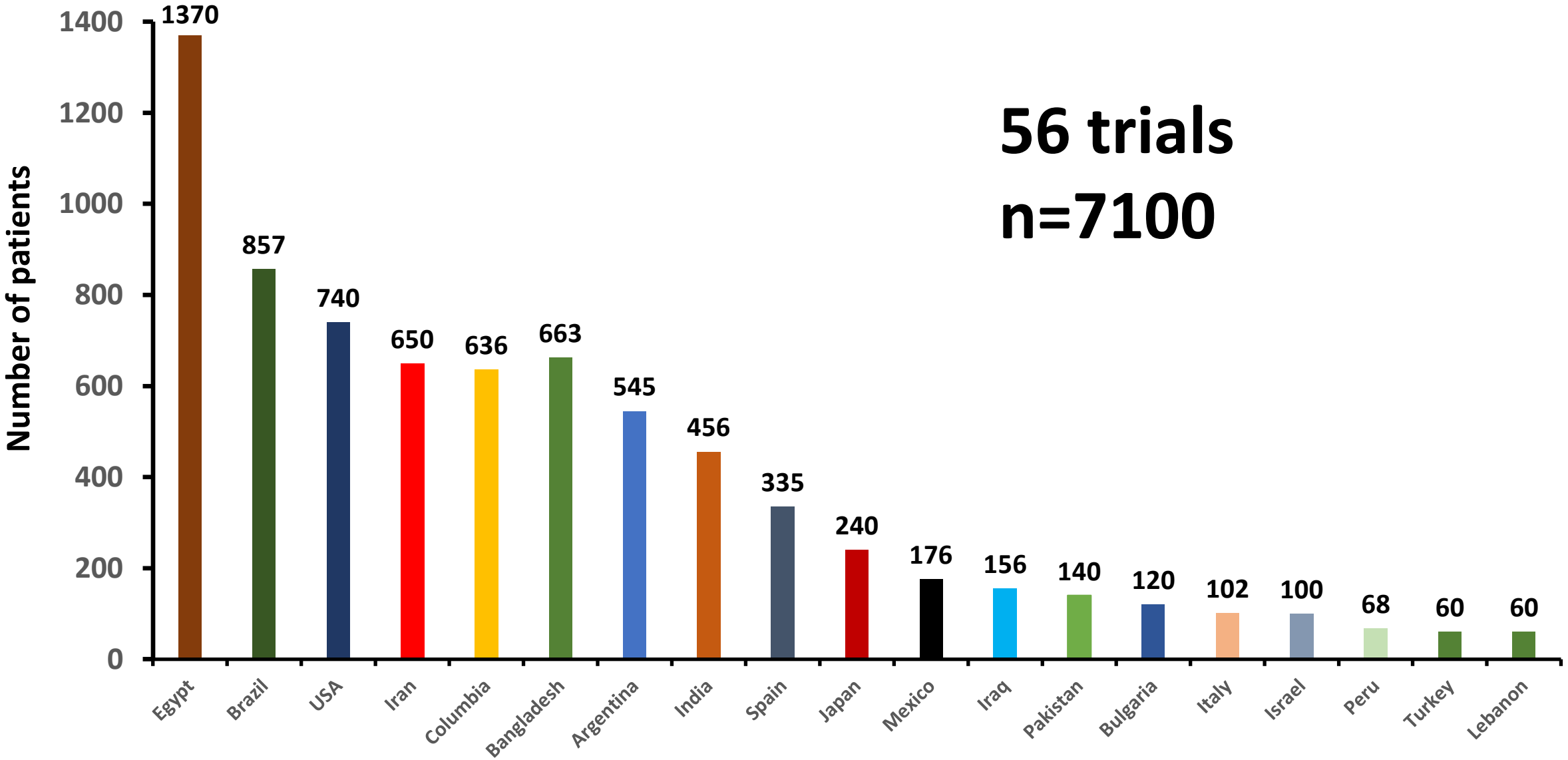
Several trials were open-label – potential for investigator bias

