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Ivermectin reduces the risk of death from COVID-19 -a rapid review and meta-analysis in support of the recommendation of the Front Line COVID-19 Critical Care Alliance.

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URGENT COVID-19 information:

Ivermectin reduces the risk of death from COVID-19 – a rapid review and meta-analysis in support of the recommendation of the Front Line COVID-19 Critical Care Alliance.

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Background to this rapid review

Recently a group of expert critical care physicians, called the Front Line COVID-19 Critical Care Alliance (FLCCC), reviewed the evidence on the effects of ivermectin on SARS-CoV-2 virus and COVID-19 infections.[1] They concluded that the evidence on ivermectin "demonstrates a strong signal of therapeutic efficacy" and recommended that ivermectin is adopted globally and systematically for the prophylaxis and treatment of COVID-19.[1] Ivermectin is an anti-parasitic medication widely used in low- and middle-income countries to treat parasitic worm infections in adults and children.[1,2] Having been used for decades for this purpose, it is considered extremely safe and effective[2,3] and has an increasing list of indications due to its antiviral and anti-inflammatory properties.[4] On the WHO's *Model List of Essential Medicines* it is retained in the form of a 3 mg tablet.[5] For parasitic infections in adults, ivermectin is commonly administered as a single 12 mg oral dose (0.2mg/kg).

The FLCCC review summarizes the findings of 27 studies evaluating ivermectin for prophylaxis and treatment of COVID-19 infection; however, it does not include meta-analyses for the majority of outcomes. The FLCCC has called upon national and international

health care agencies to devote the necessary resources to checking and confirming this groundbreaking evidence.
Given the urgency of the situation, I undertook this rapid systematic review and meta-analysis of studies included in the FLCCC paper to validate the FLCCC's conclusions.

Target audience

This report is aimed primarily at health professionals and policymakers.

Methodology

Study selection, data extraction and outcome measures

I downloaded the available texts of the 27 studies included in the FLCCC summary tables.[1] From this list, I included randomized controlled trials (RCTs) and controlled observational studies (OCTs), excluding case-control studies and case series due to their higher risk of bias. I extracted data on the characteristics of the studies, risk of bias and important COVID-19 health outcomes (see Box 1), which I compiled with reference to the FLCCC review tables. Risk of study bias was assessed using the Cochrane Handbook for Systematic Reviews of Interventions and the ROBINS-I tools for RCTs and OCTs, respectively.[6,7]

Box 1. COVID-19 outcome measures

A: Ivermectin treatment versus control

1. Death (primary outcome)
2. Condition improvement, as measured by the study authors
3. Condition deterioration, as measured by the study authors
4. Recovery time, in days
5. Length of hospital stay, in days
6. Admission to hospital (for outpatient treatment)
7. Admission to ICU or requiring ventilation
8. Serious adverse events

B. Ivermectin prophylaxis versus control

1. COVID-19 infection, defined as a positive COVID-19 test with or without symptoms (primary outcome)
2. Serious adverse events

Data analysis and evidence quality assessment

I used Review Manager (RevMan) software version 5.4 for meta-analysis.[8] For dichotomous outcomes (most outcomes), I calculated the effect size as a risk ratio (RR) with its 95% confidence intervals (CIs); for continuous outcomes (i.e. recovery time and length of hospital stay), I calculated the mean difference (MD) between treatment groups with 95% CIs. I used the random effects model for all meta-analyses because I anticipated that there would be clinical heterogeneity in the participant characteristics, control interventions and the ivermectin dose, frequency and accompanying medicines. I subgrouped studies according to the severity of COVID-19 in the sample. For the primary outcome (deaths), I performed two analyses, one with only RCT data, the other with both RCT and OCT data. For all other outcomes I used both RCT and OCT data because there was generally less RCT data for these outcomes.

Statistical heterogeneity was assessed by visual inspection of forest plots and by use of the I^2 statistic,[9] and I defined substantial statistical heterogeneity as $I^2 \geq 60\%$. Where heterogeneity was found, I conducted sensitivity analysis by excluding studies assessed as having a high risk of bias from the analysis. I graded the evidence from meta-analysis based on a set of established criteria (study design limitations, inconsistency, imprecision, indirectness and publication bias) using the GRADE approach to judging the quality (certainty) of the evidence.[10] Data extraction, including risk of bias decisions, and grading were checked by a colleague at the Evidence-based Medicine Consultancy Ltd (see acknowledgements).

Review findings

Description of studies

Fifteen study reports were included, nine of RCTs and six of OCTs. One RCT (Elgazzar 2020) reported findings of a prophylaxis study and a treatment study within the same paper and these were regarded as separate studies. Similarly, one OCT (Carvallo 2020) reported findings of a pilot study and a further multicentre study and these were treated separately. Eleven studies were excluded with reasons (see supplementary file). Five of the included studies involving 2045 participants were of COVID-19 prophylaxis among health care workers and patient contacts; the remaining 13 involving 1835 participants were of COVID-19 treatment. Study sample sizes ranged from 24 to 1195 participants and studies were conducted in Argentina (2), Bangladesh (6), Egypt (3) India (1), Iran (2), Pakistan (1), Spain (1), and the USA (1) (Table 1). Fifteen studies were at low or moderate risk of bias and two studies were at high risk of bias. Eight were registered on clinical trial registries; most

appeared to be self-funded, undertaken by clinicians working in the field not by dedicated research teams. There were no apparent conflicts of interest.

Table 1. Included study characteristics

Study ID (refs 12-27)	Country	Design	Sample size	Ivermectin dose and frequency*	Risk of bias
COVID-19 treatment studies					
Ahmed 2020	Bangladesh	RCT	72	12mg x1 or x5 (3 arms)*	Low
Cepelowicz Rajter 2020	USA	OCT	280	0.2mg/kg x 1 or 2	Low
Chaccour 2020	Spain	RCT	24	0.4mg/kg x 1	Low
Chachar 2020	Pakistan	RCT	50	12mg at 0, 12, and 24 hours	Moderate
Chowdhury 2020	Bangladesh	RCT	116	0.2mg/kg x1*	Moderate
Elgazzar 2020a	Egypt	RCT	200	0.4mg/kg daily x4	Moderate
Mahmud 2020	Bangladesh	RCT	363	12mg x 1*	Low
Podder 2020	Bangladesh	RCT	62	0.2mg/kg x1	High
Hashim 2020	Iran	RCT	140	0.2mg/kg x 2 days* Some had a 3rd dose a week later	Moderate
Khan 2020	Bangladesh	OCT	248	12mg x 1	Moderate
Niaee 2020	Iran	RCT	180	0.2mg/kg x 1 and others (6 arms)	Low
Spoorthi 2020	India	OCT	100	0.2mg/kg x 1*	Moderate
COVID-19 prophylaxis studies					
Alam 2020	Bangladesh	OCT	118	12mg tab monthly x4	Low
Carvallo 2020 pilot	Argentina	OCT	229	1 drop of 0.6mg/ml solution x 5 daily	Moderate
Carvallo 2020	Argentina	OCT	1195	12mg tab weekly	High

Elgazzar 2020b	Egypt	OCT	200	0.4mg/kg, weekly x 2	Moderate
Shouman 2020	Egypt	RCT	303	2 doses 72 hours apart -15mg tab for 60-80 kg	Moderate

OCT, observational controlled trial; RCT, randomised controlled trial
*Also administered doxycycline.
Note: 0.2 mg/kg is equivalent to giving 12 mg and 0.4 mg/kg is equivalent to giving 24 mg for a 60 kg person.

Study participant characteristics

The mean age of study participants was between 30 and 40 years old for six studies, 40 and 50 years old for four studies, and 50 to 60 years old for five studies; two studies reported a median age of participants of 26 and 35 years old, respectively; one study did not report participant age.

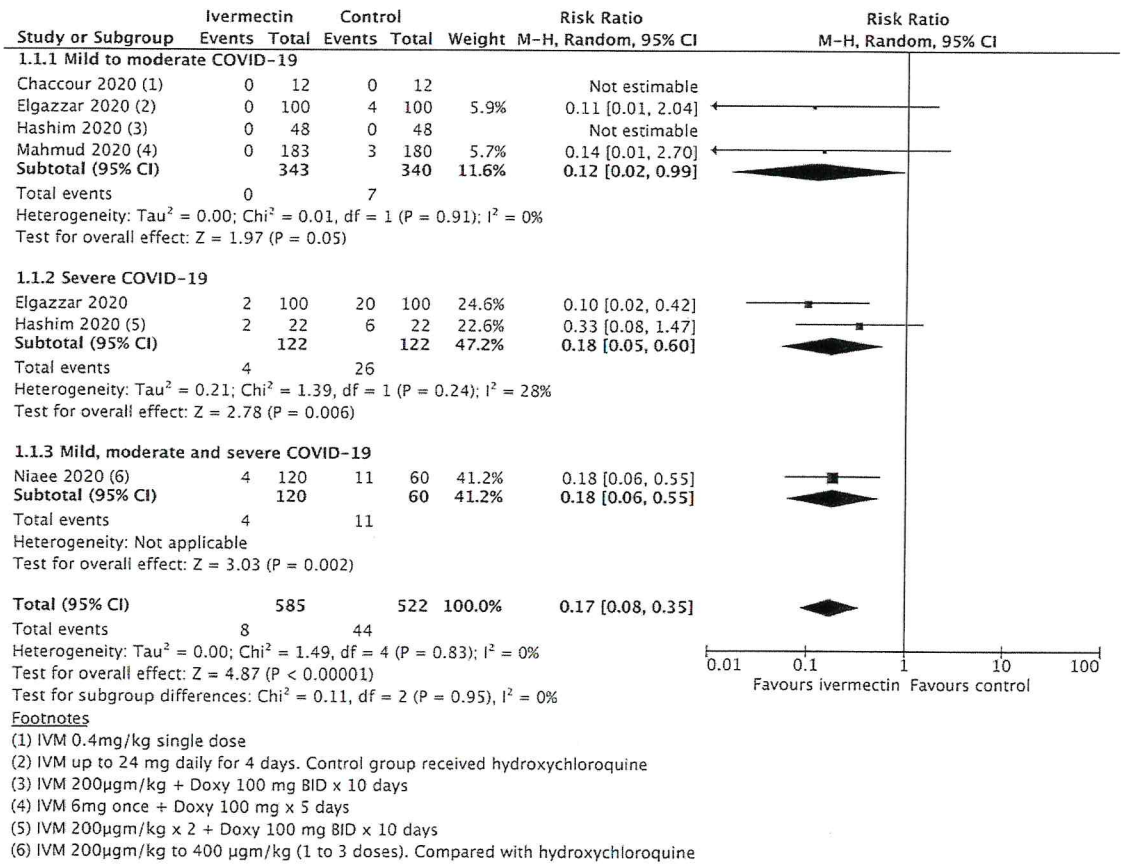
People with co-morbidities (e.g. diabetes mellitus, hypertension, cardiovascular disease, asthma, obesity) were excluded from three studies and were included in eight studies in which they occurred at a cumulative frequency ranging from 28% to the vast majority of participants; co-morbidities were not reported in seven studies. Four studies reported the proportion of smokers, which ranged from 13% to 30%. In most studies pregnant and lactating women were excluded from participation, and several studies excluded people with chronic liver or kidney disease.

