IVERMECTIN FOR TREATMENT OF COVID-19

Based on available evidence up to 2 July 2021

PURPOSE

To provide scientific evidence on the effectiveness, safety and cost-effectiveness of ivermectin for the treatment of COVID-19.

INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged rapidly and caused great mortality. As of 22 June 2021, there have been 2.5 million new cases and 64,000 new deaths occurring globally, bringing the total of 178,837,204 confirmed cases of COVID-19, including 3,880,450 deaths.[1]

The development of effective pharmacologic therapies for COVID-19 is still in progress and the current management of COVID-19 is mostly limited to general supportive care and symptomatic treatment. Recently, there have been an increased in international attention on ivermectin as a potential treatment for COVID-19 and findings from case studies, clinical trials and the “off-label” use of ivermectin have since emerged.[2]

Ivermectin is a broad spectrum anti-parasitic drug, which belongs to a group of avermectins (AVM) or macrocyclic lactone compounds.[3] It has been shown to inhibit the replication of SARS-CoV-2 in cell cultures.[3] A few pharmacokinetic and pharmacodynamic studies suggested that administration of doses up to 100-fold higher than those approved for use in humans is required to achieve plasma concentrations necessary for the antiviral efficacy.[4,5]

Ivermectin is included in WHO essential medicines list for several parasitic diseases but for humans, it is only recommended to be used in the setting of clinical trials, in which patients are monitored closely by experienced clinicians and researchers for safety and efficacy.[2] It received U.S Food and Drug Administration (FDA) approval to be used worldwide for a broad number of parasites to treat several neglected tropical diseases, including onchocerciasis, strongyloidiasis and helminthiases.[3] However, the FDA has not approved ivermectin for the use in treating or preventing COVID-19 in humans. The European Medicines Agency (EMA) have stated that ivermectin cannot be recommended for the prevention or treatment of COVID-19 outside clinical trials.[6] Several countries such as India and Philippines have reiterated and removed ivermectin from their treatment guidelines due to insufficient scientific evidence. [7,8]

In Malaysia, ivermectin is a drug mostly used in the veterinary medicine, especially in treating worm infestations.[9] The Ministry of Health Malaysia and the Institute for Clinical Research (ICR) have launched a multi-centre open-label randomised controlled trial to determine the effectiveness of ivermectin in preventing COVID-19 from progressing to a severe stage (Stage 4-5) and how it affects mortality.[9] The study is expected to be completed by September 2021.

SUMMARY OF SCIENTIFIC EVIDENCE

There were 12 articles included in this rapid review which were retrieved from the scientific databases (Medline, EMBASE, PubMed), the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] and from the references of retrieved articles. The search was conducted up to 2 July 2021. The 12 retrieved evidence included eight systematic review and meta-analysis, two systematic review and network meta-analysis, one randomised controlled trials (RCTs) and one observational study. These articles evaluated the effectiveness of ivermectin in COVID-19 patients while five articles assessed the safety of ivermectin and none was retrieved on cost-effectiveness of ivermectin. Out of all these articles, four articles were pre-print articles, which preceded formal peer review and publication in a peer-reviewed scholarly or scientific journal. Study characteristics of the included articles on effectiveness is summarised in Table 1.

Evidence on Effectiveness

A meta-analysis by Bryant et al included 24 randomised clinical trials (including three quasi-RCTs) involving 3406 subjects with 22 trials on treatment and two trials on prophylaxis of COVID-19.[10] Six trials included patients with severe COVID-19, and 16 trials primarily looked at ivermectin in people with mild and moderate COVID-19. The primary outcome was all-cause mortality, with the secondary outcomes being improvement or deterioration of COVID-19 symptoms. The primary outcome with meta-analysis of 15 trials and 2438 patients concluded that ivermectin reduced the risk of mortality by an average of 62% (95% CI: 27% to 81%) when compared to no ivermectin treatment [average RR (aRR) 0.38, 95 % CI 0.19 to 0.73; I^2=49 %]; risk of death 2.3% versus 7.8% among hospitalised patients. Secondary outcomes (recovery time to negative PCR test, time to clinical recovery, deterioration, mechanical ventilation and length of hospital stay) provided low to very low certainty evidence due to study design limitations and inconsistency. The prophylaxis trials included three RCTs with a total of 738 participants among health care workers and COVID-19 contacts found that ivermectin prophylaxis reduced COVID-19 infection by an average 86% (95% CI: 79% to 91%). However, the quality of the included RCTs in this study is questionable. Overall, there was variability in individuals participating in the studies, as were the interventions used in terms of doses and treatment duration. The methodology for calculating these outcomes was unclear. Only eight of the trials were peer reviewed; the rest came via preprints or conversations with researchers. The subgroup analyses were carried out separately for mild to moderate and severe COVID-19 patients, and the results were either not significant or slightly significant with a wide confidence interval for these sub-groups. Low quality evidence from the meta-analysis was insufficient to support ivermectin as a COVID-19 infection therapy or prophylaxis.[10]

