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03 January 2021
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 12 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	RCT	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.

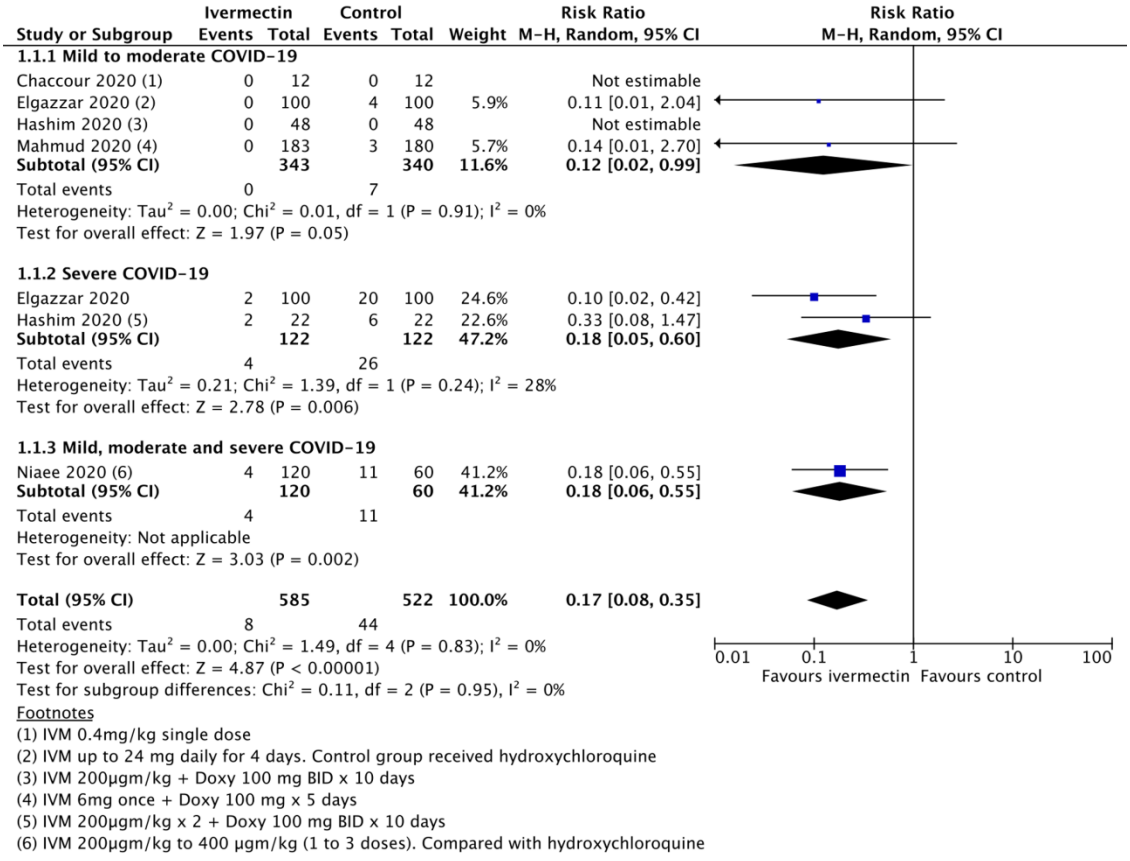
People with co-morbidities (e.g. diabetes mellitus, hypertension, cardiovascular disease, asthma, obesity) were excluded from three studies and were included in eight studies in which they occurred at a cumulative frequency ranging from 28% to the vast majority of participants; co-morbidities were not 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