Comparison 1: Ivermectin treatment versus control

Analysis 1.1: Death

Moderate certainty evidence indicates that ivermectin probably reduces deaths by an average 83% (95% CI, 65% to 92%) compared with no ivermectin treatment (5 RCTs, 1107 participants; RR 0.17, 95% 0.08 to 0.35; risk of death 1.4% versus 8.4% among participants in this analysis).

Forest plot 1.1.



Footnotes
(1) IVM 0.4mg/kg single dose
(2) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(3) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(4) IVM 6mg once + Doxy 100 mg x 5 days
(5) IVM 200µgm/kg x 2 + Doxy 100 mg BID x 10 days
(6) IVM 200µgm/kg to 400 µgm/kg (1 to 3 doses). Compared with hydroxychloroquine

A second analysis, which includes OCTs can be found in the Appendix at the end of this document. Findings from the latter analysis which included nine studies and 1735 participants are consistent with the above analysis and suggest a probable reduction in deaths of about 69% on average (RR 0.31, 95% CI 0.16 to 0.61; risk of death was 3.9% vs 9.9 %), a slightly more modest effect estimate than the analysis above that includes RCTs only.

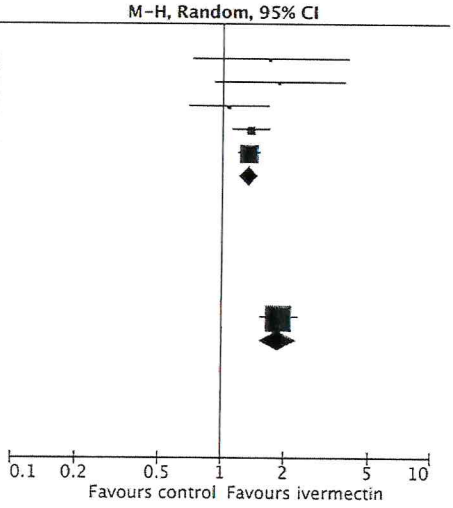
Analysis 1.2: Condition improvement

Data for 'mild to moderate COVID-19' and 'severe' COVID-19' subgroups were not pooled for this outcome because the statistical test for subgroup differences indicates that the effect size is not the same for these subgroups. Moderate certainty evidence suggests that ivermectin probably increases the likelihood of people with mild to moderate COVID-19 improving by about 34% (22% to 48%) (5 studies, 743 participants; RR 1.34, 95% CI 1.22 to 1.48; evidence certainty downgraded for study design limitations) compared with no ivermectin treatment.

For those with severe COVID-19 infection, low certainty evidence suggests that it may increase the likelihood of improvement by a greater extent than for mild to moderate infections (1 study, 200 participants, RR 1.88, 95% CI 1.54 to 2.30). This evidence was downgraded to low certainty because of study design limitations and because it was derived from a single small study.

Forest plot 1.2.

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Mild to moderate COVID-19						
Ahmed 2020 (1)	14	23	4	11	1.3%	1.67 [0.72, 3.91]
Ahmed 2020 (2)	17	22	5	12	1.9%	1.85 [0.91, 3.76]
Chaccar 2020 (3)	16	25	15	25	5.0%	1.07 [0.69, 1.65]
Mahmud 2020 (4)	111	183	80	180	23.5%	1.36 [1.12, 1.67]
Elgazzar 2020 (5)	99	100	74	100	68.2%	1.34 [1.19, 1.51]
Subtotal (95% CI)		**353**		**328**	**100.0%**	**1.34 [1.22, 1.48]**
Total events	257		178			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.22$, df = 4 (P = 0.70); $I^2 = 0\%$						
Test for overall effect: Z = 5.91 (P < 0.00001)						
1.2.2 Severe COVID-19						
Elgazzar 2020 (6)	94	100	50	100	100.0%	1.88 [1.54, 2.30]
Subtotal (95% CI)		**100**		**100**	**100.0%**	**1.88 [1.54, 2.30]**
Total events	94		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.12 (P < 0.00001)						



Test for subgroup differences: $Chi^2 = 8.70$, df = 1 (P = 0.003), $I^2 = 88.5\%$

Footnotes

(1) IVM 12mg daily x 5 days
(2) IVM 12mg s+ doxy 200mg stat then 100 mg BD x 4 days
(3) IVM 12 mg at 0, 12, and 24 hours
(4) IVM 6mg once + Doxy 100 mg x 5 days
(5) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(6) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine

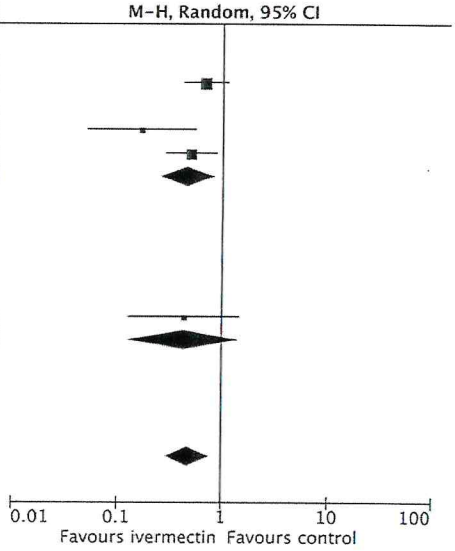
Note: Ahmed 2020 is a 3 arm study, therefore the control group has been split between its two study comparisons in this analysis.

Analysis 1.3: Condition deterioration

Moderate certainty evidence suggests that ivermectin probably reduces the risk of a person's condition deteriorating by about 53% (95% CI 23% to 71%) compared with no ivermectin treatment (5 studies, 1175 participants; RR 0.47, 95% CI 0.29 to 0.77).

Forest plot 1.3.

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Mild to moderate COVID-19						
Chaccour 2020 (1)	0	12	0	12		Not estimable
Elgazzar 2020 (2)	23	200	34	200	39.1%	0.68 [0.41, 1.11]
Hashim 2020 (3)	0	48	0	48		Not estimable
Khan 2020 (4)	3	115	21	133	13.4%	0.17 [0.05, 0.54]
Mahmud 2020 (5)	16	183	32	180	34.7%	0.49 [0.28, 0.86]
Subtotal (95% CI)		558		573	87.2%	**0.46 [0.25, 0.85]**
Total events	42		87			
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 4.89$, df = 2 (P = 0.09); $I^2 = 59\%$						
Test for overall effect: Z = 2.48 (P = 0.01)						
2.3.2 Severe COVID-19						
Hashim 2020	3	22	7	22	12.8%	0.43 [0.13, 1.45]
Subtotal (95% CI)		22		22	12.8%	**0.43 [0.13, 1.45]**
Total events	3		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
Total (95% CI)		580		595	100.0%	**0.47 [0.29, 0.77]**
Total events	45		94			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 4.97$, df = 3 (P = 0.17); $I^2 = 40\%$						
Test for overall effect: Z = 3.02 (P = 0.003)						
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.92), $I^2 = 0\%$						



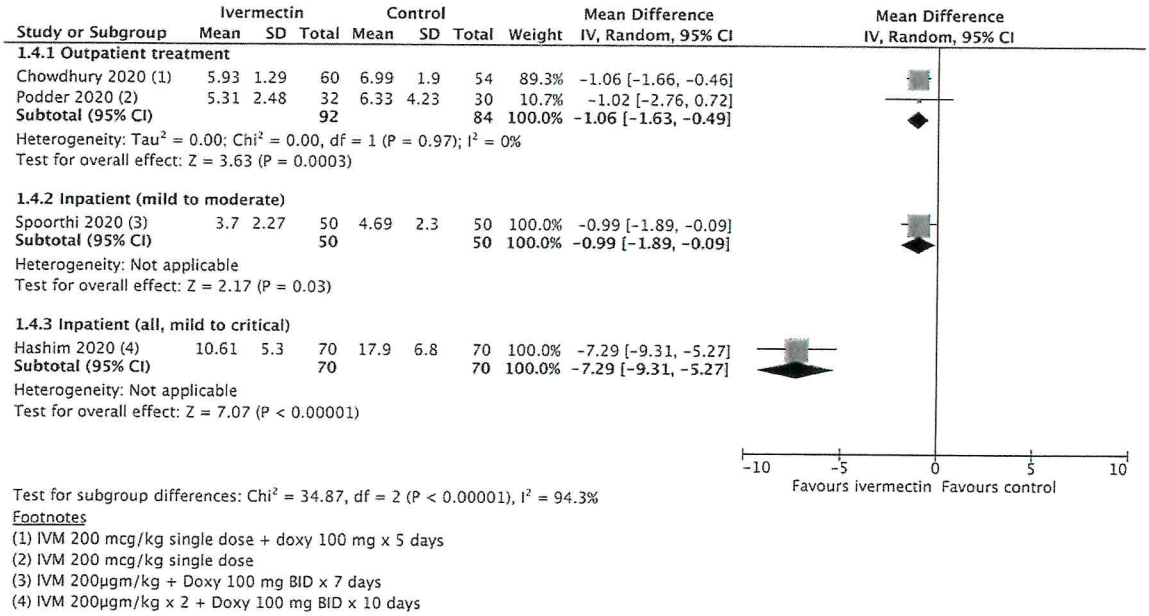
Footnotes
(1) IVM 0.4mg/kg single dose
(2) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(3) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(4) IVM 12 mg single dose
(5) IVM 6mg once + Doxy 100 mg x 5 days

Analysis 1.4: Recovery time (clinical), as measured by study authors

For the subgroup of studies evaluating ivermectin as an outpatient treatment for COVID-19 infection, low certainty evidence suggests that ivermectin may reduce recovery time compared with no ivermectin treatment by about a day (2 studies, 176 participants; MD -1.06, 95% CI -1.63 to -0.49). Although the effect is consistent across the two studies in this subgroup, the evidence was downgraded for imprecision[1] and study design limitations.

Evidence on the effect of ivermectin on recovery time among people treated in hospital (subgroup analysis 1.4.2 and 1.4.3 in the forest plot below) similarly require more data to improve the certainty of this evidence.

Forest plot 1.4.



