Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Should azithromycin be used as treatment for COVID-19?

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RECOMMENDATION

We recommend against the use of azithromycin in the treatment of patients with COVID-19 disease regardless of disease severity. *(Moderate certainty of evidence; Strong recommendation)*

Key Findings

Based on 11 RCTs and one additional RCT for asymptomatic to mild COVID -19 patients, there was no significant difference in clinical outcomes with the use of azithromycin compared to placebo among patients with COVID-19 across all disease severity. Likewise, there was no significant difference in serious adverse events and cardiac arrythmias among all patients but there was a noted significantly higher risk among those given azithromycin for non-serious adverse events for the asymptomatic to mild group with diarrhea being the most common adverse event. This was not noted among the moderate to severe group.

Introduction

Due to the urgency of the problem of the COVID-19 pandemic, many scientists and healthcare workers have looked at existing safe drugs that can be used for treating COVID-19.[1] Among these, macrolides have been one of the medications thought to have the potential to fight this infection due to its immunomodulatory and anti-inflammatory effects on top of its antimicrobial action.[2] This may also be the reason why azithromycin, a macrolide, is the most frequently used antibacterial during the pandemic.[3] This review focuses on the efficacy and safety of azithromycin in management of COVID-19 patients.

Review Methods

Comprehensive literature search was done using PubMed, MedRxiv, Google scholar and Cochrane Library on October 30,2021 with the following Mesh terms: (1) COVID-19 or SARS-CoV-2, (2) macrolides or azithromycin. Since many observational and RCTs have been published regarding this topic, we opted to add filters to include only systematic reviews and meta-analyses. Further search for additional RCTs was planned and subsequently done depending on the last search of the most recent and highest quality SR or meta-analysis available. Post-exposure or prophylactic administration of antibiotics and observational studies were excluded.

Results

We found three systematic reviews and one meta-analysis which investigated azithromycin as a treatment regimen for COVID-19. The most recent meta-analysis was published on June 2021,

which already included the studies in the other three systematic reviews.[4] This meta-analysis aimed to assess the safety and efficacy of antibiotics which have antiviral and anti-inflammatory effects (i.e., azithromycin, clarithromycin, doxycycline) for treatment of COVID-19 (see Appendix 2). The study included both peer and non-peer-reviewed articles. The review included patients who were treated as outpatients (asymptomatic to mild cases) and inpatients, including those admitted at the ICU (moderate to severe cases). The review included 11 studies covering 11281 adult participants. The studies were done in high to low healthcare-cost countries including Brazil, UK, USA, Qatar, Egypt, Iran, and Turkey. Azithromycin was the intervention across all studies, and it was compared to either placebo or standard of care. Dose of the intervention during the first day was consistent at 500mg given orally or through nasogastric tube or intravenously for severe cases. Further doses and duration of treatment however varied among studies after the first day. Four studies used the usual dose for azithromycin in bacterial infection which is 250mg per day while seven studies continued the 500mg dosage. Duration of treatment ranged from 3 days to 14 days. Standard of care (SoC) varied among the studies depending on the practice in their region with six studies using hydroxychloroquine, a drug known to have immunomodulatory and antiviral effects, as part of the SoC. Sensitivity analysis was performed whenever possible by comparing results when studies with some risk for bias, preprint articles, or mixed population (of suspected and RT-PCR confirmed cases) were removed. Risk of bias (RoB) of each included study was assessed using the Cochrane RoB 2.0 tool with half of the studies having low risk for bias and the remaining having some concerns. The overall quality of the systematic review was assessed using the AMSTAR-2 rating tool and it was noted to have a high rating for the overall confidence in the results of the review.

A follow-up search for additional randomized clinical trials using the same keywords was done to look for studies available after the last search done by the included review. One additional RCT (Oldenburg 2021) was found which used single dose oral azithromycin among outpatients with COVID-19 confirmed RT-PCR test within 7 days of the randomization period.[5] This study's initial primary outcome was hospital admission; however, due to low event rate, it was modified to resolution of symptoms at day 14. The study had some concerns for risk of bias for outcome measurement since it was based on self-reported symptoms of the participants. There was no physical contact between investigators and participants, and all communication was done electronically or via telephone. Investigational drugs and placebo were sent via courier.

Because azithromycin was used not just for its antimicrobial property, majority of the studies included participants that were given other antibiotics as part of the standard of care (SoC). We therefore added a sensitivity analysis excluding these studies. Only one study [2] which investigated the intervention in the moderate and severe group fulfilled this criterion, together with three studies who conducted their investigations among the asymptomatic and mild group.[4,5] The Recovery Trial [2] also provided separate data for patients requiring oxygen support (considered to have severe to critical disease based on the NIH severity classification). We opted to report this because those with severe disease may benefit more from the intervention.

Azithromycin vs Standard of Care/Placebo in Asymptomatic and Mild COVID-19 in the Outpatient Setting

There was inconclusive effect on all-cause mortality (RR 1.0, 95% CI 0.06-15.69) and admission to hospital or death at day 28 (RR 0.94, 95% CI 0.57-1.56) based on three studies. The trial that excluded those that received no other antibiotics showed no estimable result for all-cause mortality because of zero events in the intervention and control group, while it showed inconclusive result for admission to hospital or death within 2 days, which is similar to the overall result (RR 0.82, 95% CI 0.39-1.71). Two studies, including the additional RCT found, showed no significant difference in symptom resolution at day 14 (RR 1.03, 95% CI 0.95-1.11) while two other studies showed similar results at day 28 (RR 0.96, 95% CI 0.79-1.15).

These results were also similar when only considering studies that did not include other antibiotics in their SoC (RR 1.01, 95% CI 0.75-1.35, one study for resolution at 14 days (RR 0.90, 95% CI 0.76-1.08, one study for resolution at day 28).