In a recent systematic review and meta-analysis of randomised controlled trials conducted by Roman et al, ten RCTs (n=1173) were included.[11] In five RCTs, the controls were

standard of care, and in five RCTs, the controls were placebo. In eight RCTs, the severity of COVID-19 disease was mild, moderate in one RCT, and mild and moderate in one RCT. All-cause mortality, length of hospital stays, and adverse events were the primary outcome. SARS-CoV-2 viral clearance in respiratory samples, clinical improvement, the need for mechanical ventilation, and serious adverse events were all secondary outcomes. In overall, ivermectin did not have effect on all-cause mortality vs. controls in five RCTs (RR 0.37, 95% CI: 0.12 to 1.13, I^2=16%, very low quality of evidence), on length of stay vs. controls in three RCTs (MD 0.72 days, 95% CI: -0.86 to 2.29, I^2=0%, very low quality of evidence), and on adverse events vs. controls in three RCTs (RR 0.95, 95% CI: 0.85 to 1.07, I^2=0%, low quality of evidence). There was no effect of ivermectin on severe adverse events in comparison to the controls in three RCTs (RR 1.39, 95% CI: 0.36 to 5.30, I^2=0%, low quality of evidence) and on viral clearance in comparison to the controls in four RCTs (RR 0.96, 95% CI: 0.79 to 1.16, I^2=0%, low quality of evidence). This study (pre-print article) included studies with quality of evidence that was low or very low for all outcomes.[11]

A meta-analysis done by Hariyanto et al included a total of 19 studies (2768 subjects) where ten of them were open label RCT studies, while the rest nine studies were double-blinded RCTs.[12] It was found that ivermectin was associated with reduction in severity of COVID-19 (RR 0.43 [95% CI: 0.23 to 0.81], p = 0.008), reduction in mortality (RR 0.31 [95% CI: 0.15 to 0.62], p = 0.001), higher negative RT-PCR test results rate (RR 1.23 [95% CI: 1.01 to 1.51], p = 0.04), shorter time to negative RT-PCR test results (mean difference [MD] −3.29 [95% CI: −5.69 to −0.89], p = 0.007), higher symptoms alleviations rate (RR 1.23 [95% CI: 1.03 to1.46], p = 0.02), shorter time to symptoms alleviations (MD −0.68 [95% CI: −1.07 to −0.29], p = 0.0007) and shorter time to hospital discharge (MD −2.66 [95% CI: −4.49 to −0.82], p = 0.004). Nevertheless, the subject involved in the study, interventions used in terms of doses and treatment duration used were diverse. Pre-print studies were also included in this meta-analysis and risk of bias were high due to the small number of studies and patients included.[12]

A systematic review and meta-analysis by Padhy et al evaluated the therapeutic potential of ivermectin as an add-on therapy for the treatment of COVID-19. They included RCTs and observational studies with a total of 629 patients that were COVID-19 RT-PCR positive.[13] Among them, 397 patients received ivermectin along with usual therapy. The ivermectin treated group had 233 mild cases and 104 moderate to severe cases, while the usual treatment group had 121 mild and 57 moderate to severe cases. The random effect model showed the overall pooled OR to be 0.53 (95% CI: 0.29 to 0.96) for the primary outcome (all-cause mortality) which was statistically significant (p=0.04). Similarly, the random effect model revealed that adding ivermectin led to clinical improvement compared to usual therapy (OR=1.98, 95% CI: 1.11 to 3.53, p=0.02). However, the quality of evidence was very low.[13]