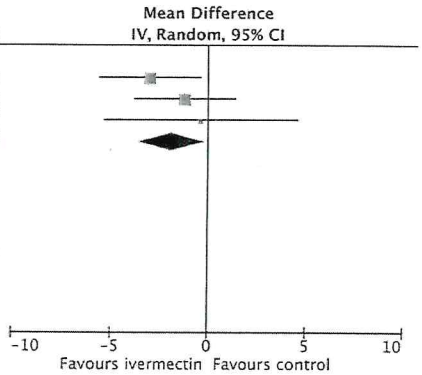
[1] According to the World Health Organization's standard operating procedure for grading evidence for guidelines, the total cumulative study population needs to be more than 300 participants for continuous data when evaluating imprecision.

Analysis 1.5: Recovery time to a negative PCR test

Low certainty evidence from two studies among outpatients suggests that ivermectin may reduce the time to a negative PCR test by about two days compared with no ivermectin treatment (2 studies, 186 participants; MD -1.88, 95% CI -3.62 to -0.15). The evidence was downgraded for imprecision and study design limitations.

Forest plot 1.5.

	Ivermectin			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.5.1 Outpatient treatment								
Ahmed 2020 (1)	9.7	4.5	24	12.7	3.4	12	43.5%	-3.00 [-5.63, -0.37]
Ahmed 2020 (2)	11.5	4.4	24	12.7	3.4	12	44.4%	-1.20 [-3.81, 1.41]
Chowdhury 2020 (3)	8.93	9.97	60	9.33	16.08	54	12.2%	-0.40 [-5.38, 4.58]
Subtotal (95% CI)			**108**			**78**	**100.0%**	**-1.88 [-3.62, -0.15]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.30$, df = 2 (P = 0.52); $I^2 = 0\%$								
Test for overall effect: Z = 2.13 (P = 0.03)								
1.5.2 Inpatient treatment								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Test for subgroup differences: Not applicable

Footnotes

(1) IVM 12 mg daily x 5 days

(2) IVM 12mg + doxy 200 mg stat then 100 mg BD x 4 days

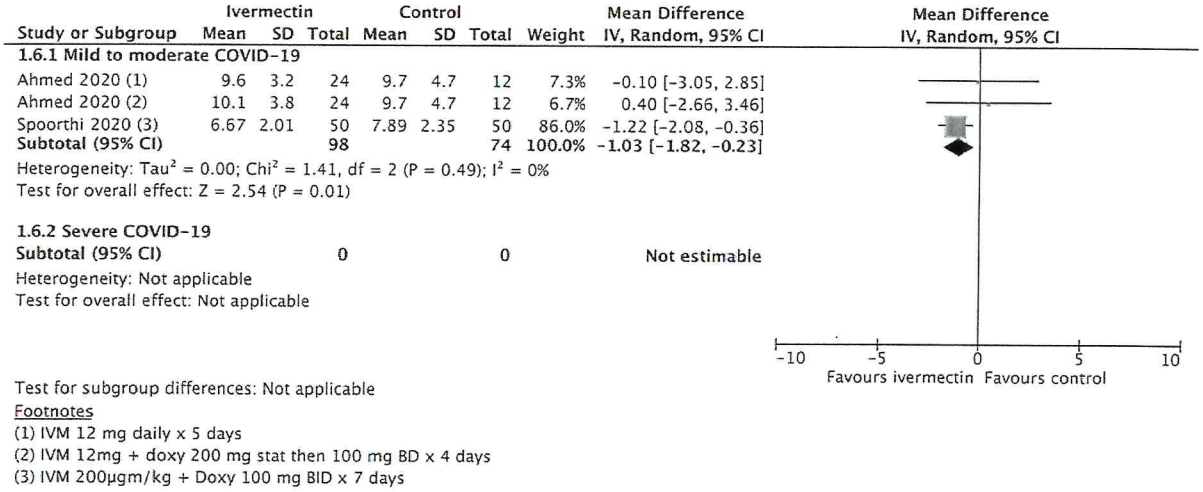
(3) IVM 200 mcg/kg single dose + doxy 100 mg x 5 days

Note: Ahmed 2020 is a 3 arm study, therefore the control group has been split between its two study comparisons in this analysis.

Analysis 1.6: Length of hospital stay

The evidence presented here is based on a sensitivity analysis whereby study data at high risk of bias (Elgazzar 2020) were excluded pending author query. The resulting low certainty evidence suggests that ivermectin may reduce the length of hospital stay by about a day in people with mild to moderate COVID-19 infection (2 studies, participants; MD -1.03, 95% CI -1.82 to -0.23; downgraded for study design limitations and imprecision).

Forest plot 1.6.



Test for subgroup differences: Not applicable

Footnotes

(1) IVM 12 mg daily x 5 days

(2) IVM 12mg + doxy 200 mg stat then 100 mg BD x 4 days

(3) IVM 200µgm/kg + Doxy 100 mg BID x 7 days

Additional data for this outcome were reported in one randomized (Niaee 2020) and three observational studies (Cepelowicz Rajter 2020, Khan 2020, Spoorthi 2020). However, these data were not presented as means and standard deviations, therefore, could not be included in this meta-analysis. Three of the studies (Khan 2020, Niaee 2020 and Spoorthi 2020) as well as the excluded Elgazzar 2020 data demonstrated reduced hospital stays with ivermectin, whereas Cepelowicz Rajter 2020 showed no difference.

Outcome 1.7: Admission to hospital (for treated outpatients)

There were no data for this outcome.

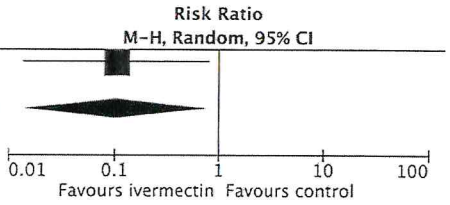
Outcome 1.8. Admission to ICU or requiring ventilation

Low certainty evidence from a single OCT suggests that ivermectin may lead to potentially large reductions in the number of people with COVID-19 infections requiring ICU admission (248 participants; RR 0.11, 95% CI 0.01 to 0.80). The evidence for this outcome was downgraded due to design limitations and imprecision.

Forest plot 1.8

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Khan 2020 (1)	1	115	11	133	100.0%	0.11 [0.01, 0.80]
Total (95% CI)		**115**		**133**	**100.0%**	**0.11 [0.01, 0.80]**
Total events	1		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.17 (P = 0.03)



Footnotes
(1) IVM 12mg single dose

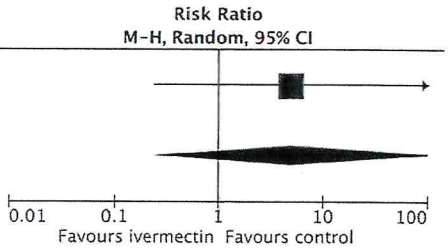
Outcome 1.9: Severe adverse events

These findings are of very low certainty. It is not possible to determine whether the two adverse events in the Mahmud 2020 study were due to ivermectin or doxycycline; however, esophagitis (the adverse event reported) is a known adverse effect associated with doxycycline. Non-severe adverse events were reported in a few studies but these data were not extracted.

Forest plot 1.9.

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahmed 2020 (1)	0	48	0	24		Not estimable
Mahmud 2020 (2)	2	183	0	180	100.0%	4.92 [0.24, 101.74]
Shouman 2020 (3)	0	203	0	101		Not estimable
Total (95% CI)		**434**		**305**	**100.0%**	**4.92 [0.24, 101.74]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)



Footnotes
(1) IVM 12 mg (24 pts) and IVM 12mg + doxy (24 pts)
(2) IVM 6mg once + Doxy 100 mg x 5 days
(3) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart

Comparison 2. Ivermectin prophylaxis versus control

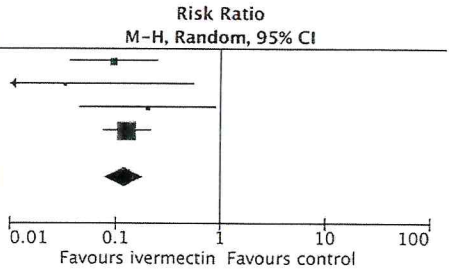
Outcome 2.1: COVID-19 infection

The evidence presented here is based on a sensitivity analysis whereby study data at high risk of bias from one study were excluded[2]. Moderate certainty evidence suggests that ivermectin prophylaxis among health care workers and COVID-19 contacts probably reduces the risk of COVID-19 infection by about 88% (4 studies, 851 participants; RR 0.12, 95% CI 0.08 to 0.18; 4.3% vs 34.5% contracted COVID-19). The certainty of this evidence was downgraded to moderate due to study design limitations (the Shouman 2020 results, reported on the clinicaltrials.gov website on 27 August 2020, were based on symptoms rather than a positive COVID-19 test).

Forest plot 2.1

	Ivermectin		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Alam 2020 (1)	4	58	44	60	20.0%	0.09 [0.04, 0.25]
Carvallo 2020a (2)	0	131	11	98	2.3%	0.03 [0.00, 0.55]
Elgazzar 2020 (3)	2	100	10	100	8.2%	0.20 [0.04, 0.89]
Shouman 2020 (4)	15	203	59	101	69.5%	0.13 [0.08, 0.21]
Total (95% CI)		**492**		**359**	**100.0%**	**0.12 [0.08, 0.18]**
Total events	21		124			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.63$, df = 3 (P = 0.65); $I^2 = 0\%$
Test for overall effect: Z = 9.70 (P < 0.00001)



Footnotes
(1) IVM 12 mg weekly x 4 doses
(2) IVM drops daily + carageenan oro-nasal spray x 14 days
(3) IVM up to 24mg weekly depending on weight x 2 doses
(4) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart

[2] The multicentre data from Carvallo 2020 were excluded; pilot study data from Carvallo 2020 are included

Table 2. Summary of findings

Review outcome	Effect estimate (95% CI)	Effect certainty
Deaths	RR 0.17 (0.08 to 0.35)	MODERATE
Condition improvement (mild to moderate COVID-19)	RR 1.34 (1.22 to 1.48)	MODERATE
Condition improvement (severe COVID-19)	RR 1.88 (1.54 to 2.30)	LOW
Condition deterioration	RR 0.47 (0.29 to 0.77)	MODERATE
Recovery time (outpatients)	MD 1.06 days (-1.63 to -0.49 days)	LOW
Recovery time to negative PCR test	MD-1.09 days (-2.55 to 0.37)	LOW
Length of hospital stay (mild to moderate COVID-19)	MD -1.03 days (-1.82 to -0.23)	LOW
Admission to ICU	RR 0.11 (0.01 to 0.80)	LOW
Prophylaxis outcome		
COVID-19 infection	RR 0.12 (0.08 to 0.18)	MODERATE

RR = relative risk; CI = confidence interval; MD = mean difference; ICU = intensive care unit

Discussion

This review and meta-analysis confirms that ivermectin substantially reduces the risk of a person dying from COVID-19 by probably somewhere in the region of 65% to 92%. The only uncertainty in the evidence relates to the precise extent of the reduction, not in the effectiveness of ivermectin itself. Similarly, when ivermectin is used as prophylaxis among health care workers and contacts, it is clear that ivermectin substantially reduces COVID-19 infections, probably somewhere in the region of 88% (82% to 92%). Data from numerous currently active RCTs will help to determine the precise extent of its protective effect in these at risk groups.