In terms of safety, two studies showed no serious adverse events for both and intervention and control groups (RR not estimable). No studies in the meta-analysis of Popp et al. presented data for cardiac arrhythmia. The RCT of Oldenburg showed that outpatients receiving azithromycin experienced more adverse events such as diarrhea, abdominal pain, nausea and vomiting than those receiving placebo after 3 days of azithromycin intake (RR 2.14, 95% CI 1.42-3.23). Diarrhea was noted to be the most common symptom with 41% of those given azithromycin experiencing it versus 17% in the placebo group.

The overall certainty of evidence was moderate for all-cause mortality and initial symptom resolution at day 14 and day 28 due to imprecision, while admission to hospital or death had low certainty due to risk of bias and imprecision. There was low certainty for serious adverse events due to risk of bias and because zero events were reported in both of the included studies, while a moderate certainty of evidence was determined for any adverse event due to some risk of bias for outcome assessment.

Azithromycin vs Standard of Care/Placebo in Hospitalized Patients with Moderate to Severe COVID-19

For efficacy, five studies were used in pooling results for this population. The primary outcome of all-cause mortality at day 28 pooled results from four studies and showed no significant effect for azithromycin (RR 0.98, 95% CI 0.90-1.06, high certainty). One study showed no effect for clinical worsening or death at day 28 (RR 0.95, 95% CI 0.87-1.03) while three studies noted no effect on clinical improvement at day 28 (RR 0.96, 95% CI 0.84-1.11).

In terms of safety, there were no noted serious adverse events (RR 1.11, 95% CI 0.89-1.40, 4 studies) or increased risk for cardiac arrhythmias when azithromycin was used (RR 0.92, 95% CI 0.73-1.15, 4 studies) for patients with moderate to severe disease. Likewise, there was no significant increase in the incidence of any adverse events although there was a small increase in risk when azithromycin was used (RR 1.20, 95% CI 0.92-1.57, 3 studies). Certainty of evidence for worsening and improvement of clinical status as well as for serious adverse events and cardiac arrhythmias were deemed moderate for issues of indirectness and risk of bias (see Appendix 4).

Azithromycin vs Standard of Care Without Other Antibiotics Among Patients With Severe COVID-19

From the total of 7763 patients included in the Recovery Trial, those who presented with severe disease (i.e., those that needed oxygen supplementation or needed mechanical ventilation) totaled 6355. For efficacy, the 28-day mortality was noted to be not significantly different between the two groups (RR 0.97, 95% CI 0.88-1.06), as with hospital discharge after 28 days of initiation of intervention (RR 1.02, 95% CI 0.98-1.06). Among those requiring oxygen supplementation during admission, there was no noted difference in those who eventually needed mechanical ventilation (RR 0.95, 95% CI 0.87-1.03). For those who were on invasive mechanical ventilation at the start of the trial, there was also no difference in cessation of mechanical ventilation (RR 1.11, 95% CI 0.85-1.45).

In terms of safety, they investigated the occurrence of any major cardiac arrhythmias, a known adverse effect of azithromycin use. Although there was no result available for the severe population, data for the entire group (including moderate disease) was available and showed no significant difference between the control and the intervention groups (RR 0.90, 95% CI 0.72-1.14).

Azithromycin versus Other Antibiotics in the Outpatient and Inpatient Settings

One study comparing azithromycin to lincomycin in patients with moderate COVID-19 showed reduced viral clearance at day 6 (RR 0.40, 95% CI 0.17-0.93). One other study comparing azithromycin to clarithromycin showed no difference in time (MD days) to resolution of symptoms between the two regimens: for fever (MD -0.3, 95% CI -0.83-0.24; p=0.27), cough (MD -0.3, 95% CI -0.95-0.35; p=0.37), dyspnea (MD 0.1, 95% CI -0.76- 0.96; p=0.81), and GIT symptoms (MD 0.6, 95% CI 0.03-1.2; p=0.04).

Other Factors in Evidence to Decision

The wide interest in the use of azithromycin for COVID-19 management is mainly due to its antiviral and immunomodulatory effects that have been shown to result in improvement in patient status in those affected by other viral infections and pneumonia.[6] However, evidence from multiple studies have already shown its ineffectiveness in the absence of any bacterial co-infection. Even if it is readily available, the threat of antibiotic resistance, which contributes to increased financial burden and longer hospital stay, should be considered. The CDC is already concerned about outbreaks of bacterial resistance among COVID-19 units. It also warns that testing for antimicrobial resistance has been delayed in many areas due to the pandemic and the full effect may only be felt many years after.[7]

Recommendations from Other Groups

Azithromycin is not recommended in all populations whether for its antimicrobial or immunomodulatory effects according to the Australian living CPG and the NICE guidelines.[8,9] The US NIH's recommendation is also against the use of azithromycin whether in combination with hydroxychloroquine or chloroquine or as an antimicrobial agent in the outpatient setting.[10]

Research Gaps

There are currently 18 listed active ongoing studies investigating antibiotics in the treatment of COVID-19 across different disease severity.

References

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[7] Center for Disease Control. COVID-19 & Antibiotic Resistance | CDC [Internet]. [cited 2021 Nov 5]. Available from: https://www.cdc.gov/drugresistance/covid19.html

[8] National Institute for Heath and Care Excellence (NICE). COVID-19 rapid guideline: Managing COVID-19 [Internet]. [cited 2021 Oct 2]. Available from: https://app.magicapp.org/#/guideline/L4Qb5n/section/E5BJJj

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[10] National institutes of Health (NIH). Nonhospitalized Adults: Therapeutic Management | COVID-19 Treatment Guidelines [Internet]. [cited 2021 Nov 5]. Available from: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