Range of doses and durations. Endpoints differ between trials

Randomised ivermectin trials in meta-analysis



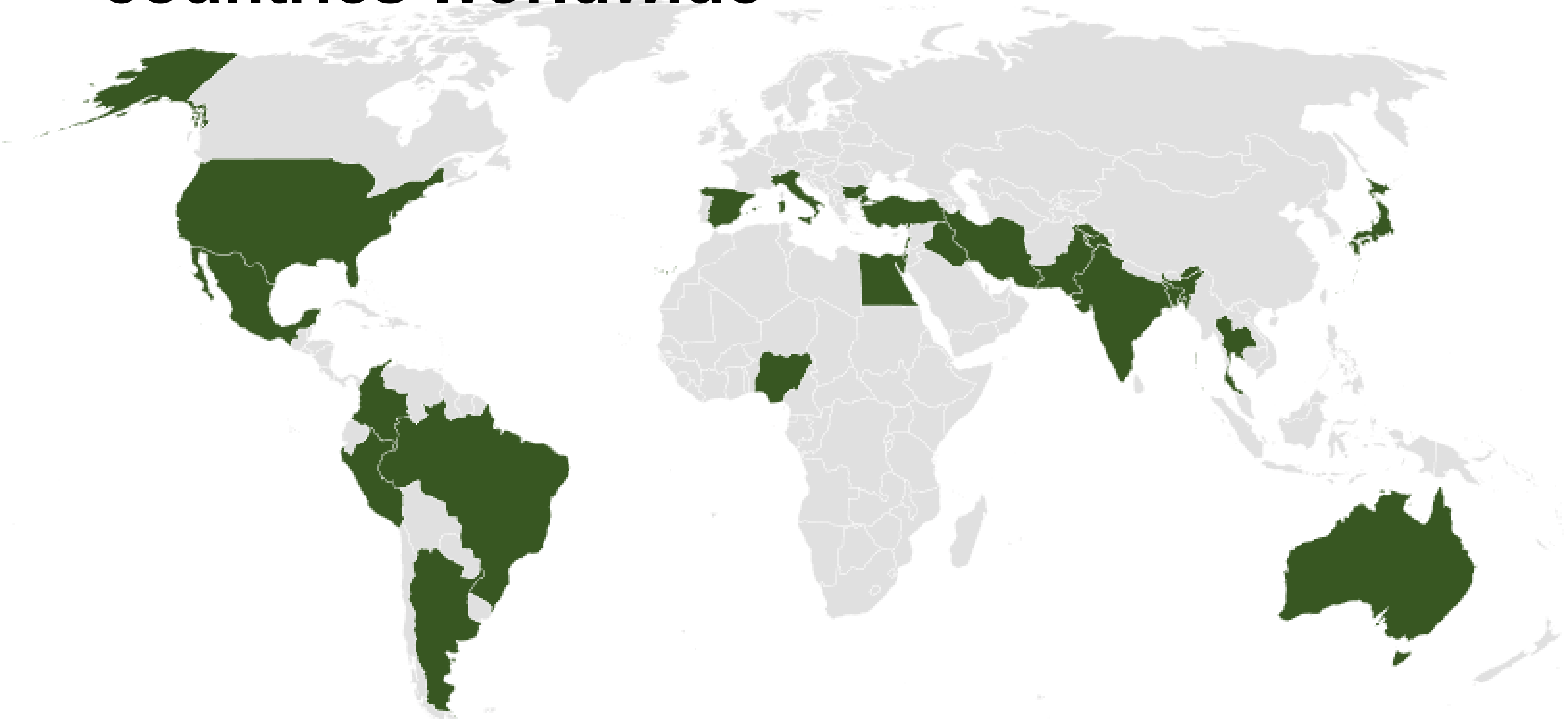
All randomised clinical trials of ivermectin



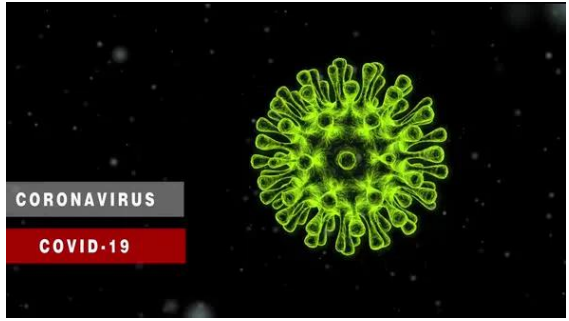
56 trials

n=7100

Clinical trials of ivermectin in at least 21 countries worldwide



Conclusions



In this meta-analysis of 11 randomised trials in 1452 patients

Ivermectin treatment was associated with:

Faster time to viral clearance
Shorter duration of hospitalisation
43% higher rates of clinical recovery (95% C.I. 21-67%)
83% improvement in survival rates (95% C.I. 65-92%)

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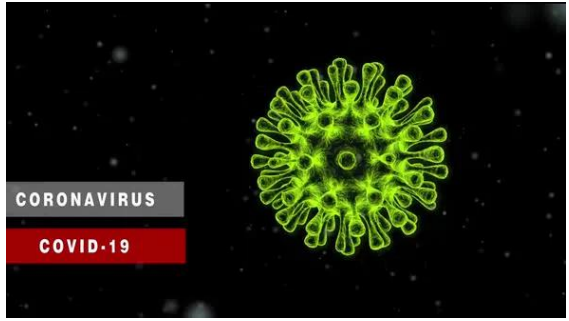
Next steps



We need more clinical trials data to confirm the clinical benefits observed in the first 11 randomized clinical trials

Efficacy is improved by dosing over several days, versus on one day only. An optimised dose regime needs to be defined

Results from three more key randomized trials will be available in January

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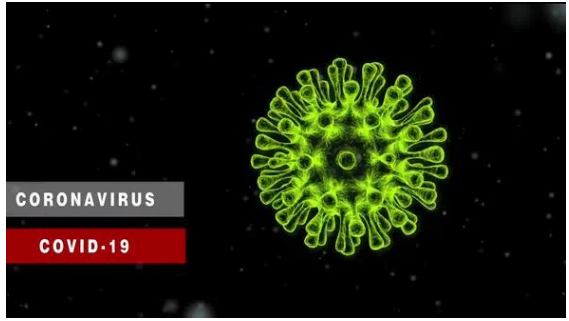

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