Despite the FLCCC's strong recommendation that ivermectin should be implemented globally to save lives from COVID-19, most governments and health professionals still appear to be unaware of this profoundly effective COVID-19 treatment. Not only is ivermectin a safe, effective and well-known medicine, at an estimated cost of less than 10 pence per person treated with a 12 mg tablet, it does indeed seem like a miracle drug in the context of the current global COVID-19 situation.[26] Guidance and protocols on using ivermectin for COVID-19 can be found on the FLCCC website https://covid19criticalcare.com.

Conclusions

- Ivermectin is an essential drug to reduce morbidity and mortality from COVID-19 infection.
- Placebo-controlled trials of ivermectin treatment among people with COVID-19 infection are no longer ethical and active placebo-controlled trials should be closed.

Declaration of interests

I am the Director of the Evidence-based Medicine Consultancy Ltd and have no conflicts of interests to declare. The business of E-BMC Ltd is to conduct independent medical evidence synthesis to inform clinical practice guidelines.

Funding

Neither I nor E-BMC Ltd have received funding for this work.

Author statement

I take full responsibility for the scientific integrity of this urgent evidence synthesis. The evidence derived from the studies included in the FLCCC review is sufficient to support a strong recommendation on ivermectin for the treatment of COVID-19.

Due to the urgency and imperative to communicate this critical information to health professionals, and in the context of the probable effect size of ivermectin on COVID-19 deaths revealed by this meta-analysis, additional exploratory analyses (for example looking at the effect of co-administration of doxycycline) have not been conducted. Neither have I sought unpublished data from the numerous ongoing trials of ivermectin on clinical trial registries.

It is my hope that both health professionals and policy makers now respond to this information with the required urgency, so that critical time in saving lives is not wasted.

Acknowledgements

Many thanks go to the FLCCC for bringing this critical evidence to the attention of health professionals and authorities, to the individual study investigators and clinicians, and to the people who have participated in the studies for the greater good of humanity. We all owe you a debt of gratitude.

With regard to this report, I gratefully acknowledge the assistance of Dr Therese Dowswell, Dr Ewelina Rogozinska, Mark Lawrie and Vicky Powell in its preparation. Dr Dowswell checked the data extraction and evidence grading, Dr Rogozinska commented on the draft manuscript, Mark Lawrie provided administrative support and Vicky Powell proof read the manuscript.

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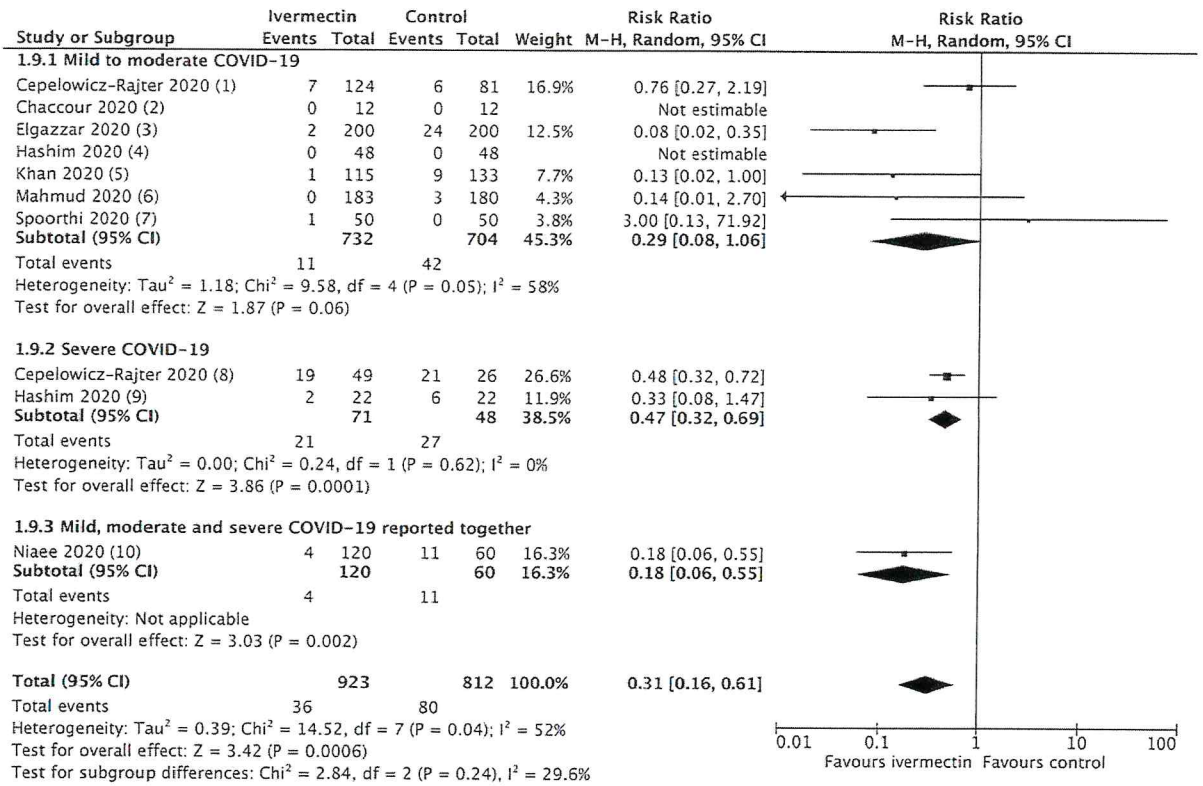
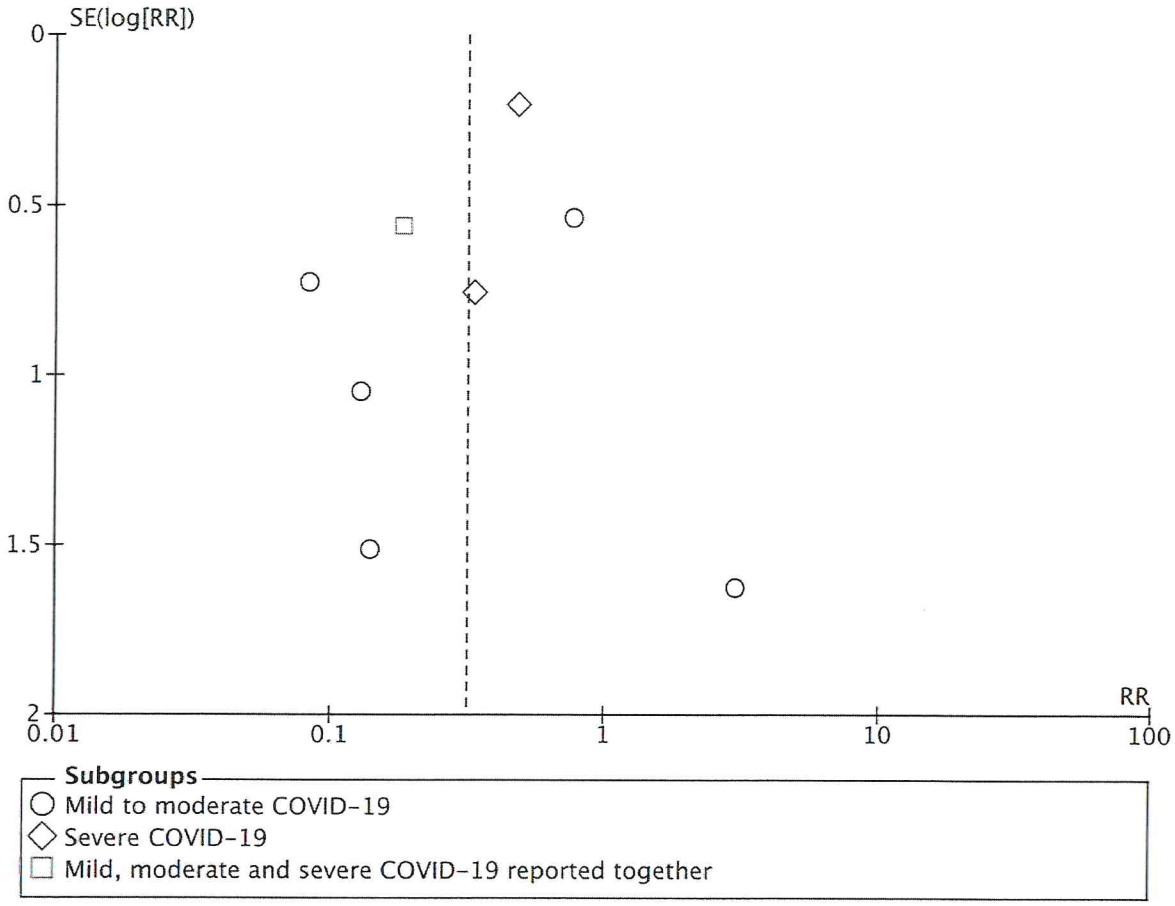
Appendix

Forest plot for the primary outcome (deaths) including RCTs and OCTs with accompanying funnel plot.



Footnotes

(1) IVM 0.2mg/kg one or two doses
(2) IVm 0.4mg/kg single dose
(3) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(4) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(5) IVM 12 mg single dose
(6) IVM 6mg once + Doxy 100 mg x 5 days
(7) IVM 200µgm/kg + Doxy 100 mg BID x 7 days
(8) IVM 0.2mg/kg one or two doses
(9) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(10) IVM 200µgm/kg to 400 µgm/kg (1 to 3 doses). Compared with hydroxychloroquine


SE(log[RR])
0
0.5
1
1.5
2
0.01
0.1
1
10
100
RR
Subgroups
Mild to moderate COVID-19
Severe COVID-19
Mild, moderate and severe COVID-19 reported together

Productie 29

Nieuwe WHO-studie: Ivermectine werkt

jan. 20, 2021

Meta-analyse laat sterke daling sterftecijfer zien

Gisteren verschenen de resultaten van een meta-analyse naar de effectiviteit van Ivermectine. Er zijn 18 gerandomiseerde klinische studies met in totaal 2282 deelnemers onderzocht.

Vastgesteld is dat Ivermectine ontstekingsremmend werkt in patiënten met COVID-19 en dat het virus sneller verdwijnt (virale klaring). Zes onderzoeken naar gemiddeld tot zwaar zieke COVID-19 patiënten laten een daling van de sterfte zien van gemiddeld 75 procent. Uit zes studies blijkt dat Ivermectine herstel versnelt en vijf studies tonen aan dat patiënten het ziekenhuis eerder verlaten als zij behandeld worden met Ivermectine.