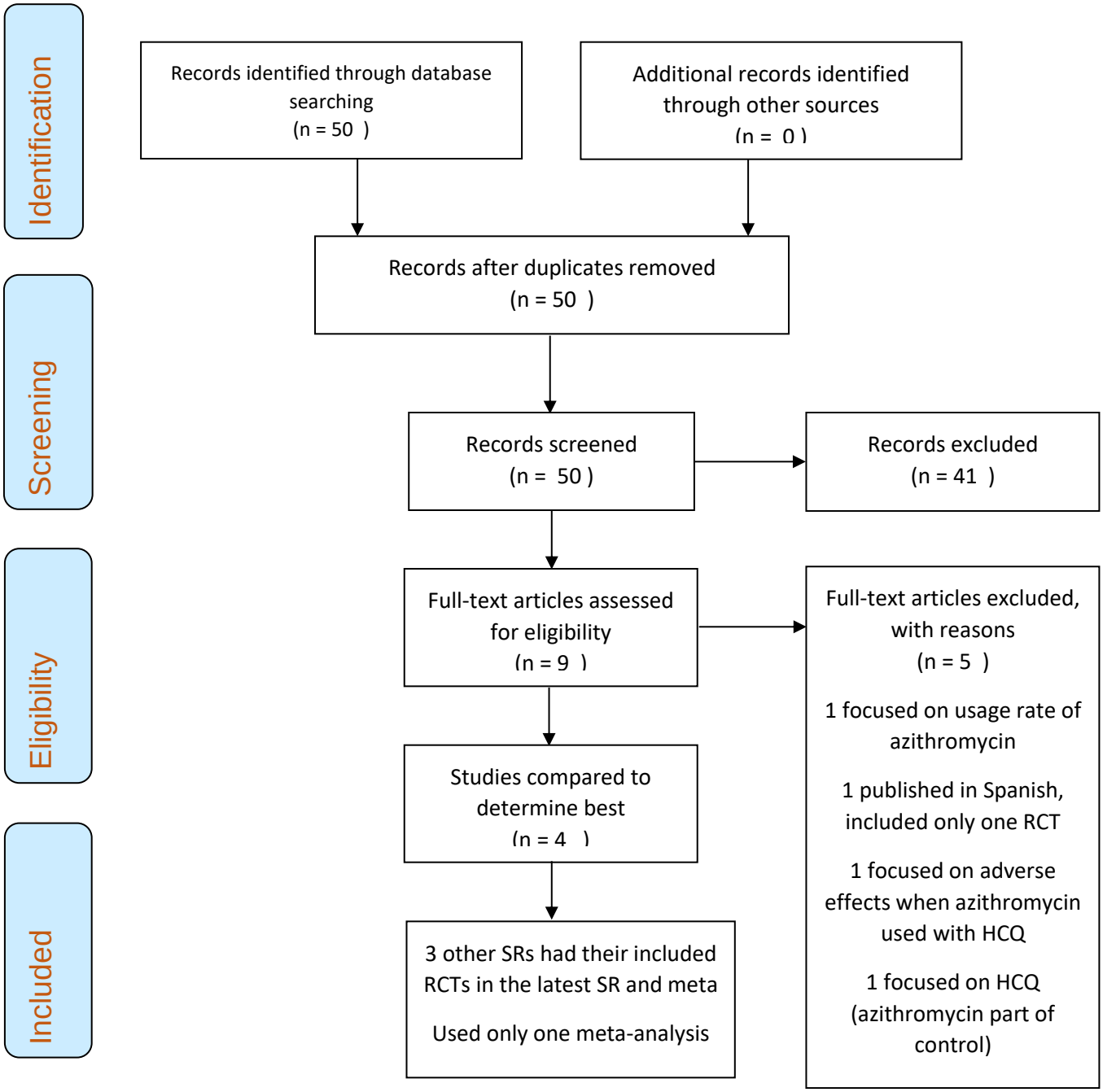
Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)				• There has been an increasing use of antimicrobials in treatment of COVID-19 despite the reported low bacterial co-infection rate. Azithromycin, a macrolide, is the most frequently used given its additional anti-inflammatory and immunomodulatory effect.
Benefits	Large	Moderate (1)	Small (3)	Uncertain (3)		• Azithromycin compared to placebo or SoC alone did not result in any significant benefit both in the inpatient (moderate to severe) and outpatient setting (asymptomatic to mild)
Harm	Large	Small (4)	Uncertain (3)			• No significant difference in serious adverse effects and cardiac arrythmias in the inpatient setting while unsure evidence in the outpatient setting (no events in treatment and control group). However no report on antimicrobial resistance rate.
Certainty of Evidence	High	Moderate (3)	Low (3)	Very low (1)		
Balance of effects	Favors drug	Does not favor drug (7)	Uncertain			• Azithromycin is readily available however the possible effect of microbial resistance can lead to longer hospital stay
Values	Important uncertainty	Possibly important	Possibly NO	No important		

	or variability (1)	uncertainty or variability (1)	important uncertainty or variability (3)	uncertainty or variability (2)			
Resources Required	Uncertain (1)	Large cost (2)	Moderate Cost (3)	Negligible cost (1)	Moderate savings	Large savings	
Certainty of evidence of required resources	No included studies (6)	Very low	Low	Moderate (1)	High		
Cost effectiveness	No included studies (5)	Favors the comparison (2)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (6)	Reduced	Probably no impact (1)	Increased			
Acceptability	Uncertain (1)	No (3)	Yes (3)				
Feasibility	Uncertain (3)	No (2)	Yes (2)				