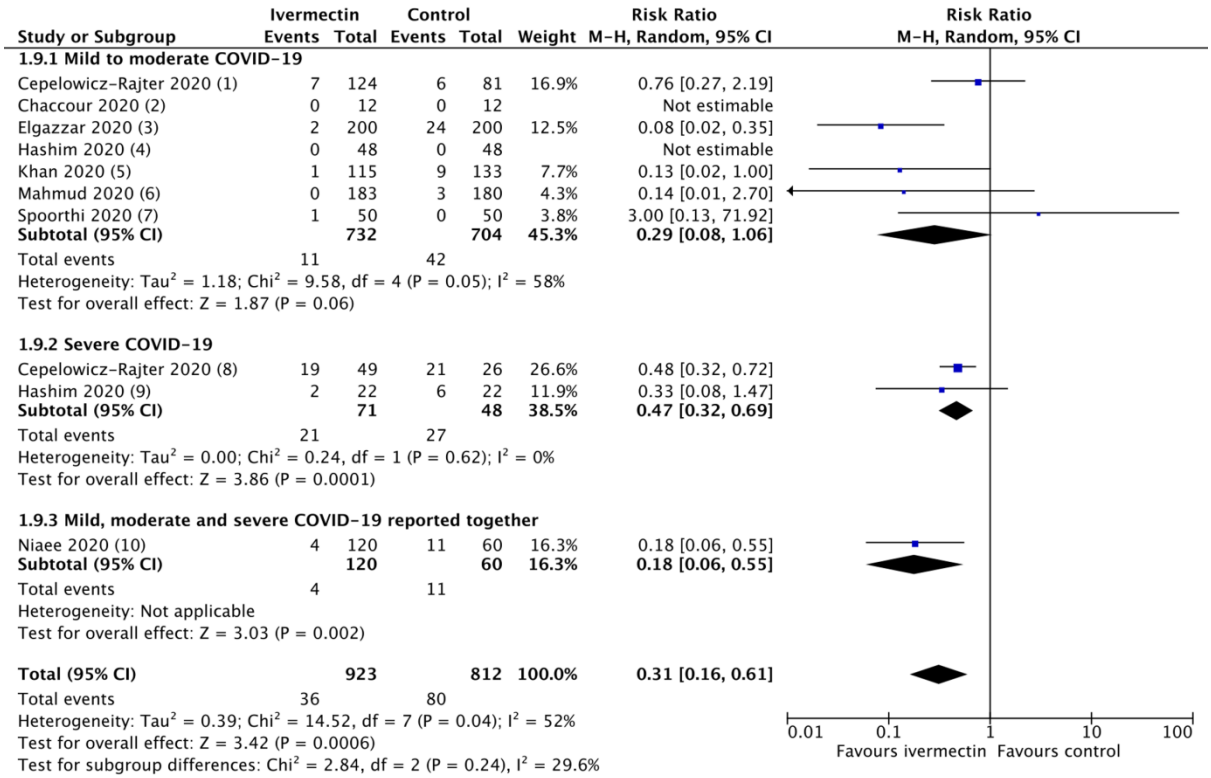
Moderate certainty evidence indicates that ivermectin probably reduces deaths by an average 83% (95% CI, 65% to 92%) compared with no ivermectin treatment (5 RCTs, 1107 participants; RR 0.17, 95% 0.08 to 0.35; risk of death 1.4% versus 8.4% among participants in this analysis).

Forest plot 1.1.a. RCTs only



A second analysis, which includes RCTs and OCTs can be found below. Findings from this 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.