In a living systematic review and meta-analysis (pre-print document) conducted by Rodríguez-Gutiérrez et al to assess the effectiveness of ivermectin in adult patients with COVID-19.[14] Ten trials including 1426 patients were included. Most studies included patients with mild/moderate COVID-19 symptoms, only three of them included patients with severe symptoms. Pooled analysis of six studies (941 patients), with an overall high risk of bias, showed ivermectin reduced mortality (OR 0.16; 95% CI: 0.08 to 0.33; I^2= 0%; p=0.81). Three studies reported time to viral clearance as outcome showing a statistically significant difference favouring the ivermectin group (median difference - 3.83; 95% CI: -5.43 to -2.22;

I^2=81%; p<0.01), but these studies had high risk of bias. No positive effect was found regarding ivermectin prophylaxis.[14]

A pre-print systematic review and meta-analysis was conducted to assess the outcomes of ivermectin in ambulatory and hospitalised patients with COVID-19.[15] Twelve studies (five retrospective cohort studies, six randomised clinical trials and one case series), were included in the qualitative synthesis (total of 7412 participants), and five studies were included in the quantitative synthesis. Their mean age was 47.5 (SD 9.5) years, and 4283 (58%) were male. The treatment was ivermectin (alone or with azithromycin, hydroxychloroquine, dexamethasone, enoxaparin, aspirin or dicloxacillin). Ivermectin was not associated with reduced mortality (logRR: 0.89, 95% CI: 0.09 to 1.70, p = 0.04, I^2= 84.7%), or reduced patient recovery (logRR 5.52, 95% CI: -24.36 to 35.4, p = 0.51, I^2= 92.6%). The selection criteria of patients was unclear as there was no description of COVID-19 severity among these patients. All studies had a high risk of bias with eight studies that were not adjusted for confounders and showed a very low certainty of the evidence.[15]

A systematic review and meta-analysis by Lawrie analysing 27 study reports by the Front Line COVID-19 Critical Care Alliance (FLCCC), RCTs and Control Observational Studies (OCTs) pertaining treatment and prophylaxis of the usage of ivermectin to COVID-19 with study sample sizes ranged from 24 to 1195 participants.[16] They reported moderate certainty evidence 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% CI: 0.08 to 0.35; risk of death 1.4% versus 8.4% among participants in this analysis). The study also found that ivermectin reduces COVID-19 infections 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). However, most studies in this review ranged from low to moderate risk of bias and the outcome measure of COVID-19 was not clearly defined.[16]

A meta-analysis conducted by Karale et al (pre-print document) evaluated efficacy and safety of ivermectin therapy against COVID-19.[17] The primary outcomes were overall mortality, need for intensive care unit (ICU) admission; secondary outcomes were - adverse effects, need for mechanical ventilation. Random-effects models were used for all analysis. A total of 38 studies (n=15,002 patients) were included in the qualitative analysis (mortality N=28, ICU admission= 8, mechanical ventilation= 10, adverse events=28) and out of these, 30 studies (n=11,291) were included in the quantitative analysis (mortality N=22, ICU admission= 5, mechanical ventilation= 9, adverse events=17). The outcome on mortality revealed odds of death to be lower (OR 0.39, 95% CI: 0.22 to 0.70; I^2=81%) in the ivermectin-arm compared to the non-ivermectin arm. Subgroup analysis of 12 randomised controlled trials looking at clinical severity, data showed similar overall mortality benefits (OR 0.33, 95% CI: 0.15 to 0.72; I^2=53%) and in the mild/moderate sub-group (OR 0.10, 95% CI: 0.03 to 0.33; I^2=0%). The need for ICU admission (OR 0.48, 95% CI: 0.17 to 1.37; I^2=59%) and mechanical ventilation (OR 0.64, 95% CI: 0.40 to 1.04; I^2=17%) benefiting from the use of Ivermectin was not significant. The quantitative analysis on adverse effects with ivermectin use showed no association, however the evidence here was graded low (OR 0.92, 95% CI: 0.64 to 1.33; I^2=14%). Although the study found that ivermectin could be effective adjuvant therapy in reducing mortality, this has to be interpreted carefully as it included several non-peer-reviewed articles that were of low quality.[17]

Bartoszko et al conducted a living systematic review and network meta-analysis to determine and compare the effects of drug prophylaxis on SARS-CoV-2 infection and COVID-19.[18] The included studies were' nine RCTs; two on ivermectin alone (total participants= 540), one RCT on ivermectin combined with iota-carrageenan (n=234), and six studied hydroxychloroquine (n=6059 participants), all compared with standard care or placebo among people at risk of COVID-19. It was found that there was low certainty whether ivermectin alone, when compared with standard care, reduces the risk of laboratory confirmed infection [Odds ratio 0.16 (95% credible interval 0.02 to 0.73]; 50 fewer per 1000 participants (59 fewer to 16 fewer) due to serious risk of bias and very serious imprecision in the study. Similarly, in reducing the risk of suspected, probable, or laboratory confirmed infection, the effect was very small (OR 0.06 (0.02 to 0.13); 159 fewer per 1000 participants (165 fewer to 144 fewer). There was no evidence on ivermectin effect on hospital admission and adverse events. Because no deaths occurred in the one ivermectin trial reporting mortality, its effect on mortality outcome is very uncertain. Most of the data has not been peer reviewed.[18]

Kim et al discovered that ivermectin (OR 0.15, 95% CI: 0.04 to 0.57, p= 0.005), high-dose intravenous immunoglobulin (OR 0.13, 95% CI: 0.03 to 0.49, p= 0.003) and tocilizumab (OR 0.62, 95% CI: 0.42 to 0.90, p= 0.012) were linked to a lower mortality rate in critically sick patients.[19] This review and network meta-analysis included a total of 110 studies (40 RCTs and 70 observational studies) but only two observational studies with ivermectin alone. Although none of the medicines studied were found to be significantly related with an elevated risk of major non-cardiac adverse events when compared to conventional care, the overall certainty of the evidence was very low in all outcomes, limiting the capacity for recommendations.[19]

A randomised, double-blind phase 2 study was conducted to assess the safety and effectiveness of ivermectin, chloroquine (CQ) and hydroxychloroquine (HCQ) in severe forms of COVID-19, in addition to identifying predictors of mortality in this group of patients.[20] A total of 168 patients were randomised in a 1:1:1 ratio with no placebo given to any group. The endpoints were need of supplemental O2, invasive ventilation, admission in ICU and death. There was no difference in terms of corticosteroid, anticoagulant or antibiotics given to these groups. Mortality rate was similar in three groups (22.2%; 21.3% and 23.0%) suggesting ineffectiveness of the drugs. No difference in the incidence of serious adverse events were observed. CQ, HCQ or ivermectin revealed a favourable safety profile but the tested drugs do not reduce the need for supplemental oxygen, ICU admission, invasive ventilation or death, in patients hospitalised with a severe form of COVID-19.[20]

A retrospective study was done by a COVID-19 unit in Bangladesh from April to June 2020 involving 325 patients confirmed with COVID-19.[21] Ivermectin plus standard care was given to 115 patients, whereas standard care was given to 133 patients, and 77 patients under the age of 18 were excluded. Ivermectin was given once at a dose of 12 mg, along with normal care, within 24 hours after admission. There were no signs of increasing pathology, such as pneumonia or cardiovascular problems, in any of the ivermectin-treated individuals. Patients who did not get ivermectin, on the other hand, suffered pneumonia 9.8% of the time and 1.5% experienced an ischaemic stroke. Ivermectin-treated patients required significantly less oxygen (9.6% vs. 45.9%), had respiratory distress (2.6 % vs. 15.8%), required antibiotic therapy (15.7% vs. 60.2%), and required critical care management (15.7 % vs. 60.2 %)

(0.9% vs. 8.3%). The ivermectin group became COVID-19 negative faster (median 4 vs. 15 days; 95% CI: 8.97 to 10.59; p=0.001) and had shorter hospital stays (median 9 vs. 15 days; 95 % CI, 5.09–7.51; p=0.001). Moreover, the mortality rate in the ivermectin group was considerably lower than in the control group (0.9 % vs. 6.8%; p=0.05). There were no issues reported by 60 patients who were scheduled for follow-up 10 and 20 days after discharge.[21]

Evidence on Safety

The overall evidence of the review by Bryant et al on safety aspects of ivermectin were deemed to be of low certainty, due to low incidence on event.[10] These include a meta-analysis of 11 studies including 1533 people which found no significant difference in the risk of severe adverse events between ivermectin and placebo (aRR 1.65, 95% CI: 0.44 to 6.09; I^2=50 %). In the ivermectin group, seven severe adverse events were observed, compared to two in the control group. Two patients in the Mahmud trial had esophagitis but this is a well-known side effect of the drug doxycycline, which was used in conjunction with ivermectin in this study. In another study, one patient suffered hyponatremia as this experiment utilised high-dose ivermectin for five days). In a study from Turkey, two patients showed serious “delirium-like behaviour, agitation, hostile attitude, and changed state of consciousness,” which the authors attributed to metabolic insufficiencies in the MDR-1/ABCB1 or CYP3A4 genes, which were screened for as part of the study feature.[10]

There were two severe adverse events in each arm of the Lopez-Medina et al trial.[13] In between the time of randomisation and day 21, 154 patients (77%) in the ivermectin group and 161 (81.3%) in the placebo group experienced adverse events. Due to adverse events, fifteen patients (7.5%) in the ivermectin group and five patients (2.5%) in the placebo group withdraw from the treatment. Serious adverse events occurred in four patients, two in each group, but none were thought to be attributable to the ivermectin by the investigators.[13]

Okumuş et al. observed nausea and vomiting in two individuals, as well as higher serum levels of liver enzymes in one, but no major side effects or treatment-related side effects with ivermectin.[22]

According to a systematic review on ivermectin use among persons with parasite illnesses, the drug is safe at the normal doses (0.2 or 0.4 mg/kg) and may be safe at larger levels.[23] The majority of ivermectin side effects on the use for scabies were modest and temporary.[5,23] There was insufficient evidence to conclude on the safety profile of ivermectin during pregnancy.[24]

Evidence on Cost/Cost-effectiveness

There was no retrievable evidence on cost-effectiveness on ivermectin in the treatment of COVID-19.

TABLE 1: STUDY CHARACTERISTICS ON EFFECTIVENESS OF IVERMECTIN INCLUDED IN THE REVIEW

STUDY, YEAR, COUNTRY	TYPE OF STUDY	INTERVENTION	COMPARATOR	CHARACTERISTICS OF STUDY POPULATION/ INCLUDED STUDIES	FINDINGS
Bryant et al[10] 2021 United Kingdom	Systematic review and meta-analysis	Ivermectin	Standard of care	No of trials: 24 RCT (including 3 quasi-RCTs) Total no of patients: 3406 **Included studies**: ***Ahmed 2020*** ***Babalola 2020*** ***Bukhari 2021*** ***Chaccour 2020*** ***Chachar 2020*** ***Chowdhury 2020*** ***Elgazzar 2020*** ***Fonseca 2021*** ***Gonzalez 2021*** ***Hashim 2020*** ***Krolewiecki 2020*** ***Lopez-Medina 2021*** ***Mahmud 2020*** ***Mohan 2021*** ***Niaee 2020*** ***Okumus 2021*** ***Petkov 2021*** ***Podder 2020*** ***Raad 2021*** ***Ravikirti 2021*** ***Rezai 2020*** ***Schwartz 2021*** **COVID-19 prophylaxis studies** ***Chahla 2021*** ***Elgazzar 2020*** ***Shouman 2020***	**Mortality**: Ivermectin reduced the risk of mortality by an average of 62% (95 % CI 27% to 81%) when compared to no Ivermectin treatment [average RR (aRR) 0.38, 95 % CI 0.19 to 0.73; I^2=49 %]; **Risk of death :** 2.3% versus 7.8% among hospitalised patients. **Prevention**: Ivermectin prophylaxis reduced COVID-19 infection by an average 86% (95% CI: 79% to 91%)

Roman et al[11] 2021 Peru, South America Pre-print article	Systematic review and meta-analysis	Ivermectin	Standard of care in 5 RCTs Placebo in 5 RCTs	No of trials: 10 RCTs Total no of patients: 1173 **Included studies** ***Ahmed 2020*** ***Beltran 2021*** ***Chaccour 2020*** ***Chachar 2020*** ***Karamat 2021*** ***Krolewiecki 2020*** ***Lopez-Medina 2021*** ***Niaee 2020*** ***Podder 2020*** ***Ravikirti 2021***	**Mortality**: No effect on all-cause mortality in five RCTs (RR 0.37, 95% CI: 0.12 to 1.13, I^2=16%, very low quality of evidence) **Length of stay** In 3 RCTs (MD 0.72 days, 95% CI: -0.86 to 2.29, I^2=0%, very low quality of evidence) **Adverse events**: in 3 RCTs (RR 0.95, 95% CI: 0.85 to 1.07, I^2=0%, low quality of evidence) No effect of ivermectin on severe adverse events in comparison to the controls (RR 1.39, 95% CI: 0.36 to 5.30, I^2=0% **Viral clearance**: Viral clearance in comparison to the controls in four RCTs RR 0.96, 95% CI: 0.79 to 1.16, I^2=0%
Hariyanto et al[12] 2021 Indonesia	Systematic review and meta-analysis	Ivermectin	Standard of care	No of trials: 19 10 RCTs and 9 double-blind RCTs Total no patients: 2768 **<u>Included studies</u>** ***Ahmed 2020*** ***Babalola 2020*** ***Bukhari 2021*** ***Chachar 2020*** ***Chowdhury 2020*** ***Elgazzar 2020*** ***Gonzalez 2021*** ***Hashim 2020*** ***Kishoria et al 2020*** ***Lopez-Medina 2021*** ***Mahmud 2020*** ***Mohan 2021*** ***Niaee 2020*** ***Okumus 2021*** ***Pott-Junior 2021*** ***Podder 2020*** ***Ravikirti 2021*** ***Shahbaznejad 2021*** ***Shouman 2020***	**Severity of disease**: RR 0.43 [95% CI: 0.23 to 0.81], p = 0.008 **Mortality**: RR 0.31 [95% CI: 0.15 to 0.62], p = 0.001 **Negative RT-PCR test results rate**: RR 1.23 [95% CI: 1.01 to 1.51], p = 0.04) **Shorter time to negative RT-PCR test results:** mean difference [MD] −3.29 [95% CI: −5.69 to −0.89], p = 0.007), higher symptoms alleviations rate (RR 1.23 [95% CI: 1.03 to 1.46], p = 0.02) **Shorter time to symptoms alleviations** (MD −0.68 [95% CI: −1.07 to −0.29], p = 0.0007) **Shorter time to hospital discharge** (MD −2.66 [95% CI: −4.49 to −0.82], p = 0.004)

Padhy et al[13] 2020 Iran, USA, Bangladesh, India	Systematic review and meta-analysis	ivermectin	standard treatment	RCTs and observational studies 629 Patients ***Gorial 2020*** ***Rajter 2020*** ***Chowdhury 2020*** ***Bhattacharya 2020***	The random effect model revealed that adding ivermectin led to significant clinical improvement compared to usual therapy (OR=1.98, 95% CI: 1.11 to 3.53, p=0.02)
Lawrie[16] 2021 Argentina, Bangladesh, Egypt, USA, Iran, India, Spain, Pakistan	Meta-analysis	Ivermectin	standard treatment	27 study reports, RCT and Observational Control Study (OCT) Total number of patients ranged from 24 to 1195 ***Ahmed 2020*** ***Cepelowicz Rajter 2020*** ***Chaccour 2020*** ***Chachar 2020*** ***Chowdhury 2020*** ***Elgazzar 2020a*** ***Mahmud 2020*** ***Podder 2020*** ***Hashim 2020*** ***Khan 2020*** ***Niaee 2020*** ***Spoorthi 2020*** ***Alam 2020*** ***Carvallo 2020*** ***Elgazzar 2020b*** ***Shouman 2020***	**Mortality** Reduction in 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 **Prophylaxis** Reduction in COVID-19 infections 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).
Rodríguez-Gutiérrez et al[14] 2021 Mexico Pre-print	Living systematic review and meta-analysis	ivermectin		10 trials 1426 patients **<u>Included studies;</u>** ***Ahmed 2020*** ***Babalola 2020*** ***Chaccour 2020*** ***Chachar 2020*** ***Elgazzar 2020*** ***Mohan 2021*** ***Niaee 2020*** ***Podder 2020***	**Mortality** Pooled analysis in 6 studies (941 patients) with an overall high risk of bias (OR 0.16; 95% CI: 0.08 to 0.33; I^2= 0%; p=0.81) **Viral clearance** 3 studies reported time to viral clearance as outcome showing a statistically significant difference favouring the ivermectin group (Median difference - 3.83; 95% CI: -5.43 to -2.22; I^2=81%; p<0.01).