Appendix 2. Search Yield and Results



Appendix 3. Characteristics of Included Reviews

Review Year Journal	Review aim	Search strategy	PICO	Data Analysis	Key Findings
Popp *et al* 2021 *Cochrane database of Systematic Reviews* [4]	To assess the efficacy and safety of antibiotics compared to each other, no treatment, standard of care alone or placebo or any other active intervention with proven efficacy for treatment of COVID-19 outpatients and inpatients	**Databases:** Medline, EMBASE, clinicaltrials.gov, WHO ICTRP, medRxiv, CENTRAL, Web of Science and WHO COVID-19 global literature on coronavirus disease **Language restrictions:** none **Strategy:** Complete search strategy available in appendix of published paper **Last date of search:** June 14, 2021 **Exclusion criteria:** Non-standard RCT designs (i.e. cluster-randomisation, cross-over trials), non-randomised interventional and observational studies. Antibiotic treatment for other coronavirus disease such as MERS or SARS	**Population:** Adults with RT-PCR confirmed diagnosis of COVID-19, both inpatient and outpatient **Intervention:** Any antibiotic given with antiviral and anti-inflammatory intent was eligible. All doses ang regimens were eligible **Control:** Standard of care, placebo, or co-interventions which is comparable to intervention arm, or other antibiotics **Outcome:** Analysed into two population groups: inpatients with moderate to severe COVID-19, and outpatients with asymptomatic or mild COVID-19 All-cause mortality at day 28, 60, time to event and at hospital discharge Clinical status at day 28, day 60, and up to the longest follow-up	**Risk of bias:** Cochrane RoB 2.0 tool to assess bias arising from randomsation process, due to deviations from the intended interventions, due to missing outcome data, in measurement of the outcome, in selection of reported result **Publication bias:** Contour-enhanced funnel plots **Subgroup analysis** Inpatients with moderate to severe COVID-19 and outpatients with asymptomatic or mild COVID-19 Severity of condition at baseline based on the WHO clinical progression scale If sufficient studies, subgroup based on dose of antibiotic, route of administration and age (not enough for current review) **Sensitivity analysis** Including only low risk of bias or some concerns	11 studies included (11,281 adult participants) in qualitative synthesis, 10 studies included in quantitative synthesis (meta-analysis) 7 studies investigated treatment in inpatient settings 3 studies treatment in outpatient settings **Azithromycin vs SoC/placebo in inpatients** All-cause mortality at day 28: RR 0.98 (95% CI, 0.90-1.06), 4 studies, 8600 participants Clinical worsening or death at day 28: RR 0.95 (95% CI, 0.87-1.03), 1 study, 7311 participants

			Quality of life Serious adverse evens Adverse events Cardiac arrhythmias Additional for outpatients: Admission to hospital or death at 28 days Symptom resolution **Study design:** RCTs **Preprints:** included	Comparison of preprint articles versus peer-reviewed artciles RT PCR confirmed COVID-19 versus mixed population **Statistical analysis** Heterogeneity using chi^2 test and I^2 statistic and 95% prediction interval If sufficiently homogenous, pooled data into meta-analysis using the random-effects model (RevMan web 2020). For dichotomous outcomes, using Mantel-Haenszel method while for continuous outcomes, used the inverse-variance method	Clinical improvement at day 28 RR 0.96 (95% CI, 0.84-1.11), 3 studies, 8172 Serious adverse evenets during study period RR 1.11 (95% CI, 0.89-1.40), 4 studies, 794 Arrythmia RR 0.92 (95% CI 0.73-1.15), 4 studies, 7865 participants Adverse events (any) RR 1.20 (95% CI, 0.92-1.57), 3 studies, 355 participants **Azithromycin vs SoC/placebo in outpatients** All-cause mortality at day 28 RR 1.0 (95% CI, 0.06-15.69), 3 studies, 876 participants Admission to hospital or death at 28 days RR 0.94 (95% CI, 0.57-1.56), 3 studies, 876 participants Symptom resolution at day 14

					RR 1.03 (95% CI, 0.95-1.12), 1 study, 138 participants Symptom resolution at day 28 RR 0.95 (95% CI, 0.79-1.15), 2 studies, 549 participants Serious adverse events 0/454, 2 studies **Azithromycin vs other antibiotics in inpatients and outpatients**

Study ID	Study Design	Setting	Total population	Population	Intervention	Comparator	Outcomes
Oldenburg et al (ACTION)	Randomized controlled trial	Outpatients throughout the US	263 participants	2:1 individuals who tested positive for SARS-CoV-2 within 7 days before enrolment (symptomatic or asymptomatic) Exclusion: younger than 18yrs old, had self-reported macrolide allergy, concurrently taking HCQ if older than 55, concurrently taking nelfinavir or warfarin, pregnant, unable to receive study drug in the mail or to complete online questionnaires	Single oral dose 1.2g azithromycin suspension (sent via overnight mail) n=171	Placebo with similar packaging n=92	Self-reported absence of COVID-19 symptoms at day 14 Adverse events at day 3 Hospitalizsation and/or death by day 21, patient reported COVID-19 symptoms at day 21

Appendix 4. AMSTAR-2 rating for systematic reviews and meta-analysis

AMSTAR Items	Popp (2021)
Date of last search	June 14, 2021
Rating of overall confidence in the results of the review[§]	**HIGH**
1. Research questions, inclusion criteria include PICO components	YES
2.* Protocol registered before commencement of the review	YES
3. Selection of study designs to be included were explained	YES
4.* Adequacy of literature search	YES
5. Study selection done by at least 2 reviewers	YES
6. Data extraction done by at least 2 reviewers	YES
7.* Justification for excluding individual studies	YES
8. Described included studies in adequate detail	YES
9.* ROB from individual studies being included in the review	YES
10. Reported sources of funding for studies included	YES
11.* Appropriateness of meta-analytical methods	YES
12. Potential impact of ROB in individual studies	YES
13.* Consideration of ROB when interpreting review results	YES
14. Sufficient explanation of heterogeneity	YES
15.* Assessment of presence and likely impact of publication bias	YES
16. Reported potential COI sources, funding they received	YES

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1. Popp M, Stegemann M, Riemer M, Metzendorf M-I, Romero CS, Mikolajewska A, Kranke P, Meybohm P, Skoetz N, Weibel S. Antibiotics for the treatment of COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 10. Art. No.: CD015025.doi: 10.1002/14651858.CD015025.

NOTES:

§ AMSTAR-2 rating for overall confidence.

