

Ivermectin

Section last reviewed and updated 6/30/2022

Last literature search conducted 5/31/2022

Recommendation 1: In hospitalized patients with COVID-19, the IDSA panel suggests against ivermectin. (Conditional recommendation^{††}, Very low certainty of evidence)

Recommendation 2: In ambulatory persons with COVID-19, the IDSA panel recommends against ivermectin. (Strong recommendation, Moderate certainty of evidence)

††The guideline panel concluded that the undesirable effects outweigh the desirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Why is ivermectin considered for treatment?

Ivermectin is an anti-parasitic agent that is FDA-approved for onchocerciasis and strongyloidiasis and is used off-label for the treatment of many parasitic infections. Although it has *in vitro* activity against some viruses, including SARS-CoV-2, it has no proven therapeutic utility. *In vitro* activity against SARS-CoV-2 [1] requires concentrations considerably higher than those achieved in human plasma and lung tissue to reach the *in vitro* IC₅₀ [2]. Ivermectin has been shown to have anti-inflammatory effects in *in vitro* and *in vivo* studies hence hypothesized to have a mechanism beyond its anti-viral effects in the treatment of COVID-19 [3, 4].

Since ivermectin is generally well tolerated, it was empirically evaluated in uncontrolled studies for COVID-19, alone and in combination with other off-label medications.

Summary of the evidence

Our search identified 21 studies in patients with COVID-19 with ages ranging between 8 and 86 years that reported on the outcomes of mortality, symptom resolution, viral clearance, and adverse events, and informed the evidence review for inpatient and outpatient therapy [5-

25]. Eligible studies compared treatment with ivermectin against a placebo or standard of care. Studies comparing ivermectin to a non-placebo, active comparison (i.e., a different agent considered a possible treatment for COVID-19 infection by clinicians) or that did not provide a comparison arm were not included in these analyses. Several studies did not meet eligibility for inclusion in this review. Three trials compared ivermectin to hydroxychloroquine (comparison to treatment with evidence of harm) [26-28]; two trials examined ivermectin as prophylactic treatment [29, 30]; and two trials did not provide study data in a peer-reviewed, published, or pre-print manuscript [28, 31].

The studies that informed the recommendations for hospitalized patients included 11 randomized controlled trials (RCTs) [5-9, 13-16, 24, 25]. Twelve RCTs [7, 8, 10-12, 17-23] informed the recommendation for ambulatory persons. Each of them compared an active treatment arm of ivermectin to an inactive comparison (e.g., standard of care with or without placebo).

The evidence informing the recommendations for treating hospitalized and ambulatory persons with ivermectin reported on the use of a range of doses (100 mcg/kg/day to 400 mcg/kg/day) and durations (one day up to seven days). Among studies reporting on hospitalized patients, substantial heterogeneity was observed, introduced by one study (**Supplementary Figure s1c**) [5]. Ahmed 2020 treated patients with ivermectin for a duration of five days, rather than one day as used by the remaining studies. This may explain the heterogeneity between studies; however, excluding Ahmed 2020, any meaningful reduction in viral clearance was still not demonstrated by the summary estimate (**Supplementary Figure s1d**). Heterogeneity was not observed for other outcomes reported for hospitalized or ambulatory persons.

Among the RCTs, the risk of bias was high in two trials because of unsuccessful randomization into treatment and control groups. Hashim et al (2020) [8] inadequately randomized participants by allocating them to respective treatment arms on odd and even days, as well as assigning all critically ill patients to the ivermectin arm, and Podder et al (2020) [9] allocated participants based on odd or even registration numbers. In addition, across many RCTs, there were concerns due to lack of blinding of study personnel, which may lead to over-

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or under-estimates of treatment effects, particularly for subjective outcomes (e.g., symptom resolution, adverse events).

Benefits

Hospitalized

The evidence from RCTs failed to demonstrate a meaningful effect on mortality or need for mechanical ventilation among persons with COVID-19 (risk ratio [RR]: 0.54; 95% confidence interval [CI]: 0.28, 1.03; moderate certainty of evidence [CoE] and RR: 0.40; 95% CI: 0.13, 1.27, low CoE, respectively). Persons receiving treatment with ivermectin rather than no ivermectin failed to demonstrate a beneficial or detrimental effect on symptom resolution or viral clearance at day seven (RR: 1.07; 95% CI: 0.69, 1.65; very low CoE and RR: 1.21; 95% CI: 0.77, 1.90; very low CoE, respectively).

Ambulatory

Treatment with ivermectin does not reduce mortality (RR: 0.83; 95% CI: 0.50, 1.37; high CoE). Treatment with ivermectin may reduce progression to severe disease; however, could not exclude no meaningful reduction (RR: 0.72; 95% CI: 0.44, 1.17; moderate CoE). Treatment with ivermectin failed to demonstrate a beneficial or detrimental effect on hospitalization or viral clearance at day seven (RR: 0.85; 95% CI: 0.65, 1.11, moderate CoE, and RR: 1.11; 95% CI: 0.85, 1.44; very low CoE, respectively). The evidence is very uncertain, but ivermectin may reduce the time to recovery among ambulatory persons with COVID-19 (mean difference: 3.46 days fewer; 95% CI: 5.40 to 1.52 days fewer; very low CoE). However, the ACTIV-6 trial did not show a reduction in time to recovery with a hazard ratio: 1.09 (0.98, 1.22) [23].

Harms

In doses typically used for the treatment of parasitic infections, ivermectin is well tolerated. We are unable to exclude the potential for serious adverse events in hospitalized patients and ambulatory persons with COVID-19 treated with ivermectin rather than no

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ivermectin, (RR: 3.10; 95% CI: 0.54, 17.89; moderate CoE and RR: 0.81; 95% CI: 0.51, 1.30; moderate CoE, respectively).

Other considerations

The panel determined the certainty of evidence of treatment of ivermectin for hospitalized patients to be very low due to concerns with risk of bias (i.e., study limitations) and imprecision. However, the panel's decision for hospitalized patients was indirectly informed by the lack of benefit of ivermectin as seen in studies in ambulatory persons. The panel determined the certainty of evidence of treatment of ivermectin for ambulatory persons to be moderate due to concerns with imprecision. The guideline panel made a conditional recommendation against treatment of COVID-19 with ivermectin outside of the context of a clinical trial for both patients with COVID-19 hospitalized or in the outpatient setting.

Conclusions and research needs for this recommendation

The guideline panel suggests against ivermectin for the treatment of hospitalized patients with COVID-19. The guideline panel recommends against ivermectin for the treatment of outpatients with COVID-19.