De Britse onderzoeker Andrew Hill van de Universiteit van Liverpool was de hoofdonderzoeker. De studie maakt deel uit van het door de WHO gesponsorde ´ACT-accelerator´ programma. De doelstelling van dit programma is om de effectiviteit van geneesmiddelen tegen COVID-19 te beoordelen.

Vrijwel alle studies naar Ivermectine zijn kleinschalig van opzet. Voor onderzoekers is het lastig om voldoende deelnemers te vinden en om subsidies te krijgen. Daarom variëren de onderzoeken in opzet en doelstelling en dat maakt het lastig om studies met elkaar te vergelijken. Meer grootschalig onderzoek is nodig om de effecten van Ivermectine definitief vast te stellen. Daarentegen, vrijwel al de klinische onderzoeken laten zien dat Ivermectine werkt tegen COVID-19.

Preliminary meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection

Authors: Andrew Hill on behalf of the International Ivermectin Project Team*

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Abstract

Introduction: Ivermectin is a well-established antiparasitic drug licensed since 1981, more recently approved for its anti-inflammatory effects against rosacea. It is being investigated for repurposing against SARS-CoV-2. In-vitro, ivermectin showed some antiviral activity but at higher concentrations than achieved in human plasma after normal oral dosing. An animal model demonstrated pathological benefits in COVID-19 but no effect on viral RNA. We aimed to assess the available global data from randomized controlled trials (RCTs) of ivermectin in COVID-19.

Methods: We conducted a systematic search of PUBMED, EMBASE, MedRxiv and trial registries. We excluded prevention studies and non-randomized or case-controlled studies. We identified and included 18 RCTs. Data were combined from 2282 patients into a systematic review and meta-analysis.

Results: Ivermectin was associated with reduced inflammatory markers (C-Reactive Protein, d-dimer and ferritin) and faster viral clearance by PCR. Viral clearance was treatment dose- and duration-dependent. Ivermectin showed significantly shorter duration of hospitalization compared to control. In six RCTs of moderate or severe infection, there was a 75% reduction in mortality (Relative Risk=0.25 [95%CI 0.12-0.52]; p=0.0002); 14/650 (2.1%) deaths on ivermectin; 57/597 (9.5%) deaths in controls) with favorable clinical recovery and reduced hospitalization.

Discussion: Many studies that were included were not yet published or peer-reviewed and meta-analyses are prone to confounding issues. Furthermore, there was a wide variation in standards of care across trials, and ivermectin dose and duration of treatment was heterogeneous. Ivermectin should be validated in larger, appropriately controlled randomized trials before the results are sufficient for review by regulatory authorities.

Keywords: SARS-CoV2, COVID-19, Ivermectin, repurposed

Introduction

The pandemic of SARS-CoV-2 continues to grow, with 650,000 new infections and over 11,000 deaths recorded worldwide daily in January 2021 [1]. Protective vaccines have been developed, but current supplies are too low to cover worldwide demand in the coming months [2]. Researchers worldwide are urgently looking for interventions to prevent new infections, or prevent disease progression, and lessen disease severity for those already infected.

While research on new therapeutic agents for COVID-19 is key, there is also great interest on evaluating the potential use against COVID-19 of already existing medicines, and many clinical trials are in progress to 're-purpose' drugs normally indicated for other diseases. The known safety profiles, shortened development timelines, and well-established markets (with low price points and higher capacity to deliver at scale) for most of already existing compounds proposed for COVID-19 are particularly advantageous compared to new drug discovery in a pandemic situation. Three re-purposed anti-inflammatory drugs have shown significant survival benefits to date: the corticosteroid dexamethasone in the UK RECOVERY trial [3], and the Interleukin-6 (IL-6) receptor antagonist drugs, tocilizumab and sarilumab, in the REMAP-CAP trial [4]. Other re-purposed antimicrobials such as, hydroxychloroquine, lopinavir/ritonavir, remdesivir and interferon-beta, have shown no significant survival benefit in two large, randomized trials [3, 5] despite initial reports of efficacy, underscoring the need for caution when interpreting early clinical trial data.

Dexamethasone is recommended for use by the WHO and has proven survival benefits for oxygen-dependent patients with COVID-19, while tocilizumab and sarilumab improves survival for patients in intensive care [3, 4]. However, there are no approved treatments for patients with mild SARS-CoV-2 infection, either to prevent disease progression or reduce viral transmission. Treatments increasing viral clearance rate, may lower risk of onward transmission but this requires empirical demonstration.

Ivermectin is a well-established anti-parasitic drug used worldwide for a broad number of parasites and also for topical use against rosacea. Antiviral activity of ivermectin has been demonstrated for SARS-CoV-2 in Vero/hSLAM cells [IB6]. However, concentrations required to inhibit viral replication in vitro (EC_{50}=2.8μM; EC_{90}=4.4μM) are not achieved systemically after oral administration of the drug to humans [6, 7]. The drug is estimated to accumulate in lung tissues (2.67 times that of plasma) [8], but this is also unlikely to be sufficient to maintain target concentrations for pulmonary antiviral activity [7, 9]. Current data suggest that the dosages of ivermectin used in human trials are unlikely to provide systemic or pulmonary concentrations necessary to exert meaningful direct antiviral activity. Notwithstanding, ivermectin is usually present as a mixture of two agents and although mainly excreted unchanged in humans, has two major metabolites [10]. Current data are insufficient to determine whether the minor form or a circulating metabolite has higher direct potency against SARS-CoV-2, but it seems likely that it would need to be profoundly more potent than the reported values.

Ivermectin has also demonstrated immunomodulatory and anti-inflammatory mechanisms of action in preclinical models of several other indications. *In-vitro* studies have demonstrated that ivermectin suppresses production of the inflammatory mediators nitric oxide and prostaglandin E2 [11]. Furthermore, avermectin (from which ivermectin is derived) significantly impairs pro-inflammatory cytokine secretion (IL-1β and TNF-α) and increases secretion of the immunoregulatory cytokine IL-10 [12]. Ivermectin also reduced TNF-α, IL-1, and IL-6, and improved survival in mice given a lethal dose of lipopolysaccharide [13]. Preclinical evidence to support these immunomodulatory and anti-inflammatory mechanisms of action have also been generated in murine models of atopic dermatitis and allergic asthma [14, 15]. Finally, in Syrian golden hamsters infected with SARS-CoV-2, subcutaneous ivermectin demonstrated a reduction in the IL-6/IL-10 ratio in lung tissues and prevented pathological deterioration [16]. The impact of ivermectin in this model appeared to be gender specific, appearing more active in females than in males. Irrespective of gender, no impact of ivermectin on viral titers in lung or nasal turbinate was observed in this model, supporting a mechanism of action not relating to direct antiviral activity.

In pharmacokinetic studies, the Area Under the Curve (AUC) and maximum concentration (Cmax) of ivermectin are generally dose proportional, and bioavailability of ivermectin increases 2.57-fold in the fed state [8]. Increasing the frequency or dose of ivermectin does increase the Cmax and AUC of total drug, but not sufficiently to reach the published EC_{50} against SARS-CoV-2 in monkey Vero/hSLAM cells [8]. Ivermectin has approximately twice the systemic availability when given as an oral solution compared to solid forms (tablets or capsules) [10].

At standard doses, of 0.2-0.4mg/kg for 1-2 days, ivermectin has a good safety profile and has been distributed to billions of patients worldwide in mass drug administration programs. A recent meta-analysis found no significant difference in adverse events in those given higher doses of ivermectin, of up to 2mg/kg, and those receiving longer courses, of up to 4 days, compared to those receiving standard doses [17]. Ivermectin is not licensed for pregnant or breast-feeding women, or children <15kg.

The objective of this systematic review and meta-analysis was to combine available results from published or unpublished randomized trials of ivermectin in SARS-CoV-2 infection.Limitations of current analysis is important as it is being performed with secondary data from a wide variety of different trials in many different parts of the world with designs that were not originally meant to be compatible. Further refined analysis, including direct data examination, are warranted.

Methods

The systematic review and meta-analysis was conducted according to PRISMA guidelines. A systematic search of PUBMED and EMBASE was conducted to identify randomized control trials (RCT) evaluating treatment with ivermectin for SARS-CoV-2 infected patients. Clinical trials with no control arm, or those evaluating prevention of infection were excluded alongside non-randomized trials and case-control studies. Key data extracted included baseline characteristics (age, sex, weight, oxygen saturation, stage of infection), changes in inflammatory markers, viral suppression after treatment, clinical recovery, hospitalization and survival. Data were extracted and cross-checked by two independent reviewers (HW and LE).

Search strategy and selection criteria

RCTs were eligible for inclusion if they compared an ivermectin-based regimen with a comparator or standard of care (SOC) for the treatment of COVID-19. Clinicaltrials.gov [18] was searched on 14th December 2020 using key words COVID, SARS-CoV-2 and ivermectin to identify studies. The WHO International Clinical Trials Registry Platform (ICTRP) was accessed via the COVID-NMA Initiative's mapping tool, updated to 9th December 2020, [19] and Stamford University's Coronavirus Antiviral Research Database (CoV-RDB), updated to 15th December 2020, [20] to identify additional trials listed on other national, and international registries.

Additionally, literature searches via PubMed, and the preprint server MedRxiv were conducted to identify published studies not prospectively or retrospectively registered in a trial registry. Duplicate registrations, non-controlled studies and prevention studies were excluded following discussion between the authors.

In a third stage of data collection, the research teams conducting unpublished clinical trials were contacted and requested to join regular international team meetings in December 2020 and January 2021. All results available from unpublished studies were also included in this systematic review.

All of the clinical trials included in this meta-analysis were approved by local ethics committees and all patients signed informed consent.

The primary outcome was all-cause mortality from randomization to the end of follow-up. Changes in inflammatory markers, viral suppression, clinical recovery and hospitalization were measured in different ways between trials and were summarized for individual clinical trials where endpoints could not be combined.

Data analysis

Statistical analyses for all-cause mortality were conducted with summary published data, on the intention-to-treat population, including all randomized patients. Clinical trials with at least two deaths reported were included in this analysis. Treatment effects were expressed as risk ratios (RR) for binary outcomes. For each outcome we pooled the individual trial statistics using the random-effects inverse-variance model; a continuity correction of 0.5 was applied to treatment arms with no deaths. Heterogeneity was evaluated by I^2. The significance threshold was set at 5% (two-sided) and all analyses were conducted using Revman 5.3.

All studies included in this analysis were assessed for risk of bias using the Cochrane Collaboration risk of bias standardized assessment tool [21] and the outcome of this assessment is given in supplementary table 1.