				Ravikirti 2021 ***Shouman 2020***	**Prophylaxis** No positive effect was found regarding ivermectin prophylaxis
Castañeda-Sabogal et al[15] 2021 Peru, US Pre-print	Systematic review and meta-analysis	ivermectin (alone or in combination with azithromycin, hydroxychloroquine, dexamethasone, enoxaparin, aspirin or dicloxacillin	standard care	In ambulatory and hospitalised patients with COVID-19 12 trials -5 retrospective cohort studies, 6 RCTs and 1 case series included in the qualitative synthesis (total of 7412 participants) -5 studies were included in the quantitative synthesis **<u>Included studies;</u>** ***Ahmed 2020*** ***Camprubi 2020*** ***Carvallo 2020*** ***Chaccour 2020*** ***Gorial 2020*** ***Khan 2020*** ***Mahmud 2020*** ***Rajter 2020*** ***Podder 2020*** ***Shakhsi 2020*** ***Shouman 2020*** ***Soto 2020***	**Mortality** Ivermectin no association with reduced mortality (logRR: 0.89, 95% CI: 0.09 to 1.70, p = 0.04, I^2= 84.7%) No reduction in **patient recovery** (logRR 5.52 , 95% CI: -24.36 to 35.4, p = 0.51, I^2= 92.6%) All studies had a high risk of bias with 8 studies that were not adjusted for confounders and showed a very low certainty of the evidence
Karale et al [17] 2021 India, US Pre-print	Systematic review and meta-analysis	ivermectin	standard care	38 studies (n=15,002 patients) was included in the qualitative analysis - 30 studies (n=11,291) were included in the quantitative analysis **<u>Included studies</u>:** ***Ahmed 2021*** ***Afsar 2020*** ***Alam 2020*** ***Babalola 2021*** ***Bhattacharya 2020*** ***Budhiraja 2020*** ***Bukhari 2021*** ***Cadegiani 2020***	**Mortality** ●Odds of death 83 were lower in the ivermectin-arm compared to the non-Ivermectin arm. (OR 0.39, 95% CI: 0.22 to 0.70; I^2=81%) ●Subgroup analysis of 12 randomised controlled trials with severity-based data showed mortality benefit overall (OR 0.33, 95% CI: 0.15 to 0.72; I^2=53%) ●In the mild/moderate sub-group (OR 0.10, 95% CI: 0.03 to 0.33; I^2=0%) **Need for intensive care unit (ICU) admission**

				Camprubi 2020 ***Carvallo 2020*** ***Chaccour 2021*** ***Chachar 2020*** ***Chowdhury 2020*** ***Elalfy 2021*** ***Elgazzar 2020*** ***Espitia-Hernandez 2020*** ***Galan 2020*** ***Gorial 2020*** ***Gonzalez 2021*** ***Guzman 2021*** ***Hashim 2020*** ***Hussain 2021*** ***Khan 2020*** ***Kishoria 2020*** ***Krolewiecki 2020*** ***Lima-Morales 2020*** ***Lopez-Medina 2021*** ***Mahmud 2020*** ***Mohan 2021*** ***Morgenstern 2020*** ***Nunez 2020*** ***Niaee 2020*** ***Okumus 2021*** ***Pott-Junior 2021*** ***Rajter 2020*** ***Ravikirti 2021*** ***Soto-Becerra 2020*** ***Spoorthi 2020***	(OR 0.48, 95% CI: 0.17 to 1.37; I^2=59%) and **mechanical ventilation** (OR 0.64, 95% CI: 0.40 to 1.04; I^2=17%) was not significant **Adverse effects** Quantitative analysis of adverse effects with ivermectin use was inconclusive (OR 0.92, 95% CI: 0.64 to 1.33; I^2=14%)
Bartoszko et al [18] 2021 Canada, China, Korea, Switzerland, Argentina, Peru	Living systematic review and network meta-analysis	-ivermectin -ivermectin combined with iota-carrageenan -hydroxychloroquine	standard care or placebo	Patients at risk of COVID-19 9 RCTs -Only 2 on ivermectin alone (total participants= 540) ***Elgazzar 2020*** ***Shouman 2021*** -one RCT on ivermectin combined with iota-carrageenan (n=234) -6 on hydroxychloroquine (n=6059 participants)	**Mortality** No deaths occurred in the one ivermectin trial reporting mortality, its effect on mortality outcome is very uncertain **Laboratory confirmed infection** Low certainty whether ivermectin alone, when compared with standard care reduces the risk (Odds ratio 0.16 (95% credible interval 0.02 to 0.73); 50 fewer per 1000 participants (59 fewer to 16 fewer) -due to serious risk of bias and very serious imprecision in the study

					Suspected, probable, or laboratory confirmed infection Effect remained very uncertain (OR 0.06 (0.02 to 0.13); 159 fewer per 1000 participants (165 fewer to 144 fewer). **Hospital admission** No effect **Adverse events** No effect Most of the data has not been peer reviewed
Kim et al [19] 2020 Korea	Systematic review and network meta-analysis	Ivermectin Corticosteroid	Standard of care	No of trials: 110 40 RCTs and 70 observational studies Only two observational study with ivermectin alone Total no patients: 2768	**Mortality**: Lower mortality rate in critically sick patients (OR 0.15, 95% CI: 0.04 to 0.57, p= 0.005)
Galan et al[20] 2021 Brazil	RCT double- blind phase 2 study	ivermectin	chloroquine (CQ) hydroxychloroquine (HCQ) No placebo	Patients hospitalised with a severe form of COVID-19 168 patients were randomised in a 1:1:1 ratio of IVM, HCQ, CQ	**Mortality** Mortality rate was similar in three groups (22.2%; 21.3% and 23.0%) suggesting ineffectiveness of the drugs. **Adverse events** No difference in the incidence of serious AE favorable safety profile for all All drugs showed no reduction in the need for **supplemental oxygen, ICU admission, invasive ventilation**
Khan et al[21] 2020 Bangladesh	Retrospective study	Ivermectin plus standard care	Standard of care	Total no of patients: 325	**Mortality**: lower in the ivermectin group than in the control group (0.9% vs. 6.8%; p=0.05). In ivermectin-treated patients - ● significantly less oxygen requirement (9.6% vs. 45.9%) ● less respiratory distress (2.6% vs. 15.8%), ● less antibiotic therapy (15.7 % vs. 60.2 %)

					● less critical care management (15.7 % vs. 60.2%) ● Become negative for COVID-19 faster (median 4 vs. 15 days; 95 % CI; 8.97 to 10.59; p=0.001) **Length of stay**: median 9 vs. 15 days; 95 % CI;, 5.09 to 7.51; p= 0.001

CONCLUSION

There were notably a number of retrievable systematic reviews and meta-analyses assessing the efficacy, effectiveness and safety of ivermectin in COVID-19 patients. However, there was a considerable overlap of selected studies in these reviews and meta-analyses which included pre-printed randomised trials and retrospective cohort studies. Furthermore, most of these studies had unclear selection criteria and process, incomplete information and significant methodological limitations such as small sample size, assessing various concomitant medications in addition to ivermectin and non-blinding in RCTs which resulted in very low certainty of the evidence.

This current paucity of high quality of evidence highlights the need for additional, higher quality and larger scale clinical trials to further investigate the effectiveness and safety of ivermectin.

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