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Table 1. GRADE evidence profile, Recommendation 1

Question: Ivermectin compared to no ivermectin for patients hospitalized with COVID-19

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	no ivermectin	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 28 days)												
8 ¹⁻⁸	randomized trials	not serious	not serious	not serious	serious ^a	none	13/593 (2.2%)	26/546 (4.8%)	RR 0.54 (0.28 to 1.03)	22 fewer per 1,000 (from 34 fewer to 1 more)	⊕⊕⊕○ MODERATE	CRITICAL
Need for mechanical ventilation (follow-up: 28 days)												
2 ^{7,8}	randomized trials	not serious	not serious	not serious	very serious ^a	none	4/283 (1.4%)	10/285 (3.5%)	RR 0.40 (0.13 to 1.27)	21 fewer per 1,000 (from 31 fewer to 9 more)	⊕⊕○○ LOW	CRITICAL
Symptom resolution (follow-up: 7 days)												
1 ⁹	randomized trials	serious ^b	not serious	not serious	very serious ^a	none	16/25 (64.0%)	15/25 (60.0%)	RR 1.07 (0.69 to 1.65)	42 more per 1,000 (from 186 fewer to 390 more)	⊕○○○ VERY LOW	CRITICAL
Viral clearance at day 7 (RCT) (follow-up: range 7 days to 29 days)												
5 ^{4,5,8,10,11}	randomized trials	serious ^c	serious ^d	serious ^e	very serious ^a	none	65/170 (38.2%)	44/136 (32.4%)	RR 1.22 (0.72 to 2.09)	71 more per 1,000 (from 91 fewer to 353 more)	⊕○○○ VERY LOW	IMPORTANT
Serious adverse events (follow-up: 28 days)												
4 ^{2,4,7,8}	randomized trials	not serious	not serious	not serious	serious ^a	none	5/319 (1.6%)	1/312 (0.3%)	RR 3.10 (0.54 to 17.89)	7 more per 1,000 (from 1 fewer to 54 more)	⊕⊕⊕○ MODERATE	CRITICAL
GRADE Working Group grades of evidence												
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect												
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different												
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect												
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect												

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Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. The 95% CI cannot exclude no meaningful effect. Few events reported do not meet the optimal information size and suggest fragility of the estimate
- b. Open label trial may lead to bias with measurement of subjective outcomes.
- c. Podder 2020 assigns participants based on odd or even registration numbers, also, 20 patients were excluded following randomization without sensitivity analysis to explore imbalance across treatment arms.
- d. Substantial heterogeneity observed (I²=62%). Possibly explained by the longer duration of treatment (5 days compared to 1 day) in Ahmed 2020.
- e. Viral clearance is a surrogate for clinical improvement, such as hospitalization, need for ICU care and mechanical ventilation.

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Table 2. GRADE evidence profile, Recommendation 2

Question: Ivermectin compared to no ivermectin for ambulatory persons for management of COVID-19

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	no ivermectin	Relative (95% CI)	Absolute (95% CI)		
Mortality												
10 ¹⁻¹⁰	randomized trials	not serious ^a	not serious	not serious	not serious	none	27/2410 (1.1%)	36/2372 (1.5%)	RR 0.83 (0.50 to 1.37)	3 fewer per 1,000 (from 8 fewer to 6 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Progression to severe disease (assessed with: need for invasive ventilation)												
6 ^{1,2,4,5,7,8}	randomized trials	not serious	not serious	not serious	serious ^b	none	28/1244 (2.3%)	40/1245 (3.2%)	RR 0.72 (0.44 to 1.17)	9 fewer per 1,000 (from 18 fewer to 5 more)	⊕⊕⊕○ MODERATE	CRITICAL
Hospitalization (follow-up: 28 days)												
2 ^{8,10}	randomized trials	not serious	not serious	not serious	serious ^b	none	89/1496 (5.9%)	104/1453 (7.2%)	RR 0.85 (0.65 to 1.11)	11 fewer per 1,000 (from 25 fewer to 8 more)	⊕⊕⊕○ MODERATE	CRITICAL
Viral clearance at day 7 (RCT) (follow-up: range 6 days to 29 days)												
5 ^{2-4,8,11}	randomized trials	not serious	not serious	serious ^{c,d}	very serious ^b	none	108/306 (35.3%)	103/326 (31.6%)	RR 1.11 (0.85 to 1.44)	35 more per 1,000 (from 47 fewer to 139 more)	⊕○○○ VERY LOW	IMPORTANT
Time to recovery (assessed with: days)												
3 ^{1,5,6}	randomized trials	serious ^e	serious ^f	not serious ^g	serious ^h	none	448	446	-	MD 3.46 days fewer (5.4 fewer to 1.52 fewer) ⁱ	⊕○○○ VERY LOW	IMPORTANT
Serious adverse events (respiratory failure, sepsis, multiorgan failure, etc.)												
6 ^{2,3,5,8,10,12}	randomized trials	not serious	not serious	not serious	serious ^j	none	31/1740 (1.8%)	40/1719 (2.3%)	RR 0.81 (0.51 to 1.30)	4 fewer per 1,000 (from 11 fewer to 7 more)	⊕⊕⊕○ MODERATE	CRITICAL

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GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

- a. Concerns with unmeasured and residual confounding. Hashim 2020 used even vs. odd days to place subjects into treatment groups with critical patients not included in the placebo group.
- b. The 95% CI includes the potential for both appreciable benefit as well as the potential for harm. Few events reported do not meet the optimal information size and suggest fragility of the estimate
- c. Viral clearance is a surrogate for clinical improvement, such as hospitalization, need for ICU care and mechanical ventilation.
- d. Ravikirti 2021 reported viral clearance at day 6.
- e. Open label trial may lead to bias with measurement of subjective outcomes.
- f. High heterogeneity $I^2=96$
- g. Ivermectin was combined with doxycycline.
- h. Number of events is less than the optimal information size, which may suggest fragility in the estimate of effect.
- i. The binary endpoint of time to recovery from the ACTIV-6 trial could not be combined with pooled continuous analysis of days to recovery; however, did not show a reduction with a HR: 1.09 (0.98, 1.22).
- j. The 95% CI cannot exclude the potential of increased SAEs in the treatment arm. Few events suggest fragility in the estimate.

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Supplementary Materials

Study characteristics

- **Table s1.** Should ambulatory or hospitalized patients with COVID-19 receive ivermectin vs. no ivermectin?