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

- **High** - No or 1 non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- **Moderate** - More than 1 non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- **Low** - 1 critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- **Critically low** - More than 1 critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

Appendix 5. Cochrane Risk of Bias Assessment

Study	Randomization	Deviation from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Oldenburg	No concern	No concern	No concern	Some concern (self -reported, all communication done via telephone or email)	No concern	Some concern due to self-reporting of outcome

Appendix 6. Summary of Findings and Forest plots [4]

Summary of findings 1. Azithromycin compared to placebo or standard of care alone for inpatients with confirmed moderate to severe COVID-19

Patient or population: people with moderate to severe disease (WHO scale 4 to 9)

Setting: inpatient

Intervention: azithromycin

Comparison: placebo or standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty in the evidence (GRADE)	Comment
	Risk with placebo or standard of care	Risk with azithromycin				
All-cause mortality at day 28	223 per 1000	**219 per 1000** (201 to 236)	**RR 0.98** (0.90 to 1.06)	8600 (4 RCTs)	⊕⊕⊕⊕ High[a]	Azithromycin has little or no effect on all-cause mortality at day 28
Worsening of clinical status: participants with clinical deterioration (new need for invasive mechanical ventilation) or death at day 28	261 per 1000	**248 per 1000** (227 to 269)	**RR 0.95** (0.87 to 1.03)	7311 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	Azithromycin probably has little or no effect on worsening of clinical status or death at day 28
Improvement of clinical status: participants discharged alive at day 28	672 per 1000	**645 per 1000** (564 to 746)	**RR 0.96** (0.84 to 1.11)	8172 (3 RCTs)	⊕⊕⊕⊖ Moderate[c]	Azithromycin probably has little or no effect on improvement of clinical status at day 28
Quality of life at longest follow-up available	NA	NA	NA	(0 RCTs)	NA	No study was found that looked at quality of life.
Serious adverse events during the study period	214 per 1000	**238 per 1000** (190 to 300)	**RR 1.11** (0.89 to 1.40)	794 (4 RCTs)	⊕⊕⊕⊖ Moderate[d]	Azithromycin probably has little or no effect on serious adverse events during the study period

Any adverse events during the study period	333 per 1000	**400 per 1000** (306 to 523)	**RR 1.20** (0.92 to 1.57)	355 (3 RCTs)	⊕⊕⊖⊖ Low[e]	Azithromycin may increase any adverse events slightly during the study period
Cardiac arrhythmias during the study period	45 per 1000	**41 per 1000** (33 to 52)	**RR 0.92** (0.73 to 1.15)	7865 (4 RCTs)	⊕⊕⊕⊖ Moderate[f]	Azithromycin probably has little or no effect on cardiac arrhythmias during the study period

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

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 the 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.

[a]No change of result in sensitivity analysis (RR 1.04; 95% CI 0.82 to 1.31; 837 participants; 3 studies) excluding studies with mixed populations (negative or unknown RT-PCR). Therefore, no downgrading of evidence for indirectness.
[b]Downgrade by one level for serious indirectness due to the effect estimate based on only one study with a mixed population (8.5% participants with negative or unknown RT-PCR).
[c]Downgrade by one level for serious heterogeneity ($I^2 = 49\%$). No change of result in sensitivity analysis (RR 0.89; 95% CI 0.65 to 1.21; 402 participants; 2 studies) excluding studies with mixed populations (negative or unknown RT-PCR). Therefore, no downgrading of evidence for indirectness.
[d]Downgrade by one level for serious risk of bias due to an as-treated analysis in the study with the highest weight (97.0%). The certainty of evidence was not downgraded due to indirectness, even if the imprecision of the effect estimate had increased in the sensitivity analysis excluding the study with a mixed population (RR 0.98; 95% CI 0.26 to 3.60; 355 participants; 3 studies), as the same study was already the reason for downgrading due to risk of bias.
[e]Downgrade by one level for serious risk of bias due to non-blinded outcome assessment in the study with the highest weight (87.7%), and one level for serious imprecision due to few small studies.
[f]Downgrade by one level for serious indirectness due to the effect estimate based mainly (weight 99.1%) on two studies with mixed populations (8.5% and 11% participants with negative or unknown RT-PCR).

Summary of findings 2. Azithromycin compared to placebo or standard of care alone for outpatients with confirmed asymptomatic or mild COVID-19

Patient or population: people with mild disease (WHO scale 1 to 3)

Setting: outpatient

Intervention: azithromycin

Comparison: placebo or standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty in the evidence (GRADE)	Comment
	Risk with placebo or standard of care	Risk with azithromycin				
All-cause mortality at day 28	2 per 1000	**2 per 1000** (0 to 31)	**RR 1.00** (0.06 to 15.69)	876 (3 RCTs)	⊕⊕⊖⊖ Low[a]	Azithromycin may have little or no effect on all-cause mortality at day 28
Admission to hospital or death within 28 days	67 per 1000	**63 per 1000** (38 to 105)	**RR 0.94** (0.57 to 1.56)	876 (3 RCTs)	⊕⊕⊖⊖ Low[b]	Azithromycin may have little or no effect on admission to hospital or death within 28 days
Serious adverse events during the study period	Two studies assessed serious adverse events during the study period, but none of the participants in either group were affected		Not estimable	454 (2 RCTs)	⊕⊖⊖⊖ Very low[d]	We are uncertain whether azithromycin increases or reduces serious adverse events.
Cardiac arrhythmias during the study period	NA	NA	NA	(0 RCTs)	NA	No study was found that looked at cardiac arrhythmias during the study period

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk on the comparison group and the __relative effect__ of the intervention (and its 95% confidence interval).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

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 the possibility that it is substantially different.

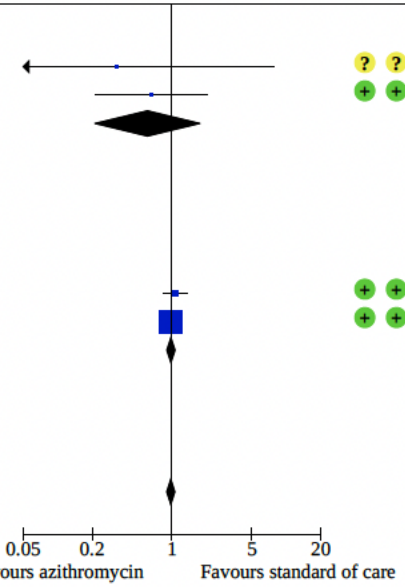
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

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.