Results

In this meta-analysis, 18 RCTs involving a total of 2282 participants were included. The sample sizes of each trial ranged from 24 to 400 participants. Of the 18 included studies, five were published papers, six were available as pre-prints, six were unpublished results shared for this analysis; one reported results via a trial registry website.

Overall, nine trials investigated ivermectin as a single dose (Table 1A), nine trials investigated multi-day dosing up to seven days (Table 1B), of which three trials were dose-ranging. In this meta-analysis, ivermectin was largely investigated in mild/moderate participants (11 trials). Overall, 12 trials were either single or double-blinded and six were open-label.

Effects on Inflammatory Markers

Five trials provided results of the effect of ivermectin on inflammatory markers including C-reactive protein (CRP), ferritin and d-dimer (Table 2). Four of these trials demonstrated significant reductions in CRP compared to control. Furthermore, in the Elgazzar trial [22], ivermectin significantly reduced ferritin levels compared to control in the severe patient population while no significant difference was demonstrated in the mild/moderate population. The Okumus trial [23] showed significantly greater reductions in in ferritin on day 10 of follow-up for ivermectin versus control. The Chaccour [24] and Ahmed [25] trials showed no significant difference in ferritin count between ivermectin and control. Elgazzar [22] showed significant differences in d-dimer between ivermectin and control in both the mild/moderate and severe populations. Okumus [23] showed significant differences in d-dimer on day 5 whilst Chaccour [24] found no differences between ivermectin and control, but with a smaller sample size.

Effects on Viral Clearance

Three different endpoints were used to analyze viral clearance: the percentage of patients undetectable on a set day (Table 3A), the number of days from randomization to negativity (Table 3B), and other measures such as cycle time (Ct) values and dose-response correlations (Table 3C). The Kirti [26] and Okumus [23] trials included viral load analysis only in a subset of patients. The effects of ivermectin on viral clearance were generally smaller when dosed on only one day. Several studies showed no statistically significant effect of ivermectin on viral clearance [27, 28, 29].

The three studies randomizing patients to different doses or durations of ivermectin showed apparent dose-dependent effects on viral clearance. Firstly, in the Babalola trial [30], the 0.4mg/kg dose showed trends for faster viral clearance than the 0.2mg/kg dose. Secondly, in the Mohan trial [28], the 0.4 mg/kg dose of ivermectin led to a numerically higher percentage of patients with viral clearance by day five than the 0.2mg/kg dose. Thirdly, in the Ahmed trial [25], ivermectin treatment for five days led to a higher percentage of patients with viral clearance at day 13 compared with one day of treatment. Finally, in Krolewiecki [31], PK/PD correlations showed significantly faster viral clearance for patients with PK exposures above 160ng/mL.

The effect of ivermectin on viral clearance was most pronounced in the randomized trials evaluating doses of up to five days of ivermectin treatment, using doses of 0.4mg/kg (Figure 1). At these doses, there were statistically significant effects on viral clearance in all four randomized trials.

Effects on Clinical Recovery and Duration of Hospitalization

Definitions of clinical recovery varied across trials, as shown in Table 4. In Table 4A, four of the six trials showed significantly faster time to clinical recovery on ivermectin compared to control. In five trials, ivermectin showed significantly shorter duration of hospitalization compared to control (Table 4B).

Effects on Survival

Six randomized trials reported that at least two people had died post-randomization and were included in the analysis (Table 5). Across these six trials in 1255 patients, there were 14/658 (2.1%) deaths in the ivermectin arms, versus 57/597 (9.5%) deaths in the control arms. In a combined analysis using inverse variance weighting ivermectin showed a 75% improvement in survival (RR 0.25 [95%CI 0.12-0.52]; p=0.0002, Figure 2). Heterogeneity was moderate, I^2 = 34%.

Evaluation of Studies.

An evaluation of the quality of the studies included in this meta-analysis was conducted according to the Cochrane Collaboration tool to assess the risk of bias. Of the 18 trials, 11 were of poor quality and seven of fair or high quality. Further evaluation with access to original data from the trials is warranted to increase quality of evidence. [Supplementary table 1]

Discussion

This systematic review of 18 RCTs (n = 2282) showed ivermectin treatment reduces inflammatory markers, achieves viral clearance more quickly and improves survival compared with SOC. The effects of ivermectin on viral clearance were stronger for higher doses and longer durations of treatment. These effects were seen across a wide range of RCTs conducted in several different countries. However, the data should be interpreted carefully in the context that meta-analyses are highly prone to confounding bias, and current viral PCR assays have several important limitations. Many of the studies assessed have not been peer-reviewed. Larger, appropriately controlled randomized trials are needed before rigorous evaluation of the clinical benefits of ivermectin can be undertaken.

The results from this analysis have emerged from the International Ivermectin Project Team meetings in December 2020 and January 2021. Independent research teams were conducting the trials across 12 countries and agreed to share their data, which was often unpublished, to accelerate the speed of reporting and to ensure their fragmented research, widespread across the world, could contribute to global learning. Viral clearance was evaluated by Polymerase Chain Reaction (PCR) assays in all the studies. We have only included randomized clinical trials in this meta-analysis. The 18 RCTs included were designed and conducted independently, with results combined in December 2020.

Limitations

Key limitations to this meta-analysis include the comparability of the data, with studies differing in dosage, treatment duration, and inclusion criteria. Furthermore, the SOC used in the background treatment differed between different trials. Additionally, ivermectin was often given in combination with doxycycline or other antimicrobials. Individual trials may not have power to detect treatment effects on rare endpoints such as survival. Outcome measures were not standardized; viral clearance was measured in most trials, but at different time points and with different PCR cycle thresholds. The reliability of PCR tests for quantification purposes has been the subject of substantive debate. Most studies were conducted in populations

with only mild/moderate infection and some trials excluded patients with multiple co-morbidities.

For open label studies, there is a risk of bias in the evaluation of subjective endpoints such as clinical recovery and hospital discharge. However, the risk is lower for objective endpoints such as viral clearance and survival. We have attempted to control for publication bias by contacting each research team conducting the trials directly. This has generated more results than would be apparent from a survey of published clinical trials only but means that many of the included trials have not been peer-reviewed. Review and publication of RCTs generally takes three to six months. It has become common practice for clinical trials of key COVID-19 treatments to be evaluated from pre-prints, such as for the WHO SOLIDARITY, RECOVERY and REMAP-CAP trials [3, 4, 5].

These RCTs have been conducted in a wide range of countries, often in low-resource conditions and overburdened healthcare systems. The evidence from this first set of studies will require validation in larger RCTs evaluating fixed dosing schedules, preferably using higher doses for between 3-5 days. Larger RCTs are currently underway in Mexico, South America and Egypt, with results expected in February and March 2021.

Despite limitations, this analysis suggests a dose and duration-dependent impact of ivermectin on rate of viral clearance. These trials evaluated a wide range of ivermectin dosing, from 0.2mg/kg for 1 day to 0.6mg/kg for 5 days. This wide range of doses allowed an estimation of dose-dependency on viral clearance but reduces the number of patients included that were consistently administered the same dose for the same duration. The maximum effective dose of ivermectin is not yet clear and new clinical trials are evaluating higher doses, up to 1.2mg/kg for 5 days.
The 75% survival benefit seen in this meta-analysis is based only on 71 deaths, in six different clinical trials. This is a smaller total number of deaths than in either the RECOVERY or REMAP-CAP trials, which led to the approval of dexamethasone, tocilizumab and sarilumab. However, the observed survival benefit of 75% is stronger than for the other re-purposed drugs. Emerging mortality results from larger

studies of ivermectin will require careful evaluation and may change the conclusions from the current analysis.

Secondary endpoints for some RCTs included biomarkers of disease severity. Some of these provide evidence for an anti-inflammatory mechanism of action of ivermectin in SARS-CoV-2 infected patients. Previous meta-analyses have demonstrated that high levels of CRP, ferritin, d-dimer and lymphocytopenia are related to COVID-19 severity and hyper-inflammation [32, 33]. Studies of IL-6 receptor antagonists have been shown to reduce CRP and d-dimer levels in patients with COVID-19 [4].

Across three studies, in a cumulative 683 patients, we found a slight increase in lymphocyte counts [22, 34, 35] following ivermectin administration. CRP, a marker of infection and inflammation, were reduced following ivermectin administration across four trials [22, 23, 25, 34]. D-dimer is a fibrin degradation product, often raised in severe COVID-19 due to thrombus formation. Ferritin can also be raised in severe COVID-19 due to the cytokine storm and hyperinflammation. Levels of both d-dimer and ferritin following one week of ivermectin treatment in severe COVID-19 cases were reduced to levels less than half of those receiving SOC [22]. These reductions in D-dimer and ferritin were more significant in patients with severe disease compared to those with mild/moderate disease at baseline. Furthermore, erythrocyte sedimentation rate and lactate dehydrogenase, non-specific markers of inflammation and tissue damage, respectively, were both reduced slightly following ivermectin administration in two separate studies of patients with COVID-19 [34, 36].

A key component of SARS-CoV-2 pathogenesis is its pro-thrombotic effect, leading to blood clots in the kidneys, brain and pulmonary emboli in the lungs. By reducing hyper-inflammation, the risk of clots may be reduced. One histopathology study in dogs with *Dirofilaria immitis* (heartworm) showed that ivermectin plus doxycycline reduced lung tissue perivascular inflammation and endothelial proliferation leading to fewer arterial lesions and virtually removed the risk of thrombi [37]. However, the relevance of these findings to SARS-CoV-2 infection are unclear.

Ivermectin may also have a role in short-term prevention of SARS-CoV-2 infection, suggested by pilot studies [38, 39]. This potential benefit also needs to be validated in larger randomized trials.

At the time of writing, knowledge gaps prevent a robust conclusion about the mechanism of action, but current *in vitro* data do not support a direct antiviral activity of the drug. Interestingly, ivermectin has been demonstrated to induce autophagy as part of a proposed mechanism of action in cancer [40, 41] with autophagy providing an innate defense against virus infection [42]. Furthermore, other viruses such as cytomegalovirus have mechanisms to activate cyclooxygenase 2 and prostaglandin E2 promoting the inflammatory response, which supports their replication [43] and it is also possible that a pro-inflammatory phenotype may aid SARS-CoV-2 replication [44]. However, immunological mechanisms of action are usually highly complex and require careful empirical evaluation to understand the plausibility, which is currently absent for ivermectin use in COVID-19.

Conclusion

This meta-analysis of 18 RCTs in 2282 patients showed a 75% improvement in survival, faster time to clinical recovery and signs of a dose-dependent effect of viral clearance for patients given ivermectin versus control treatment.