Forest plots

- **Figure s1a.** Outcome of mortality for ivermectin vs. no ivermectin among hospitalized patients (from RCTs)
- **Figure s1b.** Outcome of need for mechanical ventilation for ivermectin vs. no ivermectin among hospitalized patients
- **Figure s1c.** Outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (all studies)
- **Figure s1d.** Outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (without Ahmed 2020)
- **Figure s1e.** Outcome of serious adverse events for ivermectin vs. no ivermectin among hospitalized patients
- **Figure s1f.** Outcome of mortality for ivermectin vs. no ivermectin among ambulatory patients
- **Figure s1g.** Outcome of progression to severe disease for ivermectin vs. no ivermectin among ambulatory patients
- **Figure s1h.** Outcome of viral clearance at seven days for ivermectin vs. no ivermectin among ambulatory patients
- **Figure s1i.** Outcome of time to recovery for ivermectin vs. no ivermectin among ambulatory patients
- **Figure s1j.** Outcome of hospitalization for ivermectin vs. no ivermectin among ambulatory patients
- **Figure s1k.** Outcome of serious adverse events for ivermectin vs. no ivermectin among ambulatory patients

Risk of bias

- **Table s2a.** Randomized controlled studies (ivermectin vs. no ivermectin)

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Table s1. Should ambulatory or hospitalized patients with COVID-19 receive ivermectin vs. no ivermectin?

Study/year	Country/Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Abbas/2022 ¹	China/China University of Medical Sciences hospitals	RCT	202 (99/103)	42	Mean: Intervention: 38.33 (6.84) Control: 37.33 (5.84)	Patients age 18-50 years old with COVID-19	Ivermectin 300 mcg/kg/day divided into 2 doses by mouth for 5 days	Placebo	None	All-cause mortality Time to complete symptom resolution Deterioration of WHO clinical status scale by 2 or more points Development of fever Escalation of care Adverse events	Unspecified
Abd-Elsalam/2021 ²	Egypt/ 2 hospitals	RCT	164 (82/82)	50	Intervention: Mean of 42.4 (16) Control: Mean of 39.4 (16.9)	Hospitalized mild-moderate disease (no definition given)	Ivermectin 12 mg by mouth every day for 3 days and SoC	SoC	Paracetamol, oseltamivir, hydrocortisone	Mortality at one month Length of hospital stay Progression to mechanical ventilation Safety	None
ACTIV-6/2022 ³	USA	RCT	1591 (817/774)	58.6	Median: 47.0 (39.0-56.0)	Patients ≥30 years old with confirmed SARS-CoV-2 infection within 10 days,	Ivermectin 400 µg/kg for 3 days	Placebo	N/A	Time to sustained recovery	National Center for Advancing

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Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co- interventions	Outcomes reported	Funding source
						and experiencing ≥2 symptoms of acute COVID-19 for ≤7 days from enrollment				Hospitalization pr death by day 28 COVID clinical progression scale on days 7, 14 and 28 Mortality Hospitalization, urgent care, or emergency department visit Adverse events	Translational Sciences
Ahmed/ 2020 ⁴	Banglade sh	RCT	68: ivermectin alone vs. ivermectin plus doxycycline vs. placebo (22/23/23)	54	Mean: 42	Hospitalized with a fever, cough, or sore throat	Ivermectin alone (12mg once daily for 5 days) Ivermectin plus doxycycline combination therapy (12mg ivermectin single dose plus doxycycline 200mg once, followed by 100mg twice daily for 4 days)	Placebo	N/A	Length of hospitalization Incidence of hypoxia Time to virologic clearance Biomarker levels Adverse events	Beximco Pharmaceuti cal Limited
Beltran Gonzalez / 2021 ⁵	Mexico/ Hospital Centenar io Miguel Hidalgo	RCT	106 (33 hydroxychloro quine/ 36 ivermectin/ 37 placebo)	37.8	Mean: 53.8 (16.9)	COVID-19 pneumonia requiring hospitalization and recently established	Ivermectin 12 mg (<80 kg) or 18 mg (>80 kg) by mouth once	SoC	Dexamethaso ne, pharmacologi c	In-hospital mortality Length of hospital stay	Agascalienes State Health Institute

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Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co- interventions	Outcomes reported	Funding source
						hypoxemic respiratory failure or acute worsening of pre-existing lung or heart disease, but not requiring mechanical ventilation	Hydroxychloroquine 400 mg by mouth every 12 hours on day 1, followed by 200 mg every 12 hours for 4 days Both groups in addition to SoC		thrombopropylaxis	Discharge without respiratory deterioration or death Time to respiratory deterioration or death	
Biber/ 2021 ⁶	Israel/ hotels in 3 cities designated as isolation areas	RCT	89 (47/42)	21.6	Median: 35 (20-71)	Mild-moderate disease (non-hospitalized and not requiring oxygen)	Ivermectin 12 mg (40-69 kg) or 15 mg (≥ 70 kg) by mouth every day for 3 days	Placebo	None	Proportion with viral clearance at day 6 Culture viability days 2-6 Safety	None
Bukhari/ 2021 ⁷	Pakistan/ Combined Military Hospital Lahore	RCT	86 (41/45)	15.1	Mean age: Intervention: 42.2 ± 12.0 Comparator: 39.0 ± 12.6	Mild-moderate disease. Mild disease defined as clinical symptoms, excluding dyspnea or gasping, with no imaging findings of pneumonia. Moderate disease defined as fever, respiratory symptoms, and	Ivermectin 12mg once plus standard of care	(1) SoC	Standard of care, which consisted of Vitamin C 500mg daily, Vitamin D3 50,000 units weekly, and paracetamol 500mg as needed.	Negative PCR test by day 3, 7 and 14 Adverse reactions	None

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Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						imaging findings of pneumonia.					
Buonfrate/ 2022 ⁸	Italy/ 4 outpatient centers	RCT	87 (30 high-dose/28 low-dose/29 placebo)	41.9	Median: 47 (31-58)	Adult outpatients with newly diagnosed SARS-CoV-2 infection by RT-PCR not requiring supplemental oxygen or hospitalization	Ivermectin 1200 mcg/kg/day for 5 days OR Ivermectin 600 mcg/kg/day for 5 days	Placebo	Unspecified therapies related to COVID-19 treatment (61.3% overall)	Change in viral load at day 7 Severe adverse drug reactions Trend in quantitative viral load Proportion of patients with virologic clearance day 14 and 30 Hospitalizations COVID-19 severity score day 14 and 30	Italian Ministry of Health
Chaccour / 2021 ⁹	Spain/ Clínica Universidad de Navarra	RCT	24 (12/12)	50%	Median (IQR) Ivermectin: 26 years (19-36) Placebo: 26 years (21-44)	RT-PCR positive for SARS-CoV-2 and non-severe symptoms compatible with COVID-19 and symptom onset <72 hours	Ivermectin 400 mcg/kg x one dose	Placebo (not matched)	Symptomatic treatments	Mortality Viral clearance at day 7 Progression to severe disease Viral load at days 4, 7, 14, and 21	ISGlobal and University of Navarra

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Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co- interventions	Outcomes reported	Funding source
										Symptom resolution at days 4, 7, 14, and 21 Seroconversion day 21	
Chachar/ 2020 ¹⁰	Pakistan/ Fatima Memoria I Hospital	RCT	50 (25/25)	38%	Mean: 41.84 (15.7)	Outpatients with positive RT-PCR	Ivermectin 12mg every 12 hours x 3 doses total	No ivermectin	Symptomatic treatment	Symptom improvement at day 7 Rate of heartburn	N/A
Hashim/ 2020 ¹¹	Iraq/ Alkarkh and Alforat hospitals	RCT	140 (70/70)	48	Range: Total population: 16-86 Mean (SD): Patients receiving ivermectin/ doxy: 50.1 (9.3) Patients not receiving ivermectin: 47.2 (7.8)	Mild, moderate, severe, or critical disease defined according to WHO guidelines	Ivermectin 200 mcg/kg daily for 2 days, with a possible 3rd dose 7 days after the first dose based on clinical improvement, plus doxycycline 100mg twice daily for 5- 10 days, based on clinical improvement	(1) SoC	Standard of care, according to clinical status of the patients, which could include: acetaminoph en as needed, Vitamin C, zinc, Vitamin D3, azithromycin, dexamethaso ne, oxygen therapy/mech anical ventilation if needed	Mortality Disease progression after 3 days Time to recovery	Baghdad- Alkarkh General Directorate of Health

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Study/year	Country/Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Krolewiecki/ 2021 ¹²	Argentina/ 4 hospitals	RCT	45 (30/15)	44	Intervention: Mean of 38.1 (11.7) Control: Mean of 42.3 (12.8)	Hospitalized but not receiving intensive care	Ivermectin 600 mcg/kg by mouth every day for 5 days	SoC	None	Proportion with viral clearance at day 5 Clinical evolution at day 7 and 30 Safety	Grant from Agencia Nacional de Promoción de la Investigación, Argentina
Lim/ 2022 ¹³	Malaysia (20 hospitals, 1 quarantine center)	RCT	490 (241/249)	54.5	Mean: 62.5 (8.7)	Mild-moderate disease (at least 1 symptom but not on supplemental oxygen) within 7 days of laboratory-confirmed SARS-CoV-2 infection, considered high risk for progression (≥ 50 years old with ≥ 1 comorbidity)	Ivermectin 0.4 mg/kg/day for 5 days plus standard of care	Standard of care	Therapies considered standard of care per Malaysia guidelines (steroids, tocilizumab, convalescent plasma, anticoagulants)	28-day in-hospital all-cause mortality Proportion of patients progressing to severe COVID-19 Time of progression to severe disease Mechanical ventilation rate ICU admissions Length of hospitalization Adverse events	Institute for Clinical Research, Ministry of Health Malaysia
López-Medina/ 2021 ¹⁴	Columbia/ Centro de Estudios en	RCT	398 (200/198)	58	Median (IQR): 37 (29-48)	Mild disease (Home or hospitalized but not receiving high-flow nasal oxygen or	Ivermectin 300 $\mu\text{g}/\text{kg}/\text{day}$ for 5 days	Placebo	N/A	Mortality Time to symptom resolution	Grant from Centro de Estudios en Infectología Pediátrica

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Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co- interventions	Outcomes reported	Funding source
	Infectologia Pediatrica					mechanical ventilation) within 5 days of illness onset				Clinical deterioration Hospitalization Oxygen supplementation Adverse events	
Mahmud / 2021 ¹⁵	Bangladesh/ Dhaka Medical College	RCT	400 (200/200)	41	Mean: 40	Mild-moderate disease (patients excluded if: >30 breaths/min, <90% SpO2 or requiring supplemental oxygenation, admitted to intensive care)	Ivermectin 12 mg by mouth every day for 5 days and doxycycline 100mg twice a day for 5 days in addition to SoC	SoC	Antihistamine s, paracetamol, vitamins, low molecular weight heparin, remdesivir, “other antiviral drugs”	Mortality Disease progression Time to clinical recovery Proportion with positive test on day 14 Safety	None
Manomai piboon/ 2022 ¹⁶	Thailand / Vajira Hospital	RCT	72 (36/36)	62.5	Mean age: 48.57 (14.8)	Patients age 18- 80 years with mild (cough, runny nose, anosmia, fever, or diarrhea, without dyspnea or tachycardia) or moderate (pneumonia with oxygen saturation > 90%) COVID-19	Ivermectin 12mg by mouth once daily for 5 days plus standard of care	SoC	Favipiravir, andrographoli de, cetirizine	All-cause mortality Viral clearance on day 7 and 14 Length of hospitalization Frequency of clinical worsening Mechanical ventilation	Grant from Navamindra dhiraj University

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Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co- interventions	Outcomes reported	Funding source
										Adverse events	
Mohan/ 2021 ¹⁷	India/ All India Institute of Medical Sciences	RCT	Ivermectin 24mg vs 12mg vs placebo: mITT population (40/40/45)	11.2	Mean: 35.3 (10.4)	Non-severe COVID-19 (SpO ₂ on room air > 90%, no hypotension, no mechanical ventilation)	Ivermectin elixir at a dose of 12mg or 24mg once	Placebo	Hospital standard protocol, which included some patients receiving hydroxychlor oquine, favipiravir, remdesivir, dexamethaso ne, dalteparin, antibiotics	Reduction in viral load Conversion to negative PCR by day 5 Time to clinical resolution Clinical status on day 14 on WHO ordinal scale Hospital-free days on day 28 Adverse effects	Research grant from Department of Science and Technology, Government of India
Podder/ 2020 ¹⁸	Banglade sh/ Debidwa r Upazila Health Complex	RCT	62 (32/30)	29%	Mean (SD) Total enrolled population: 39.16 (12.07) Ivermectin: 38.41 (11.02) Control: 39.97 (13.24)	Positive RT-PCR with mild (no evidence of pneumonia and SpO ₂ >93% on RA) to moderate COVID-19 (signs of pneumonia with SpO ₂ >90%)	Ivermectin 200 mcg/kg on day 1	SOC	Symptomatic treatment with doxycycline 100 mg every 12 hours for 7 days	Viral clearance at day 10 Duration of symptoms Time to resolution of symptoms	None

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Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co- interventions	Outcomes reported	Funding source
Ravikirti/ 2021 ¹⁹	India/ All India Institute of Medical Sciences	RCT	112 (55/57)	27.7	Mean age: 52.5 ± 14.7	Mild-moderate disease. Mild defined as having no evidence of breathlessness or hypoxia. Moderate defined as breathlessness and/or hypoxia (90-95% SpO ₂ on room air), respiratory rate >23, no features of severe disease.	Ivermectin 12mg daily for 2 days	Placebo	Hydroxychlor oquine, corticosteroid s, enoxaparin, antibiotics, remdesivir, convalescent plasma, tocilizumab	In-hospital mortality PCR positivity rate at day 6 Symptom resolution Discharge by day 10 Admission for ICU Mechanical ventilation	All India Institute of Medical Sciences
Reis/ 2022 ²⁰	Brazil/ 12 public health clinics	RCT	1358 (679/679)	58.2	Median: 49 (38-57)	Adult outpatients not requiring hospitalization with laboratory- confirmed SARS- CoV-2 infection within 7 days with ≥1 risk factor for progression	Ivermectin 400 mcg/kg/day for 3 days plus standard of care	Standard of care	None specified	All-cause mortality Hospitalization or ED visit by day 28 due to COVID-19 SARS-CoV-2 viral clearance Length of hospitalization Mechanical ventilation Health-related quality of life Adverse reactions	FastGrants Rainwater Charitable Foundation

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Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co- interventions	Outcomes reported	Funding source
Vallejos/ 2021 ²¹	Argentina	RCT	501 (250/251)	47	Intervention: Mean of 42.6 (15.3) Control: Mean of 42.4 (15.8)	RT-PCR positive and non- hospitalized and not requiring home oxygen	Ivermectin weight- based dosing at 12 mg, 18 mg, or 24 mg every day for 2 days, plus SoC	SoC	Supplements including zinc and vitamin c	Mortality All-cause hospitalization Mechanical ventilation Proportion with viral clearance at day 12 Adverse events	None

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Figure s1a. Forest plot for the outcome of mortality for ivermectin vs. no ivermectin among hospitalized patients (from RCTs)

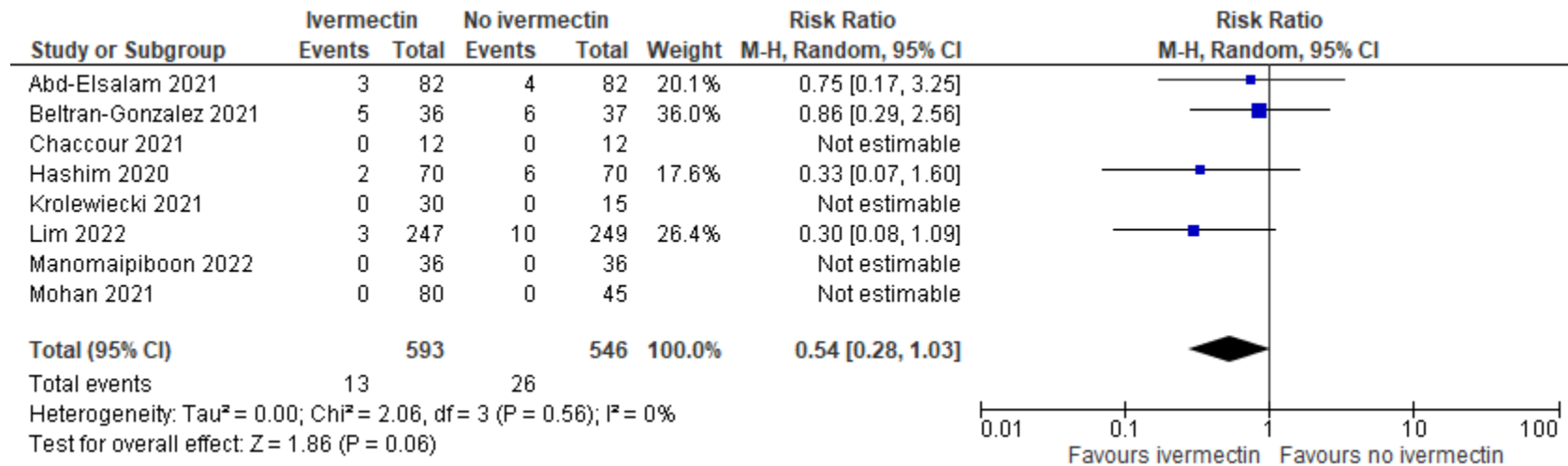
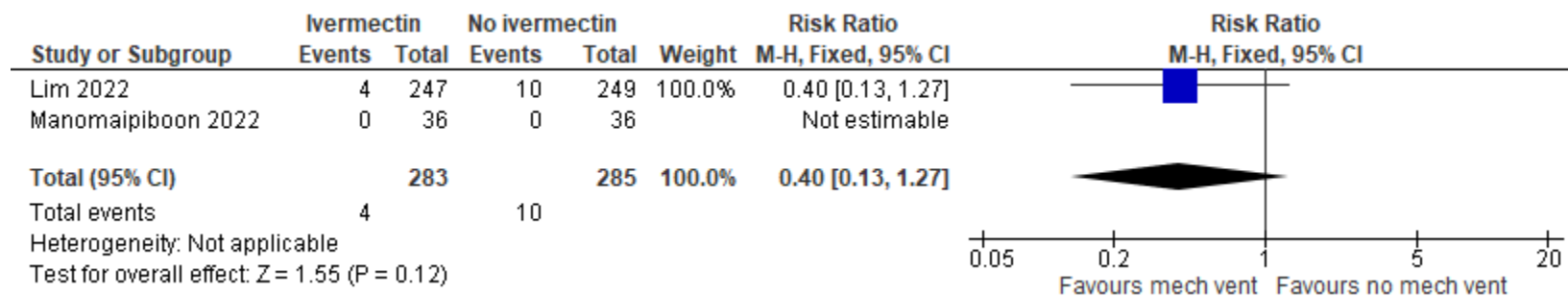


Figure s1b. Forest plot for the outcome of need for mechanical ventilation for ivermectin vs. no ivermectin among hospitalized patients



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Figure s1c. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (all studies)

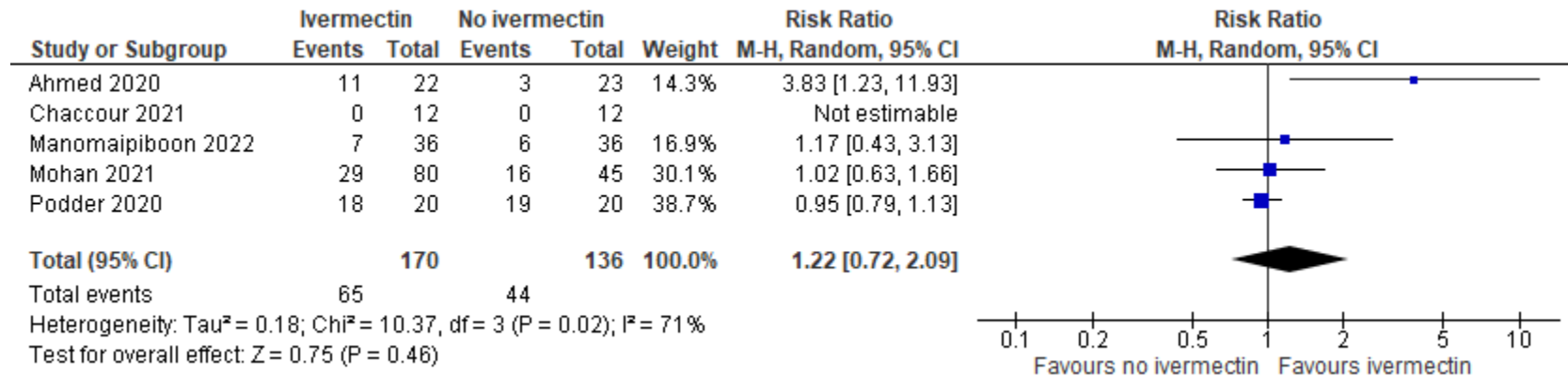
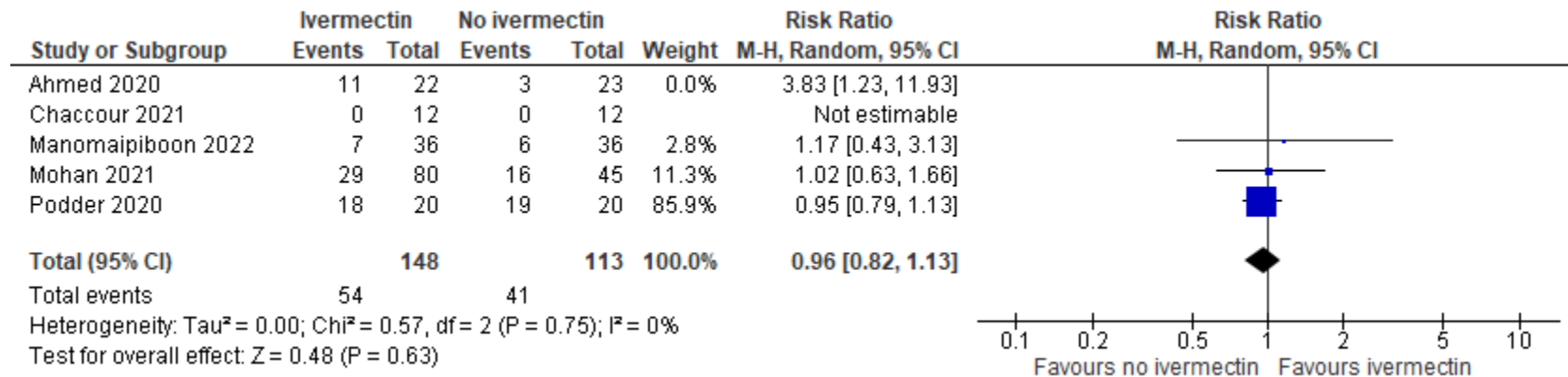


Figure s1d. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (without Ahmed 2020)



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Figure s1e. Forest plot for the outcome of serious adverse events for ivermectin vs. no ivermectin among hospitalized patients

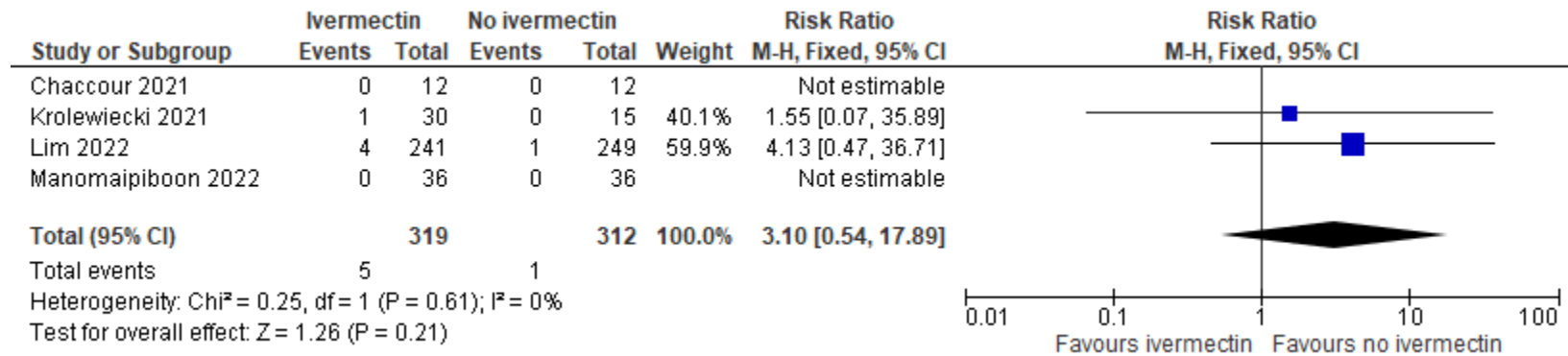
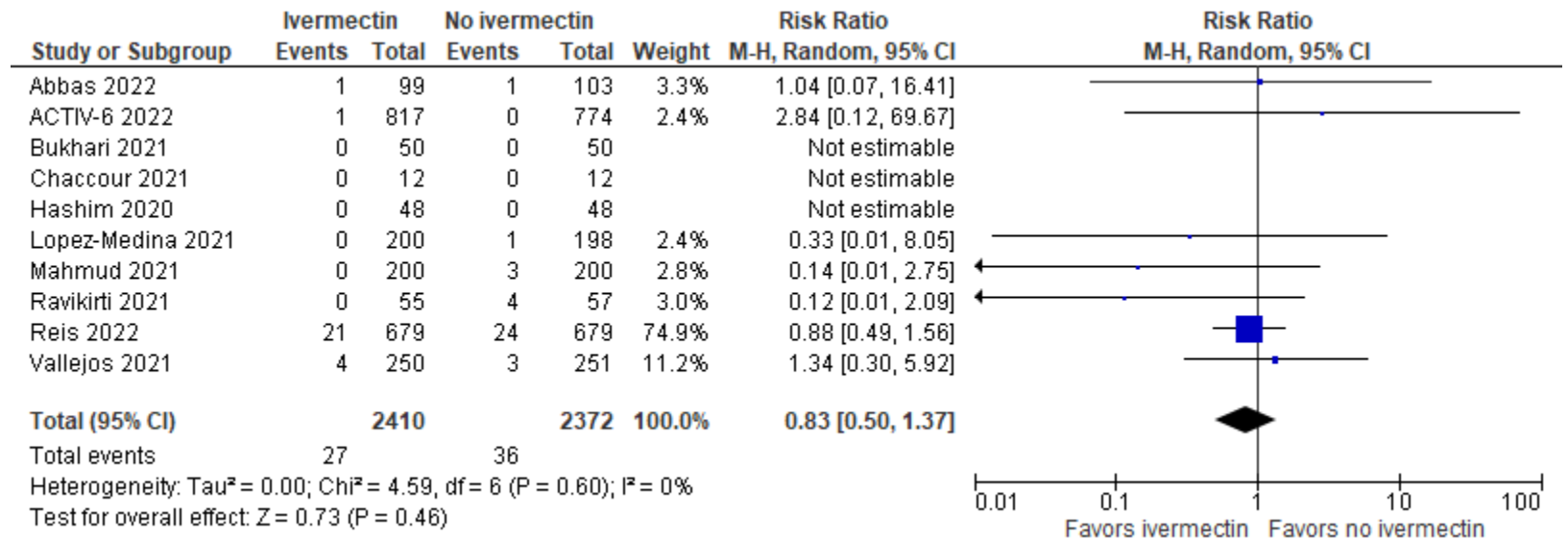


Figure s1f. Forest plot for the outcome of mortality for ivermectin vs. no ivermectin among ambulatory patients



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Figure s1g. Forest plot for the outcome of progression to severe disease for ivermectin vs. no ivermectin among ambulatory patients

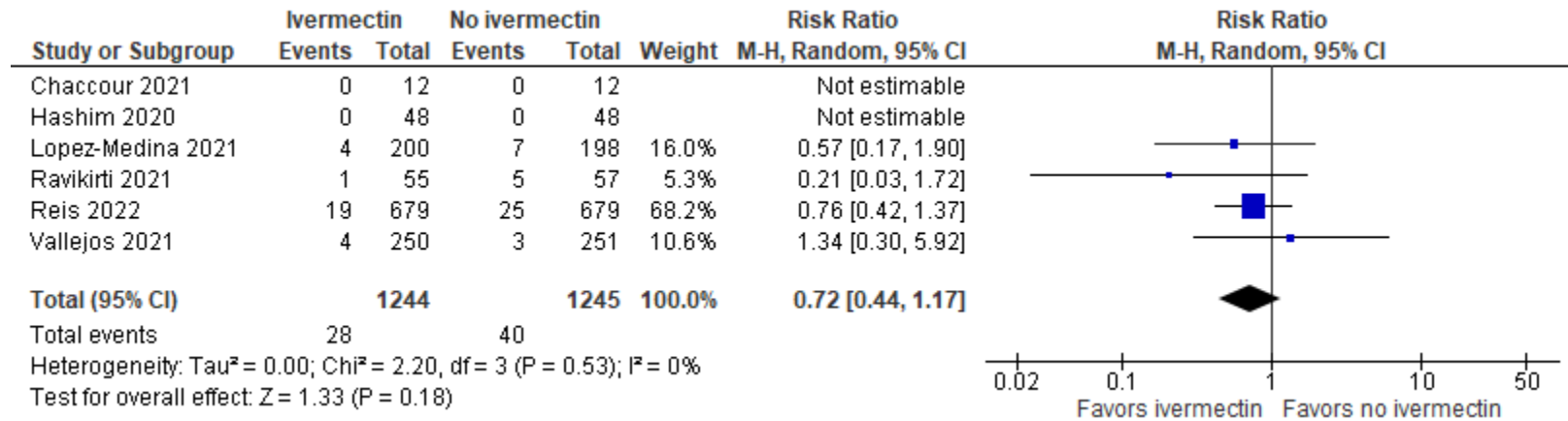
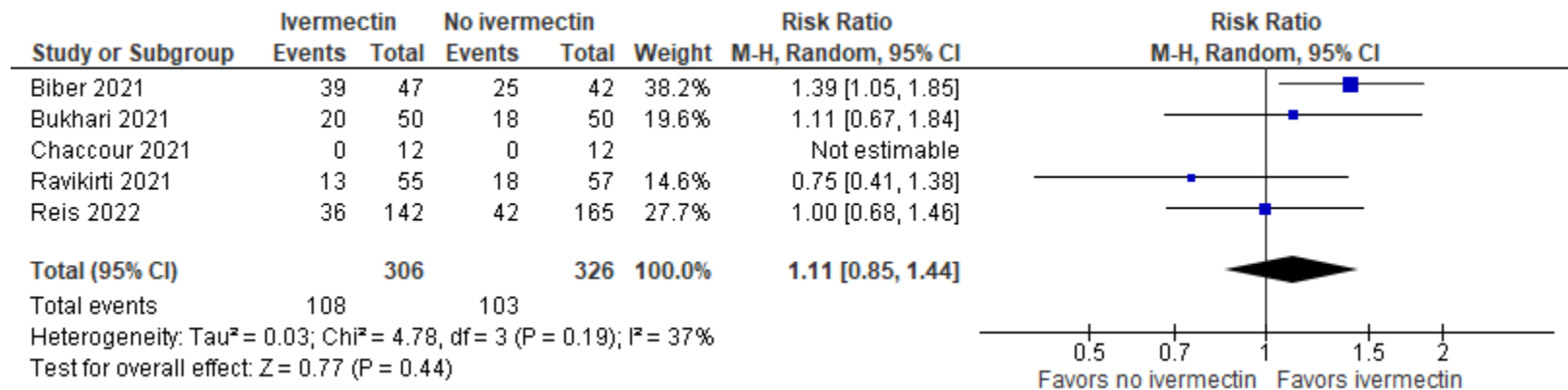


Figure s1h. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among ambulatory patients



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Figure s1i. Forest plot for the outcome of time to recovery for ivermectin vs. no ivermectin among ambulatory patients

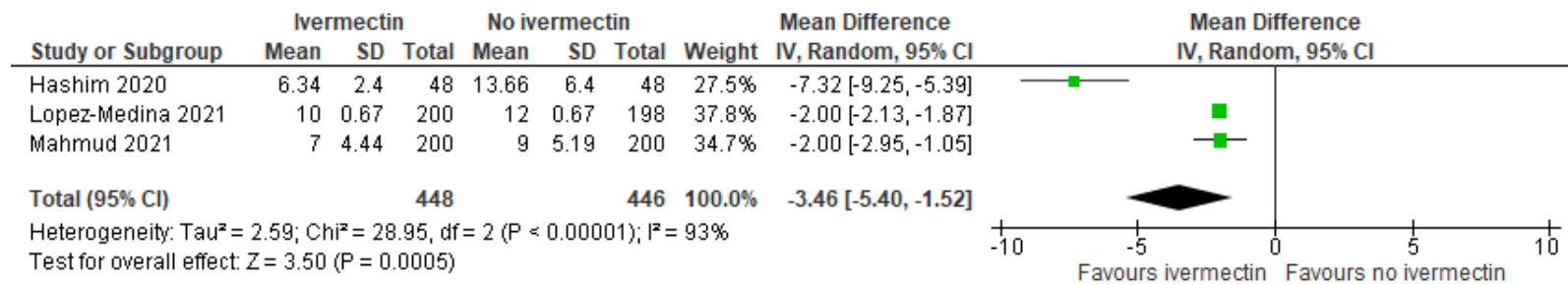
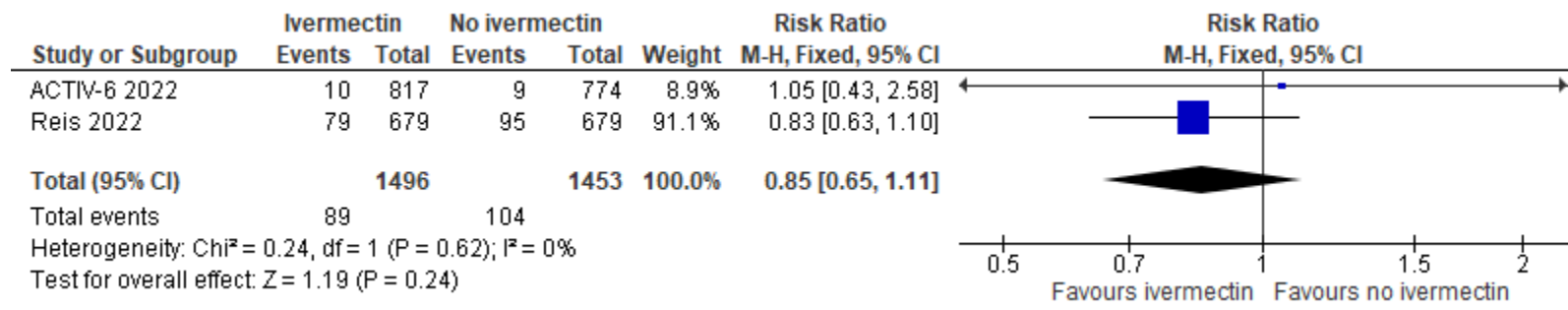


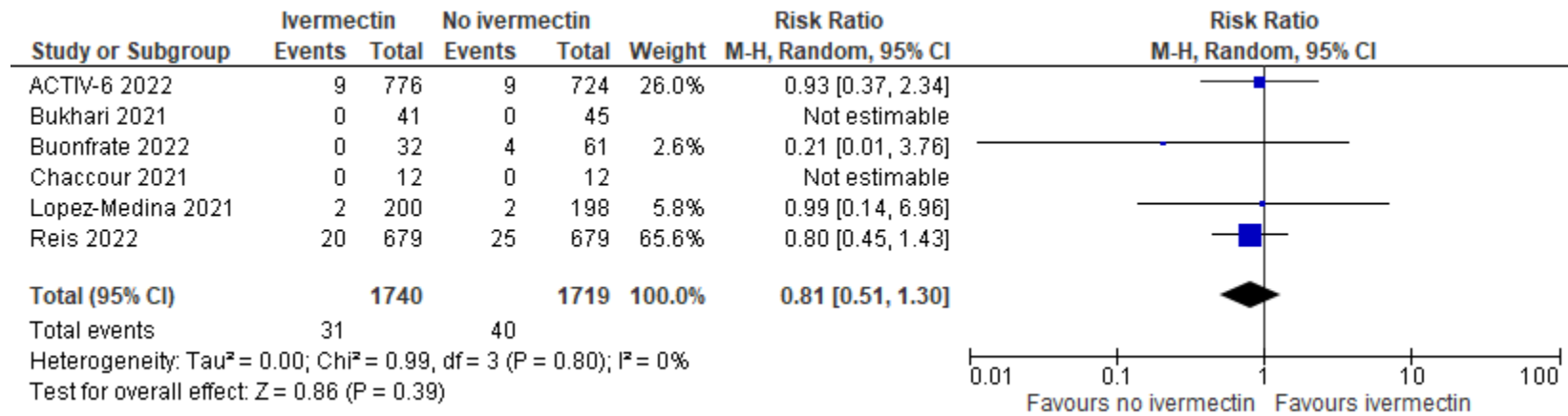
Figure s1j. Forest plot for the outcome of hospitalization for ivermectin vs. no ivermectin among ambulatory patients



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Figure s1k. Forest plot for the outcome of serious adverse events for ivermectin vs. no ivermectin among ambulatory patients



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Table s2a. Risk of bias for randomized controlled studies (ivermectin vs. no ivermectin)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Abbas 2022 ¹	Green	Green	Green	Green	Yellow	Green	Green
Abd-Elsalam 2021 ²	Green	Green	Green	Green	Green	Green	Green
ACTIV-6 2022 ³	Green	Green	Green	Green	Green	Green	Green
Ahmed 2020 ⁴	Yellow	Yellow	Green	Green	Green	Red	Green
Beltran Gonzalez 2022 ⁵	Green	Green	Green	Green	Green	Green	Green
Biber 2021 ⁶	Green	Green	Green	Green	Red	Green	Green
Bukhari 2021 ⁷	Green	Yellow	Green	Green	Green	Green	Green
Buonfrate 2022 ⁸	Green	Green	Green	Green	Green	Green	Red
Chaccour 2021 ⁹	Green	Yellow	Red	Red	Green	Green	Green
Chachar 2020 ¹⁰	Green	Red	Red	Red	Green	Green	Green
Hashim 2020 ¹¹	Red	Red	Red	Red	Green	Green	Green
Krolewiecki 2021 ¹²	Green	Green	Green	Green	Green	Green	Green
Lim 2022 ¹³	Green	Green	Red	Red	Green	Green	Red
López-Medina 2021 ¹⁴	Green	Green	Green	Green	Green	Red	Green
Mahmud 2021 ¹⁵	Green	Green	Green	Green	Green	Green	Green
Manomaipiboon 2022 ¹⁶	Green	Green	Green	Green	Yellow	Green	Green
Mohan 2021 ¹⁷	Green	Green	Green	Green	Green	Green	Green
Podder 2020 ¹⁸	Red	Red	Red	Red	Yellow	Green	Green

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Ravikirti 2021 ¹⁹							
Reis 2022 ²⁰							
Vallejos 2021 ²¹							

Low	High	Unclear
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