[a]Downgrade by one level for serious risk of bias due to possible trial context related deviations from the intended interventions in that study contributing events to the analysis; and by one level for serious imprecision due to a wide confidence interval and few events.
[b]Downgrade by one level for serious risk of bias due to possible trial context related deviations from the intended interventions in one study and lack of registering the outcome in another study; and by one level for serious imprecision due to a wide confidence interval.
[c]Downgrade by two levels for very serious imprecision due to the effect estimate based on one small study.
[d]Downgrade by one level for serious risk of bias due to possible trial context related deviations from the intended interventions in one study and lack of registering the outcome in the other study; and by two levels for very serious imprecision due to zero events in both studies.

Analysis 1.1. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 1: All-cause mortality at day 28

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Moderate disease (WHO 4 to 5)						
Sekhavati 2020 (1)	0	56	1	55	0.1%	0.33 [0.01 , 7.87]
Cavalcanti 2020 (2)	5	172	7	159	0.5%	0.66 [0.21 , 2.04]
Subtotal (95% CI)		**228**		**214**	**0.6%**	**0.61 [0.21 , 1.77]**
Total events:	5		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
1.1.2 Moderate to severe disease (WHO 4 to 9)						
Furtado 2020 (3)	90	212	73	183	12.3%	1.06 [0.84 , 1.35]
RECOVERY 2021 (4)	561	2582	1162	5181	87.1%	0.97 [0.89 , 1.06]
Subtotal (95% CI)		**2794**		**5364**	**99.4%**	**0.98 [0.90 , 1.07]**
Total events:	651		1235			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**3022**		**5578**	**100.0%**	**0.98 [0.90 , 1.06]**
Total events:	656		1243			
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 3 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Chi² = 0.76, df = 1 (P = 0.38), I² = 0%						



Footnotes

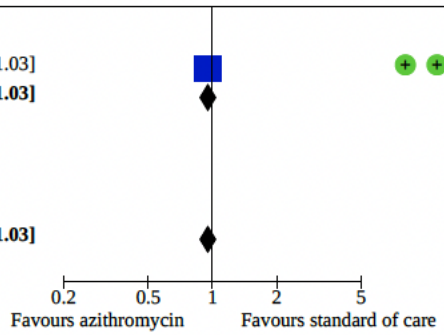
(1) Time point of outcome assessment (30 days); participants (WHO 4; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (28 days); participants (WHO 4-5; only RT-PCR positive); comparator (standard of care)
(3) Time point of outcome assessment (29 days); participants (WHO 5-7; only RT-PCR positive); comparator (standard of care)
(4) Time point of outcome assessment (28 days); participants (WHO 4-7; 91.5% RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 2: Worsening of clinical status: participants with clinical deterioration (new need for invasive mechanical ventilation) or death at day 28

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Moderate to severe disease (WHO 4-9)						
RECOVERY 2021 (1)	603	2430	1273	4881	100.0%	0.95 [0.87 , 1.03]
Subtotal (95% CI)		**2430**		**4881**	**100.0%**	**0.95 [0.87 , 1.03]**
Total events:	603		1273			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.16 (P = 0.24)						
Total (95% CI)		**2430**		**4881**	**100.0%**	**0.95 [0.87 , 1.03]**
Total events:	603		1273			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.16 (P = 0.24)						
Test for subgroup differences: Not applicable						



Footnotes

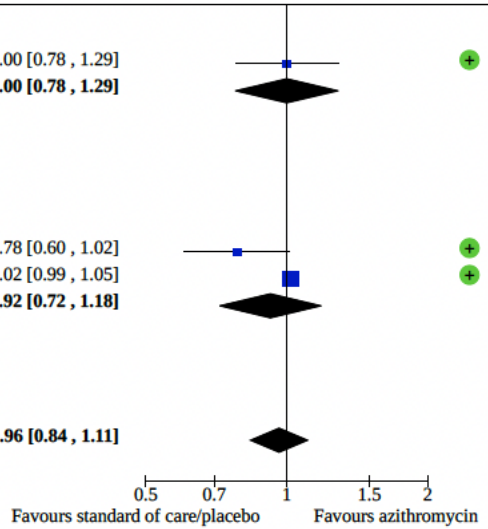
(1) Time point of outcome assessment (28 days); participants (WHO 4-6; 91.5% RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 3: Improvement of clinical status: participants discharged alive at day 28

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.3.1 Moderate disease (WHO 4-5)							
CJWT629A12301 (1)	7	7	7	7	20.5%	1.00 [0.78 , 1.29]	+ + + + + +
Subtotal (95% CI)		**7**		**7**	**20.5%**	**1.00 [0.78 , 1.29]**	
Total events:	7		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
1.3.2 Moderate to severe disease (WHO 4-9)							
Furtado 2020 (2)	69	212	76	183	19.9%	0.78 [0.60 , 1.02]	+ + + + + +
RECOVERY 2021 (3)	1788	2582	3525	5181	59.6%	1.02 [0.99 , 1.05]	+ + + + + +
Subtotal (95% CI)		**2794**		**5364**	**79.5%**	**0.92 [0.72 , 1.18]**	
Total events:	1857		3601				
Heterogeneity: Tau² = 0.03; Chi² = 3.91, df = 1 (P = 0.05); I² = 74%							
Test for overall effect: Z = 0.63 (P = 0.53)							
Total (95% CI)		**2801**		**5371**	**100.0%**	**0.96 [0.84 , 1.11]**	
Total events:	1864		3608				
Heterogeneity: Tau² = 0.01; Chi² = 3.92, df = 2 (P = 0.14); I² = 49%							
Test for overall effect: Z = 0.53 (P = 0.60)							
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%							