Despite the encouraging trend this existing data base demonstrates, it is not yet a sufficiently robust evidence base to justify the use or regulatory approval of ivermectin. However, the current paucity of high-quality evidence only highlights the clear need for additional, higher-quality and larger-scale clinical trials, warranted to investigate the use of ivermectin further.

The maximum effective dose of ivermectin needs to be clarified and new clinical trials should use a consistent multi-day dosing regime, with at least 0.4mg/kg/day. The appropriate dose and schedule of ivermectin still requires evaluation and the current randomized clinical trials of ivermectin need to be continued until ready for rigorous review by regulatory agencies.

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List of Tables and figures

Table 1: Trial Summaries

Table 1: Trial Summaries

Table 1A: Ivermectin trials with Dosing on day 1 only

Study	Country	Sample Size	Daily dose	Duration	Patients	Intervention Arm	Comparator Arm
Mahmud et a l [45]	Bangladesh	363	12 mg	1 day (DB)	Mild/ moderate	Ivermectin + Doxycycline + SOC	SOC
Mohan et al [28]	India	157	0.2-0.4 mg/kg (elixir)	1 day (DB)	Mild / moderate	Ivermectin + SOC	Placebo + SOC
Chowdhury [29]	Bangladesh	116	0.2 mg/kg	1 day (DB)	PCR positive	Ivermectin + Doxycycline	HCQ + Azithromycin
Rezai et al [35]	Iran	103	0.2 mg/kg	1 day (DB)	Moderate / severe	Ivermectin + SOC	SOC
Spoorthi et al [46]	India	100	0.2 mg/kg	1 day (DB)	Mild to moderate	Ivermectin + Doxycycline	Placebo
Raad et al [47]	Lebanon	100	0.2 mg/kg	1 day (SB)	Mild	Ivermectin + SOC	SOC
Asghar et al [48]	Pakistan	100	0.2 mg/kg	1 day (OL)	Mild / moderate	Ivermectin + SOC	SOC
Podder et al [27]	Bangladesh	62	0.2 mg/kg	1 day (OL)	Mild	Ivermectin + SOC	SOC
SAINT [24]	Spain	24	0.4 mg/kg	1 day (DB)	Moderate	Ivermectin	Placebo

SOC = Standard of care; OL= open label; SB= single-blind; DB= double-blind

Table 1B: Ivermectin trials with multi-day dosing

Study	Country	Sample Size	Daily dose	Duration	Patients	Intervention Arm	Comparator Arm
Elgazzar et al [22]	Egypt	400	0.4 mg/kg	5 days (OL)	Mild to severe	Ivermectin + SOC	HCQ + SOC
Niaee et al [34]	Iran	180	0.2 - 0.4 mg/kg	1-3 days (DB)	Mild / moderate	Ivermectin + SOC	SOC + Placebo
Hashim et al [36]	Iraq	140	0.2 mg/kg	2-3 days (SB)	Symptomatic	Ivermectin + Doxycycline + SOC	SOC
Kirti et al [26]	India	112	12 mg	2 days (DB)	Mild / moderate	Ivermectin + SOC	SOC + Placebo
Ahmed et al [25]	Bangladesh	72	0.2 mg/kg	5 days (DB)	Mild	Ivermectin + SOC	SOC + Placebo
Okomus et al [23]	Turkey	60	0.2 mg/kg	5 days (DB)	Severe	Ivermectin + SOC	FAVI/HQ/AZI (SOC)
Babaloa et a [30]	Nigeria	60	0.1-0.2 mg/kg	2 / week (DB)	Mild	Ivermectin + SOC	Placebo + LPV/r (SOC)
Chachar et al [49]	Pakistan	50	0.2 mg/kg	2 days (OL)	Mild	Ivermectin + SOC	SOC
Krolewiecki et al [31]	Argentina	45	0.6 mg/kg	5 days (OL)	Mild to moderate	Ivermectin + SOC	SOC

SOC = Standard of care

Table 2: Changes in Inflammatory Markers

	CRP (mg/L)			Ferritin (µg/L)			D-dimer (mg/L)		
	Ivermectin	Control	p value	Ivermectin	Control	p value	Ivermectin	Control	p value
Elgazzar, Egypt (n=200, mild/moderate COVID-19)									
Baseline	48.4	50.6		168	172		4.8	5.4	
Day 7	4.8	8.3	p<0.001	95	98	n.s	0.5	0.7	p<0.001
Elgazzar, Egypt (n=200, severe COVID-19)									
Baseline	64.8	68.2		420	334		8.2	8.6	
Day 7	28.6	58.6	p<0.001	104	294	p<0.001	0.7	1.9	p<0.001
Okomus, Turkey (n=60)									
Baseline	340.3	215.0		683	747		1.3	1.3	
Day 5	51.8	194.3	p<0.01	875	1028	n.s	5.9	3.6	n.s
Day 10	36.1	92.4	p<0.05	495	1207	p<0.01	0.7	1.5	p<0.05
Chaccour, Spain (n=24)*									
Baseline	3.5	3.0		165	156		0.3	0.3	
Day 7	1.0	1.1	n.s	125	199	n.s	0.3	0.3	n.s
Day 14	0.8	0.6	n.s	152	145	n.s	0.3	0.3	n.s
Ahmed, Bangladesh (n=45, Ivermectin 5 days)									
Baseline	22.0	29.0		269	222		-	-	
Day 7	3.0	14.0	p<0.05+	211	218	n.s+	-	-	
Ahmed, Bangladesh (n= 46, Ivermectin 1 day)									
Baseline	26.0	29.0		259	222		-	-	
Day 7	11.0	14.0	n.s+	213	218	n.s+	-	-	
Iran Niaee (n=60, Ivermectin- 0.2 mg)*									
Baseline	200.0	270.0		-	-		-	-	
Day 5	85.0	245.0	p<0.001++	-	-		-	-	
Iran Niaee (n=60, Ivermectin- 0.2, 0.2, 0.2 mg)*									
Baseline	390.0	270.0		-	-		-	-	
Day 5	200.0	245.0	p<0.001++	-	-		-	-	
Iran Niaee (n=60, Ivermectin- 0.4 mg)*									
Baseline	250.0	270.0		-	-		-	-	
Day 5	80.0	245.0	p<0.001++	-	-		-	-	
Iran Niaee (n=60, Ivermectin- 0.4, 0.2, 0.2 mg)*									
Baseline	340.0	270.0		-	-		-	-	

Day 5	170.0	245.0	p<0.001++	-	-	-	-

*Median presented, all other data mean.

+p value compares within group changes from baseline to end point of ivermectin group. ++p value shows significance of total changes from baseline. All other p values compare ivermectin vs. control

*Normal ranges: CRP(<10mg/L), Ferritin(***11-336µg/L***) D-dimer(<0.5mg/L).*

Table 3: Effects of ivermectin on viral clearance

Table 3A:

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVA vs Control	P value
Number Detectable or Undetectable (%)						
Mahmud et al	Bangladesh, n=363	12 mg	1 day (DB)	Undetectable Day 14	92% vs 80%	$p < 0.001$
Asghar et al	Pakistan, n=103	0.2 mg/kg	1 day	Undetectable Day 7	90% vs 44%	$p < 0.001$
Mohan et al	India, n=157	0.2mg/kg Elixir	1 day	Undetectable Day 5	35% vs 31%	p = n.s.
Mohan et al	India, n=157	0.4mg/kg Elixir	1 day	Undetectable Day 5	48% vs 31%	p = n.s.
Kirti et al	India, n=112	12 mg	2 days	Undetectable Day 6	24% vs. 32%	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.
Okomus et al	Turkey, n=60	0.2 mg/kg	5 days (DB)	Day 10 PCR Neg	88% vs 38%	p = 0.01

Table 3B: Effects of Ivermectin on Time to Viral Clearance

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVA vs Control	P value
Time to Viral Clearance (Days)						
Chowdhury	Bangladesh, n=112	0.2 mg/kg	1 day (DB)	Time to PCR neg	9 vs 9.3 days	p = n.s.
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
Babaloa et al *	Nigeria, n=60	0.1 mg/kg	2 / week (DB)	Time to PCR neg	6 vs 9 days	p = 0.003
Babaloa et al *	Nigeria, n=60	0.2 mg/kg	2 / week (DB)	Time to PCR neg	4.7 vs. 9 days	p = 0.003
Ahmed et al *	Bangladesh, n=72	0.2 mg/kg	5 days (DB)	Time to PCR neg	10 vs 13 days	p = 0.02
Ahmed et al *	Bangladesh, n=72	0.2 mg/kg	1 days (DB)	Time to PCR neg	11.5 vs. 13 days	p = n.s

Table 3C: Effect of ivermectin on other measures of viral clearance.

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVA vs Control	P value
Other Measures of Viral clearance						
Raad et al	Lebanon, n=100	0.2 mg/kg	1 day	Day 3	Ct values **30.1 ± 6.22 vs. 18.96 ± 3.26**	p = 0.01
Krolewiecki et al*	Argentina, n=45	0.6 mg/kg	5 days	PK/PD	Dose-related	p = 0.02

*Dose-response effect seen

Table 4: Effects on of ivermectin on clinical recovery and hospitalization

Table 4A: Time to clinical recovery

Study	Country	Daily dose	Duration	Endpoint	Results IVS vs control	P value
Time to clinical recovery						
Mohan et al	India n=157	0.2 mg/kg Elixir	1 day (SB)	Time to clinical recovery	4.8 vs 4.6 days	p = n.s.
Mohan et al	India n=157	0.4 mg/kg Elixir	1 day (SB)	Time to clinical recovery	4.3 vs 4.6 days	p = n.s.
Hashim et al	Iraq n=140	0.2 mg/kg	2-3 days (SB)	Time to clinical recovery	10.6 vs 17.9 days	p < 0.001
Chowdhury et al	Bangladesh n=116	0.2 mg/kg	1 day (DB)	Time to clinical recovery	5.9 vs 6.9 days	p = 0.071
Podder et al	Bangladesh n=62	0.2 mg/kg	1 day (OL)	Time to clinical recovery	5.3 vs 6.3 days	p = n.s.
Rezai et al	Iran n=103	0.2 mg/kg	1 days (OL)	Time to clinical recovery	4.1 vs 5.2 days	p = 0.018
Spoorthi et al	India n=100	0.2 mg/kg	1 day (SB)	Time to clinical recovery	3.7 vs 4.7 days	p=0.03

Table 4B: Effect of Ivermectin on duration of hospitalization

Study	Country	Daily dose	Duration	Endpoint	Results IVS vs control	P value
Duration of hospitalization						
Rezai et al	Iran n=103	0.2 mg/kg	1 days (OL)	Days in hospital	6.9 vs 8.4 days	p = 0.01
Raad et al	Lebanon n=100	0.2 mg/kg	1 day (OL)	Hospitalization	0% vs 6%	p = 0.00
Spoorthi et al	India n=100	0.2 mg/kg	1 day (SB)	Time in hospital	6.7 vs 7.9 days	p=0.01
Niaee et al	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
Elgazzar et al Mild/moderate	Egypt n=200	0.4 mg/kg	5 days (OL)	Days in hospital	5 vs 15 days	p < 0.001
Elgazzar et al Severe	Egypt n=200	0.4 mg/kg	5 days (OL)	Days in hospital	6 vs 18 days	p < 0.001

Table 4C: Number of Participants with clinical recovery by Day 7 to 10 post-randomization

Study	Country	Daily dose	Duration	Endpoint	Results IVS vs control	P value
Number of Participants Recovered (%)						
Chachar et al	Pakistan n=50	0.2 mg/kg	2 days (OL)	Day 7 Clinical recovery	64% vs 60%	p = n.s.
Okomus et al	Turkey n=60	0.2 mg/kg	5 days (DB)	Day 10 Clinical improvement	73% vs 53%	p = 0.10
Mahmud et al	Bangladesh n=400	12 mg	1 day (DB)	Day 7 Clinical Recovery	61% vs 44%	p <0.03

Table 5: Effects of ivermectin on survival

Trial	Country	Dosing	Ivermectin	Control
Mahmud et al	Bangladesh	0.2 mg/kg, 1 day	0/183	3/180
Niaee et al	Iran	0.2 mg/kg 1-3 days	4/120	11/60
Hashim et al	Iraq	0.2-0.4 mg/kg 2-3 days	2/70	6/70
Elgazzar et al	Egypt	0.4 mg/kg 5 days	2/200	24/200
Okomus et al	Turkey	0.2 mg/kg, 5 days	6/30	9/30
Kirti et al	India	12 mg, 5 days	0/55	4/57
Total			**14/658 (2.1%)**	**57/597 (9.5%)**

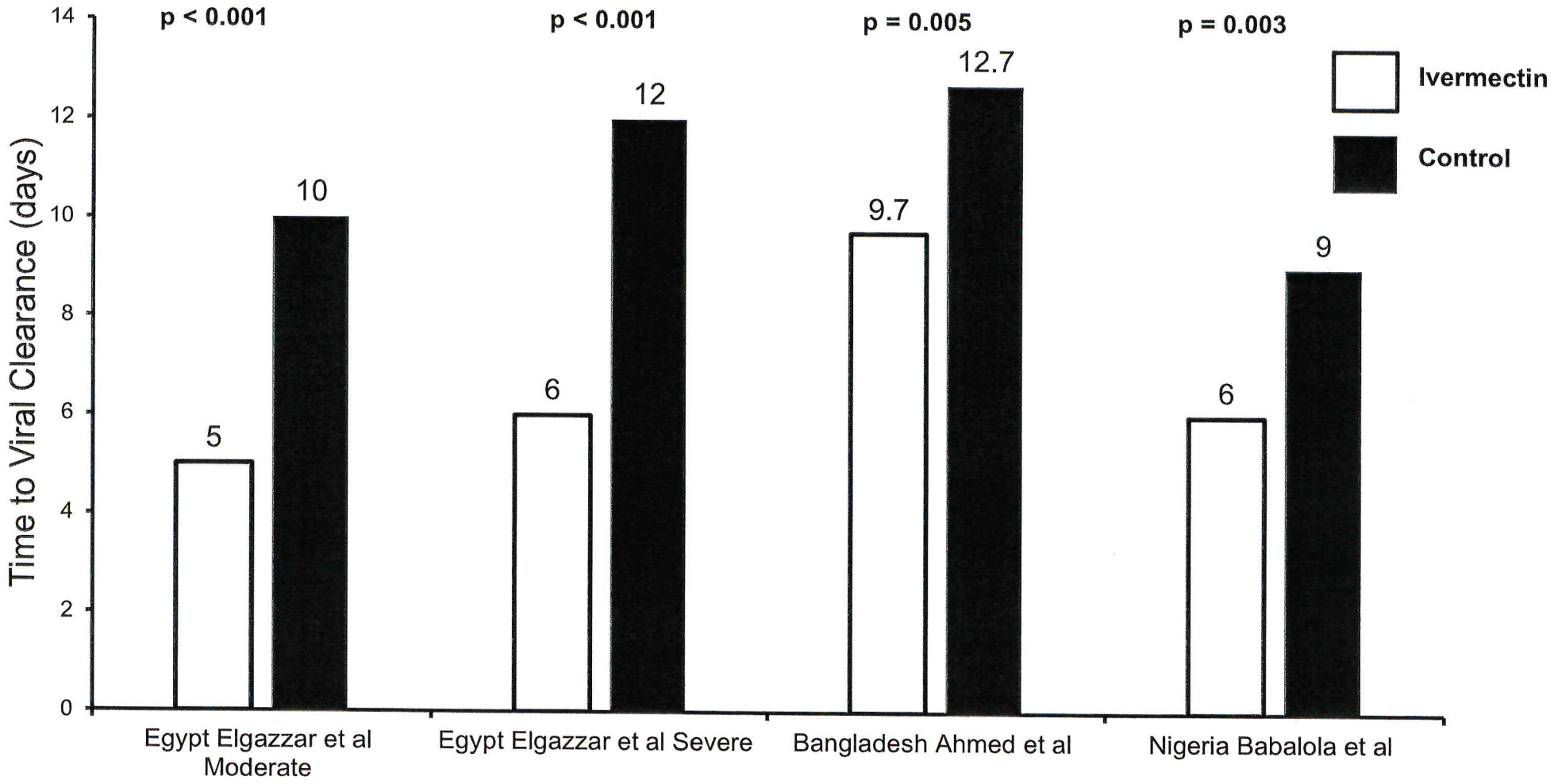

Figure 1: Effects of ivermectin on time to viral clearance

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bangladesh Mahmud et al	0	183	3	180	5.7%	0.14 [0.01, 2.70]
Egypt Elgazzar et al	2	200	24	200	18.0%	0.08 [0.02, 0.35]
India Kirti et al	0	55	4	57	5.9%	0.12 [0.01, 2.09]
Iran Niaee et al	4	120	11	60	24.6%	0.18 [0.06, 0.55]
Iraq Hashim et al	2	70	6	70	15.9%	0.33 [0.07, 1.60]
Turkey Okumus et al	6	30	9	30	29.8%	0.67 [0.27, 1.64]
Total (95% CI)		**658**		**597**	**100.0%**	**0.25 [0.12, 0.52]**
Total events	14		57			

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 7.54$, df = 5 (P = 0.18); $I^2 = 34\%$

Test for overall effect: Z = 3.67 (P = 0.0002)

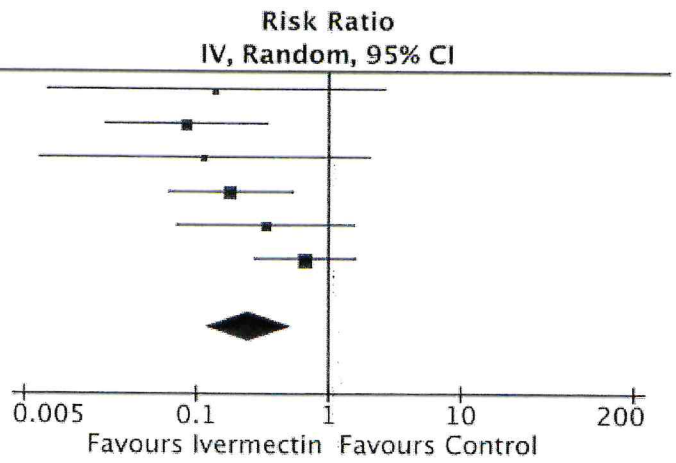

Figure 2: Forest plot of survival.

Supplementary table 1. Assessment of Risk of Bias

Graded low, high or unclear risk of bias on the bases of the prespecified criteria set out in the Cochrane Risk of Bias Tool

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Quality of Evidence
Mahmud et a l [R2]	Low	Low	Low	Low	High *(21% of patients randomized not included in the analysis)*	Unclear	**Limited**
Mohan et al [R14]	Unclear	Unclear	Low *(Unblinded but objective outcome measure (PCR and viral load)*	Unclear	Unclear	Low	**Limited**
Chowdhury [R15]	High *(Odd/Even randomization based on registration numbers)*	Unclear	Unclear	Unclear	Low	Low	**Limited**
Rezai et al [R13]	Low	Low	Low	Low	Low	Unclear	**Fair**
Spoorthi et al [R10]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	**Limited**
Raad et al [R11]	Unclear	Unclear	Low	Low	Unclear	Unclear	**Limited**
Asghar et al	Unclear	Unclear	Unclear	Low	High *(5% (control) vs 18% (ivermectin) attrition rate between arms)*	Low	**Limited**
Podder et al [R6]	High *(Odd/Even randomization based on registration*	Unclear	High *(Open Label + primary endpoint symptoms resolution (subjective element))*	High *(Open Label + primary endpoint symptoms resolution*	Unclear	Unclear	**Limited**

	numbers)			*(subjective element))*			
SAINT [R9]	Low	Low	Low	Low	Low	Low	Good
Elgazzar et al [R1]	Unclear	Unclear	Low *(Unblinded but primary endpoint based on PCR and laboratory markers)*	High *(Investigators interpreting and collating results were unblinded)*	Unclear	Unclear	**Limited**
Niaee et al [R3]	Low	Low	Low *(Unblinded - but objective outcome measures used (lab markers)*	Unclear	Low	Low	Fair
Hashim et al [R4]	High *(Randomization based on date of enrollment)*	High *(Randomization based on date of enrollment)*	High *(Unblinded and outcome dependent on reporting of symptoms)*	High *(Unblinded - outcome dependent on subjective judgement of disease progression)*	Unclear	Low	**Limited**
Ahmed et al [R5]	Unclear	Unclear	Low	Low	Low	Low	Fair
Okomus et al [R16]	Unclear	Unclear	Low *Objective measures (Lab/PCR/FiO2/Mortality)*	Unclear	Unclear	Unclear	**Limited**
Babaloa et a [R17]	Unclear	Unclear	Low	Low	Low	Low	Fair
Chachar et al [R7]	Low	Low	High *Open Label + primary endpoint symptoms resolution (subjective element)*	High *Open Label + primary endpoint symptoms resolution (subjective element)*	Low	Unclear	**Limited**
Krolewiecki et al [R8]	Unclear	Unclear	Low (*Low Risk Bias - Objective measures*	Unclear	Unclear	Unclear	**Limited**

			(Lab/PCR/FiO2/Mortality))				
Kirti et al [R18]	Low	Low	Low	Low	Low	Low	Good