Forest plot 1.1.b. RCTs and OCTs



Footnotes

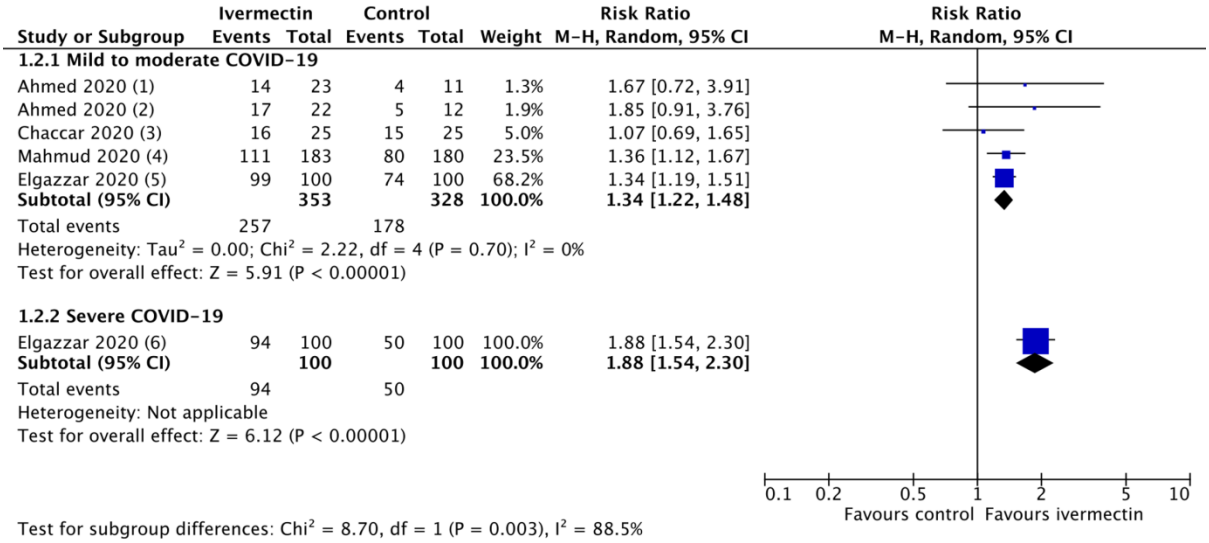
(1) IVM 0.2mg/kg one or two doses
(2) IVm 0.4mg/kg single dose
(3) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(4) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(5) IVM 12 mg single dose
(6) IVM 6mg once + Doxy 100 mg x 5 days
(7) IVM 200µgm/kg + Doxy 100 mg BID x 7 days
(8)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

Analysis 1.2: 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.



Test for subgroup differences: Chi² = 8.70, df = 1 (P = 0.003), I² = 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

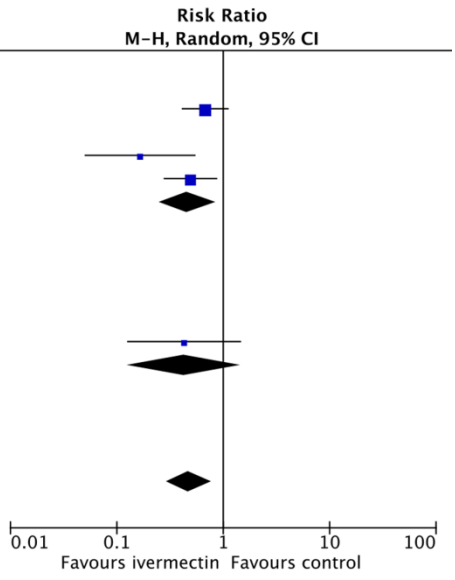
Note: Ahmed 2020 is a 3 arm study, therefore the control group has been split between its two study comparisons in this analysis.

Analysis 1.3: 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	Ivermectin Total	Control Events	Control 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), $I^2 = 0\%$						



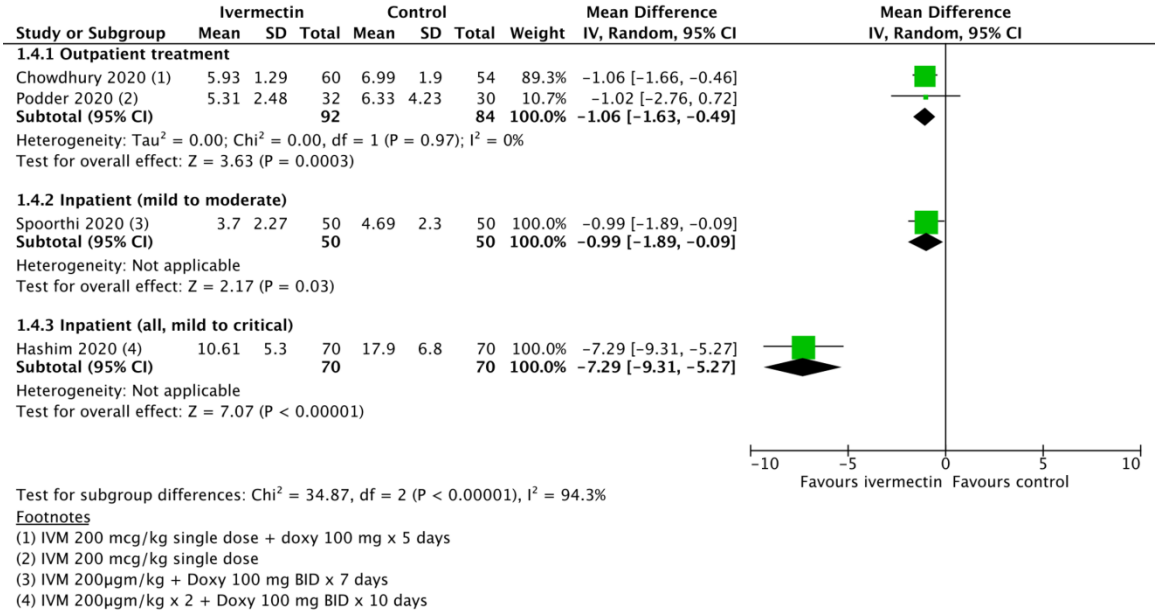
Footnotes
(1) IVM 0.4mg/kg single dose
(2) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(3) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(4) IVM 12 mg single dose
(5) IVM 6mg once + Doxy 100 mg x 5 days

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) require more data to improve the certainty of this evidence. One study (subgroup analysis 1.4.3) showed a large treatment effect favouring the ivermectin group. However, this evidence was graded as very low certainty as all people with critical illness were allocated to the ivermectin group for ethical reasons.

Forest plot 1.4.

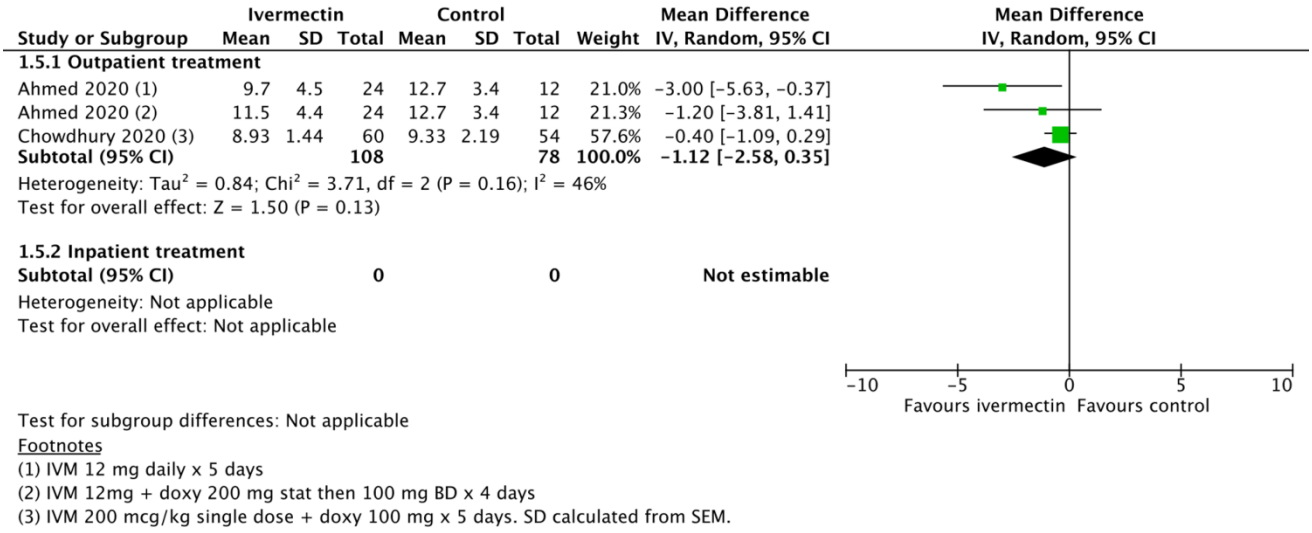


[1] According to the World Health Organization's standard operating procedure for grading evidence for guidelines, the total cumulative study population needs to be more than 300 participants for continuous data when evaluating imprecision.

Analysis 1.5: Recovery time to a negative PCR test

Evidence for this outcome was graded as very low certainty (2 studies, 186 participants; MD -1.12, 95% CI -2.58 to 0.35); downgrading was performed twice for imprecision and also because most of the data were derived from a study only available as pre-print at the time of writing.

Forest plot 1.5.

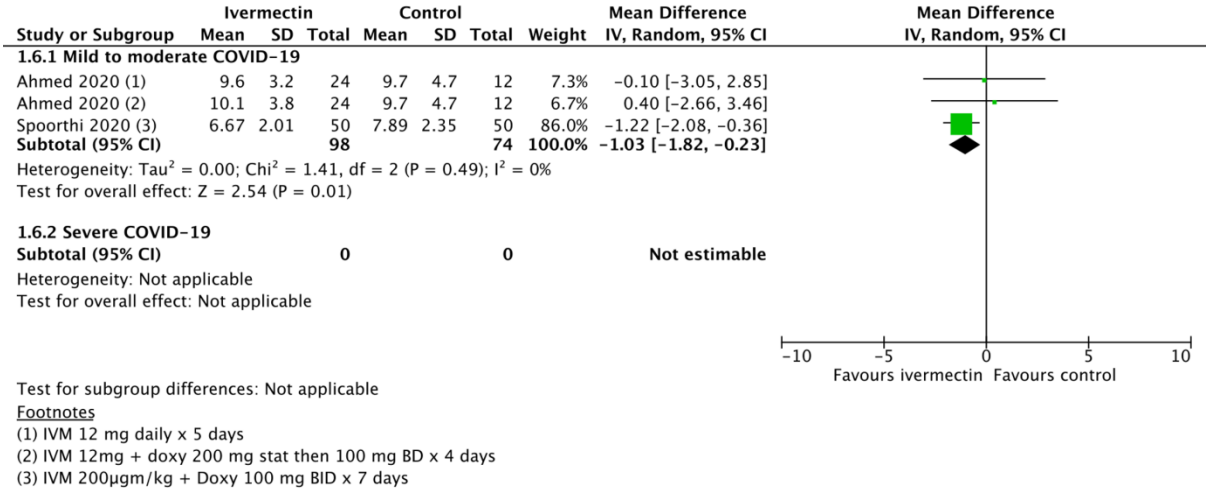


Note: Ahmed 2020 is a 3 arm study, therefore the control group has been split between its two study comparisons in this analysis.

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.



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.

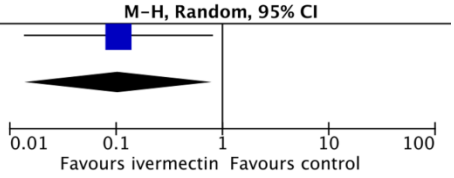
Outcome 1.8. Admission to ICU or requiring ventilation

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

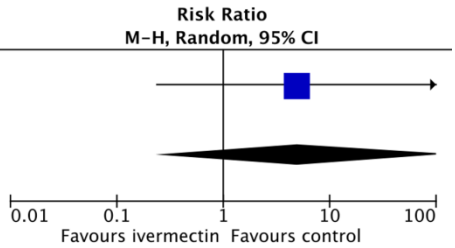
Outcome 1.9: Severe adverse events

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

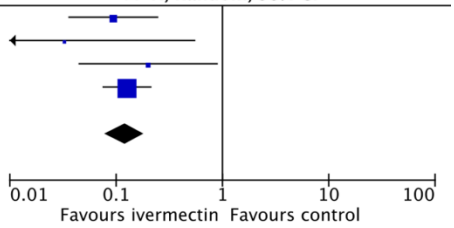
Outcome 2.1: COVID-19 infection

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	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 (RCTs only)	RR 0.17 (0.08 to 0.35)	MODERATE
Deaths (RCTs and OCTs)	RR 0.31 (0.16 to 0.61)	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 (in-patients with mild to moderate COVID-19)	MD -0.99 days (-1.89 to -0.09)	LOW
Recovery time (in-patients with mild to critical COVID-19)	MD -7.29 days (-9.31 to -5.27)	LOW
Recovery time to negative PCR test	MD-1.12 days (-2.58 to 0.35)	VERY 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% according to RCT data. The 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

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Versions

v1.0	**Urgent preliminary report**	**03/01/2021**
v1.1	Typo corrections	04/01/2021
v1.2	Feedback incorporated –Forest 1.5 SD for Chowdhury corrected; edits to summary of findings table; second forest plot for death (RCT's and OCT's) moved from appendix to page 7.	06/01/2021

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Appendix

Funnel plot for the primary outcome analysis 1.1.b. (Death) including RCTs and OCTs