Footnotes

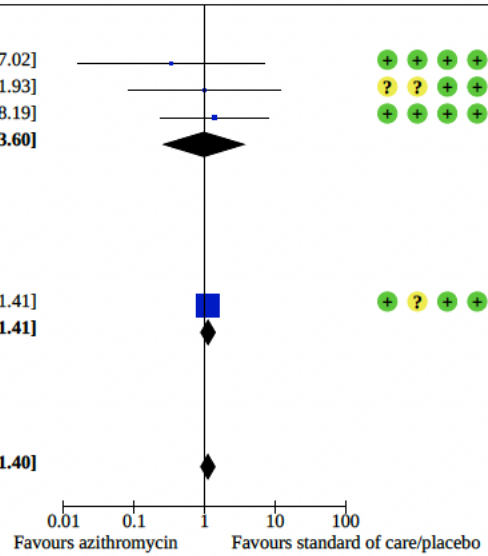
(1) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (placebo)
(2) Time point of outcome assessment (29 days); participants (WHO 5-7; only RT-PCR positive); comparator (standard of care)
(3) Time point of outcome assessment (28 days); participants (WHO 4-7; 91.5% RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 4: Serious adverse events during the study period, defined as number of participants with any event

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.4.1 Moderate disease (WHO 4-5)												
CJWT629A12301 (1)	0	7	1	7	0.6%	0.33 [0.02 , 7.02]	+	+	+	+	+	+
NCT04335552 (2)	1	5	1	5	0.8%	1.00 [0.08 , 11.93]	?	?	+	+	?	?
Cavalcanti 2020 (3)	3	172	2	159	1.6%	1.39 [0.23 , 8.19]	+	+	+	+	+	+
Subtotal (95% CI)		**184**		**171**	**3.0%**	**0.98 [0.26 , 3.60]**						
Total events:	4		4									
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%												
Test for overall effect: Z = 0.04 (P = 0.97)												
1.4.2 Moderate to severe disease (WHO 4-9)												
Furtado 2020 (4)	102	241	75	198	97.0%	1.12 [0.89 , 1.41]	+	?	+	+	+	?
Subtotal (95% CI)		**241**		**198**	**97.0%**	**1.12 [0.89 , 1.41]**						
Total events:	102		75									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.94 (P = 0.35)												
Total (95% CI)		**425**		**369**	**100.0%**	**1.11 [0.89 , 1.40]**						
Total events:	106		79									
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 3 (P = 0.88); I² = 0%												
Test for overall effect: Z = 0.92 (P = 0.36)												
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%												



Footnotes

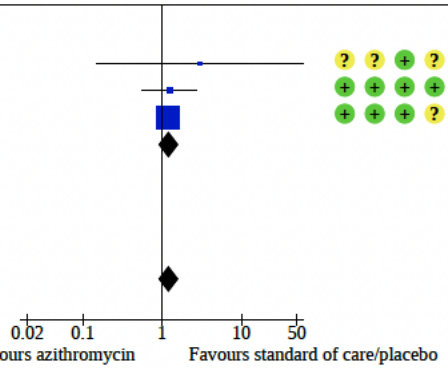
(1) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (placebo)
(2) Time point of outcome assessment (60 days); participants (WHO min. 4; only RT-PCR positive); comparator (standard of care)
(3) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (standard of care)
(4) Time point of outcome assessment (29 days); participants (WHO 5-7; 89% RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 5: Adverse events (any grade) during the study period, defined as number of participants with any event

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.5.1 Moderate disease (WHO 4-5)												
NCT04335552 (1)	1	5	0	5	0.8%	3.00 [0.15 , 59.89]	?	?	+	?	?	?
CJWT629A12301 (2)	5	7	4	7	11.5%	1.25 [0.56 , 2.77]	+	+	+	+	+	+
Cavalcanti 2020 (3)	68	172	53	159	87.7%	1.19 [0.89 , 1.58]	+	+	+	?	+	?
Subtotal (95% CI)		**184**		**171**	**100.0%**	**1.20 [0.92 , 1.57]**						
Total events:	74		57									
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.83); I² = 0%												
Test for overall effect: Z = 1.34 (P = 0.18)												
Total (95% CI)		**184**		**171**	**100.0%**	**1.20 [0.92 , 1.57]**						
Total events:	74		57									
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.83); I² = 0%												
Test for overall effect: Z = 1.34 (P = 0.18)												
Test for subgroup differences: Not applicable												



Footnotes

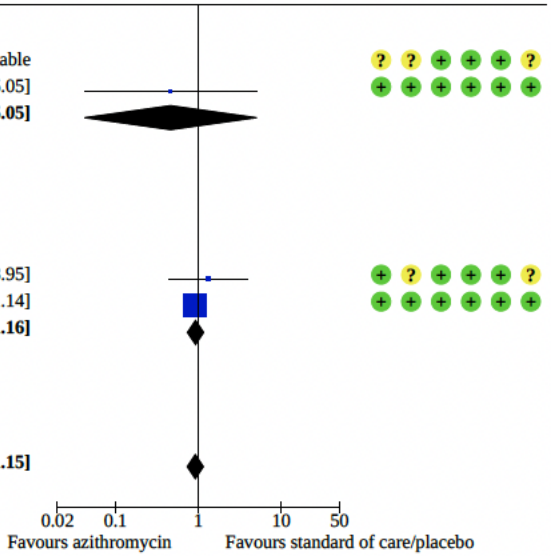
(1) Time point of outcome assessment (60 days); participants (WHO min. 4; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (placebo)
(3) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Azithromycin compared to placebo or standard of care for inpatients with confirmed moderate to severe COVID-19, Outcome 6: Cardiac arrhythmias during the study period

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Moderate disease (WHO 4-5)						
Sekhavati 2020 (1)	0	56	0	55		Not estimable
Cavalcanti 2020 (2)	1	172	2	159	0.9%	0.46 [0.04 , 5.05]
Subtotal (95% CI)		**228**		**214**	**0.9%**	**0.46 [0.04 , 5.05]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.6.2 Moderate to severe disease (WHO 4-9)						
Furtado 2020 (3)	8	241	5	198	4.1%	1.31 [0.44 , 3.95]
RECOVERY 2021 (4)	101	2314	224	4670	95.0%	0.91 [0.72 , 1.14]
Subtotal (95% CI)		**2555**		**4868**	**99.1%**	**0.92 [0.74 , 1.16]**
Total events:	109		229			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$, df = 1 (P = 0.52); $I^2 = 0\%$						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**2783**		**5082**	**100.0%**	**0.92 [0.73 , 1.15]**
Total events:	110		231			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 2 (P = 0.69); $I^2 = 0\%$						
Test for overall effect: Z = 0.75 (P = 0.46)						
Test for subgroup differences: $Chi^2 = 0.32$, df = 1 (P = 0.57), $I^2 = 0\%$						



Footnotes

(1) Time point of outcome assessment (30 days); participants (WHO 4; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (15 days); participants (WHO 4-5; only RT-PCR positive); comparator (standard of care)
(3) Time point of outcome assessment (29 days); participants (WHO 5-7; 89% RT-PCR positive); comparator (standard of care)
(4) Time point of outcome assessment (28 days); participants (WHO 4-7; 91.5% RT-PCR positive); comparator (standard of care)

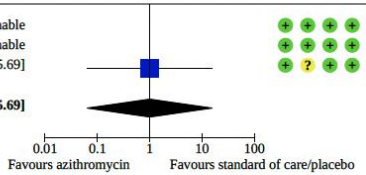
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.1. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 1: All-cause mortality at day 28

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Omrani 2020 (1)	0	152	0	152		Not estimable	+ + + + + +
PRINCIPLE 2021 (2)	0	186	0	236		Not estimable	+ + + + + +
Hinks 2020 (2)	1	75	1	75	100.0%	1.00 [0.06 , 15.69]	+ ? + + + ?
Total (95% CI)		**413**		**463**	**100.0%**	**1.00 [0.06 , 15.69]**	
Total events:	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



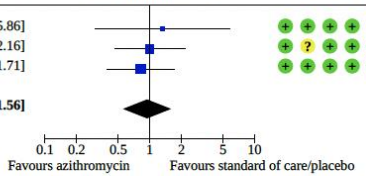
Footnotes
(1) Time point of outcome assessment (21 days); participants (WHO 1-3; only RT-PCR positive); comparator (placebo)
(2) Time point of outcome assessment (28 days); participants (WHO 2-3; only RT-PCR positive); comparator (standard of care)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 2: Admission to hospital or death within 28 days

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Omrani 2020 (1)	4	152	3	152	11.4%	1.33 [0.30 , 5.86]	+ + + + ? ?
Hinks 2020 (2)	11	75	11	75	42.0%	1.00 [0.46 , 2.16]	+ ? + + + ?
PRINCIPLE 2021 (2)	11	186	17	236	46.5%	0.82 [0.39 , 1.71]	+ + + + + +
Total (95% CI)		**413**		**463**	**100.0%**	**0.94 [0.57 , 1.56]**	
Total events:	26		31				

Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



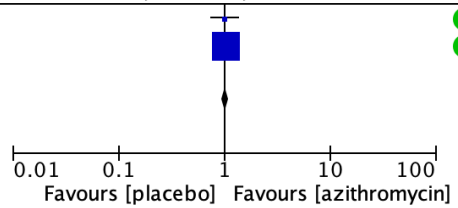
Footnotes
(1) Time point of outcome assessment (21 days); participants (WHO 1-3; only RT-PCR positive); comparator (placebo)
(2) Time point of outcome assessment (28 days); participants (WHO 2-3; only RT-PCR positive); comparator (standard of care)

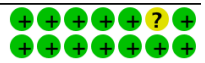
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 3: All initial symptoms resolved (asymptomatic) at day 14

Study or Subgroup	azithromycin Events	Total	placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Oldenburg	66	131	35	70	7.6%	1.01 [0.75, 1.35]
Omrani	66	69	64	69	92.4%	1.03 [0.95, 1.12]
Total (95% CI)		**200**		**139**	**100.0%**	**1.03 [0.95, 1.11]**
Total events	132		99			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0\%$
Test for overall effect: Z = 0.71 (P = 0.48)



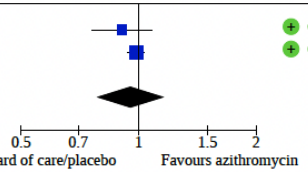


Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Analysis 2.4. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 4: All initial symptoms resolved (asymptomatic) at day 28

Study or Subgroup	Azithromycin Events	Total	Standard of care/placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
PRINCIPLE 2021 (1)	98	186	131	225	40.6%	0.90 [0.76 , 1.08]
Omrani 2020 (2)	67	69	68	69	59.4%	0.99 [0.94 , 1.04]
Total (95% CI)		**255**		**294**	**100.0%**	**0.95 [0.79 , 1.15]**
Total events:	165		199			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.51$, df = 1 (P = 0.03); $I^2 = 78\%$
Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Not applicable



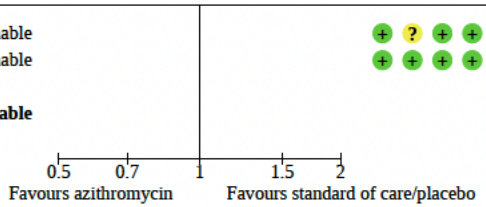
Footnotes
(1) Time point of outcome assessment (28 days); participants (WHO 2-3; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (21 days); participants (WHO 1-3; only RT-PCR positive); comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.5. Comparison 2: Azithromycin compared to placebo or standard of care for outpatients with confirmed asymptomatic or mild COVID-19, Outcome 5: Serious adverse events during the study period, defined as number of participants with any event

Study or Subgroup	Azithromycin Events	Azithromycin Total	Standard of care/placebo Events	Standard of care/placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Hinks 2020 (1)	0	75	0	75		Not estimable	+	?	+	+	+	?
Omrani 2020 (2)	0	152	0	152		Not estimable	+	+	+	+	?	?
Total (95% CI)		**227**		**227**		**Not estimable**						
Total events:	0		0									

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Footnotes

(1) Time point of outcome assessment (28 days); participants (WHO 2-3; only RT-PCR positive); comparator (standard of care)
(2) Time point of outcome assessment (21 days); participants (WHO 1-3; only RT-PCR positive); comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias