National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[B] Evidence review for azithromycin

NICE guideline NG191

June 2021

Guideline version (Final)

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Objective

This evidence review aims to evaluate the clinical effectiveness of azithromycin in people with COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the effectiveness and safety of azithromycin for acute symptoms and complications of COVID-19?

Methodology

Because there is a need for prompt guidance on managing COVID-19, NICE collaborated with other guideline development teams to produce evidence reviews. NICE has reused data from the National Australian COVID-19 clinical evidence taskforce for this review.

Evidence provided by the National Australian COVID-19 clinical evidence taskforce was used through the sharing of RevMan files, which the NICE team used to populate the evidence summary section and GRADE profiles for this review. Data extraction and risk of bias is done in line with NICE's interim process and methods for guidelines developed in response to health and social care emergencies.

Included studies

People who are hospitalised with COVID-19

Evidence comes from 4 randomised controlled trials that compared azithromycin with standard care in almost 10,000 adults hospitalised with COVID-19. (Furtado 2020; Sekhavati 2020; Cavalcanti 2020; Horby 2020). Most data are from the RECOVERY trial (Horby 2020) which included 7763 adults hospitalised with moderate-to-critical COVID-19.

Standard care within the trials varied. There were 3 trials that included hydroxychloroquine as part of standard care (Furtado 2020; Cavalcanti 2020; Sekhavati 2020). One trial also included lopinavir/ritonavir as part of standard care

as well as hydroxychloroquine (Sekhavati 2020). The largest trial, which was conducted in the UK, did not include hydroxychloroquine as part of standard care (Horby 2020). The use of corticosteroids were permitted in 3 of the trials (Horby 2020; Furtado 2020; Cavalcanti 2020).

Due to the variability in standard care, subgroup analyses were conducted for key outcomes. These subgroup analyses were for hydroxychloroquine as standard care versus no hydroxychloroquine.

All studies have been peer-reviewed.

Non-hospitalised people with COVID-19

Evidence comes from 3 randomised controlled trials that compared azithromycin with standard care in over 2000 adults with COVID-19 managed as outpatients or in the community (Omrani 2020; Butler 2021; Hinks 2021). Of these trials, 2 were conducted in the UK (Butler 2021; Hinks 2021).

Standard care within the trials varied. There was 1 trial that included hydroxychloroquine as part of standard care (Omrani 2020). The 2 trials conducted in the UK did not include hydroxychloroquine as part of standard care (Butler 2021; Hinks 2021). Concomitant corticosteroids use was reported in 1 trial (Hinks 2021).

Due to the variability in standard care, subgroup analyses were conducted for key outcomes. These subgroup analyses were for hydroxychloroquine as standard care versus no hydroxychloroquine.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 3 and 14 days. All studies used the oral route of administration for azithromycin.

There was 1 trial that was stopped early due to meeting its prespecified futility criterion (Butler 2021).

There was 1 study which is currently only available as a pre-print which means it has not yet been peer-reviewed (Hinks 2021).

Results

People who are hospitalised with COVID-19

Key results

Compared to standard care, azithromycin is no better at reducing risk of death in people in hospital with COVID-19.

Study characteristics

The mean age in the studies ranges between 50 and 67 years and the proportion of women ranged between 33 and 58%. The severity of COVID-19 across the studies was moderate-to-critical. One study only included people who required no oxygen or supplemental oxygen at baseline (Cavalcanti 2020). In the largest study, 76% of people were receiving supplemental oxygen at baseline. One study had 42% of people receiving oxygen at baseline and 49% people receiving mechanical ventilation at baseline.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 5 and 10 days. All studies used the oral route of administration for azithromycin. Two studies also used the IV route of administration (Furtado 2020 and Horby 2020) and 1 study used a nasogastric route as an option (Furtado 2020).

Children and pregnant women were excluded from the trials.

What are the main results?

Critical outcomes

All-cause mortality

Moderate quality evidence from 3 studies found no significant difference for all-cause mortality at 28-30 days with azithromycin compared with standard care for people who were hospitalised (5 fewer deaths per 1000 people [RR 0.98 95% CI 0.90 to 1.06; 8271 people in 3 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine was no different from the overall results.

Low quality evidence from 2 studies found no significant difference for all-cause mortality at 15 days with azithromycin compared with standard care for people who were hospitalised (0 fewer deaths per 1000 people [RR 1.00 95% CI 0.75 to 1.34; 728 people in 2 studies]).

Invasive mechanical ventilation

Moderate quality evidence from 1 study found no significant difference for requirement of IMV at 28-30 days with azithromycin compared with standard care for people who were hospitalised (8 fewer events per 1000 people [RR 0.92 95% CI 0.79 to 1.07; 7311 people in 1 study]).

Very low-quality evidence from 1 study found no significant difference for requirement of IMV at 15 days with azithromycin compared with standard care for people who were hospitalised (35 more events per 1000 people [RR 1.46 95% CI 0.73 to 2.92; 331 people in 1 study]).

Serious adverse events

Low quality evidence from 3 studies found no significant difference for serious adverse events with azithromycin compared with standard care for people who were hospitalised (2 more events per 1000 people [RR 1.14 95% CI 0.91 – 1.43; 8640 people in 3 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine were no different from the overall results.

Important outcomes

Discharge from hospital

Low quality evidence from 2 studies found no significant difference for discharge from hospital at 29 days with azithromycin compared with standard care for people who were hospitalised (54 fewer events per 1000 people [RR 0.92 95% CI 0.71 to 1.19; 8161 people in 2 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine remained non-significant. However, there were differences in direction of effect (with hydroxychloroquine RR 0.78 95% CI 0.6 to 1.01; 397 people in 1 study; without hydroxychloroquine RR 1.02 95% CI 0.99 to 1.05; 7764 people in 1 study).

Very low-quality evidence from 2 studies found no significant difference for discharge from hospital at 15 days with azithromycin compared with standard care for people who were hospitalised (42 fewer events per 1000 people [RR 0.92 95% CI 0.82 to 1.02; 728 people in 2 studies]).

ICU admission

Low quality evidence from 1 study found no significant difference for ICU admission with azithromycin compared with standard care for people who were hospitalised (91 fewer events per 1000 people [RR 0.28 95% CI 0.06 to 1.29; 111 people in 1 study]).

Duration of hospital stay

Very low-quality evidence from 2 studies found no significant difference for duration of hospital stay with azithromycin compared with standard care for people who were hospitalised (MD -0.41 days 95% CI -2.42 to 1.59; 442 people in 2 studies).

Adverse events

Very low-quality evidence from 1 study found no significant difference for adverse events with azithromycin compared with standard care for people who were hospitalised (57 more events per 1000 people [RR 1.17 95% CI 0.91 to 1.50; 438 people in 1 study]).

See appendix D for full GRADE profiles and see appendix C for forest plots.

Our confidence in the results

There were few concerns around risk of bias of studies. Although all studies were open label, it was not considered high risk of bias for the outcomes reported. This is because the objective outcomes such as all-cause mortality will not likely be affected by knowledge of intervention allocation. Other outcomes such as discharge from hospital could be affected by knowledge of intervention, but is probably unlikely in the pandemic situation. One study reported minor deviation from intervention protocols where some patients in the standard care arms also received azithromycin (Cavalcanti 2020). Outcomes that included this study were downgraded for risk of bias (serious adverse events, adverse events, duration of hospital stay and discharge from hospital).

The outcome discharge from hospital was downgraded for serious inconsistency due to statistical heterogeneity of I^2 of more than 50%.

Where an outcome was informed only by studies that had hydroxychloroquine as standard care, the outcome was downgraded due to serious indirectness. This is because hydroxychloroquine is not the current standard of care in the UK. This included 15-day all-cause mortality, 15-day invasive mechanical ventilation, 15-day discharge from hospital, ICU admission, duration of hospital stay and adverse events outcomes.

All outcomes were downgraded for imprecision due to the 95% CI crossing the line of no effect or if only 1 study informed the outcome.

Non-hospitalised people with COVID-19

Key results

Compared to standard care, azithromycin probably does not reduce the risk of hospitalisation or death in people with COVID-19 managed in the community.

Study characteristics

The mean age in the studies ranges between 40 and 60 years and the proportion of women ranged between 48 and 57%. The PRINCIPLE trial recruited people who were 65 years or older or 50 years older with at least 1 comorbidity (Butler 2021). Whilst the Q-PROTECT trial planned to recruit women, over 98% were males (Omrani 2020). This was due female quarantine areas in Qatar often being inaccessible to male study physicians.

The severity of COVID-19 across the studies was mild to moderate but without the need for hospital admission.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 3 and 14 days.

Children and pregnant women were excluded from the trials.

What are the main results?

Critical outcomes

All-cause mortality
Low quality evidence from 3 studies found no significant difference for all-cause mortality with azithromycin compared with standard care for people who were managed as outpatients (0 fewer deaths per 1000 people [RR 1.01 95% CI 0.06 to 16.05; 1919 people in 3 studies]). There were no deaths reported in 2 of these studies (Omrani 2020 and Butler 2020). This meant that subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine was not possible.

Hospitalisation or death (composite)
Low quality evidence from 2 studies found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 people [RR 0.92 95% CI 0.59 to 1.43; 1615 people in 2 studies]).

Low quality evidence from 1 study found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients (13 fewer events per 1000 people [RR 0.82 95% CI 0.39 to 1.71; 422 people in 1 study]).

NIV/IMV or death (composite)
Moderate quality evidence from 1 study found no significant difference for NIV/IMV or death for azithromycin compared with standard care for people who were managed as outpatients (0 fewer events per 1000 [RR 1.01 95% CI 0.14 to 7.10; 292

people in 1 study]).

Invasive mechanical ventilation or ECMO
Low quality evidence from 1 study found no significant difference for IMV or ECMO for azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 [RR 0.50 95% CI 0.10 to 2.59; 1121 people in 1 study]).

Important outcomes

Virologic clearance
Low quality evidence from 1 study found no significant difference for virologic clearance at day 6 for azithromycin compared with standard care for people who were managed as outpatients (22 fewer events per 1000 [RR 0.83 95% CI 0.44 to 1.54; 301 people in 1 study]).

Low quality evidence from 1 study found no significant difference for virologic clearance at day 14 for azithromycin compared with standard care for people who were managed as outpatients (86 fewer per 1000 [RR 0.70 95% CI 0.46 to 1.05; 295 people in 1 study]).

Patient-reported clinical recovery
Patient reported recovery was defined as the first instance that a participant reported feeling recovered (Butler 2021).

Very low-quality evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients (38 more events per 1000 [RR 1.05 95% CI 0.99 to 1.11; 1323 people in 1 study]).

Very low-quality evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients (41 more events per 1000 people [RR 1.06 95% CI 0.94 to 1.20; 422 people in 1 study]).

Sustained clinical recovery
Sustained clinical recovery was defined as a participant who reported feeling recovered and subsequently remained well until 28 days after random assignment (Butler 2021).

Very low-quality evidence from 1 study found no significant difference for sustained clinical recovery at 28 days for azithromycin compared with standard care for people

who were managed as outpatients (26 fewer events per 1000 people [RR 0.96 95% CI 0.88 to 1.05; 1129 people in 1 study]).

ICU admission
Very low-quality evidence from 1 study found no significant difference for ICU admission at 28 days for azithromycin compared with standard care for people who were managed as outpatients (2 fewer ICU admissions per 1000 people [RR 0.76 95% CI 0.18 to 3.15; 1120 people in 1 study]).

Supplemental oxygen
Very low-quality evidence from 1 study found no significant difference for need for supplemental oxygen at 28 days for azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 people [RR 0.84 95% CI 0.38 to 1.85; 1122 people from 1 study]).

See appendix D for full GRADE profiles and see appendix C for forest plots.

Our confidence in the results

Although all studies were open label, it was not considered high risk of bias for the mortality and invasive mechanical ventilation outcomes reported. However, outcomes which were considered more subjective were downgraded for risk of bias due to lack of blinding (patient-reported clinical recovery, sustained clinical recovery, ICU admission and supplemental oxygen). 1 study was unclear in how it accounted for missing data. Outcomes that included this study were downgraded for risk of bias (all-cause mortality, hospitalisation or death, invasive mechanical ventilation, patient-reported recovery, sustained clinical recovery, ICU admission and supplemental oxygen).

All outcomes were downgraded for imprecision due to the 95% CI crossing the line of no effect or if only 1 study informed the outcome.

Evidence to decision

Benefits and harms

The panel considered that the results from studies of azithromycin for moderate to critical COVID-19 in the hospital setting and mild to moderate COVID-19 in the community setting showed no meaningful benefit in any of the critical outcomes. They were also aware of the known cardiotoxicity risks associated with macrolide antibiotics. Considering this, the panel decided that the findings could not justify the use of azithromycin to treat COVID-19. They were also concerned that using azithromycin in this way may increase antimicrobial resistance and could have important antibiotic stewardship implications.

Certainty of the evidence

For people in hospital, the certainty of the evidence for azithromycin for COVID-19 on all-cause mortality and invasive mechanical ventilation is moderate. This is because of serious imprecision with the confidence interval crossing the line of no effect. The certainty of the evidence for serious adverse events is low. This is because of serious risk of bias for some concerns around deviation from treatment protocols and serious imprecision for very few events.

The certainty of the evidence for other important outcomes for azithromycin for COVID-19 in people in hospital ranges from low to very low. This is because of serious risk of bias (for some concerns around deviation from treatment protocols) and serious imprecision (for very few events; only 1 study contributing to an outcome or the confidence interval crossing the line of no effect). The panel also considered that using hydroxychloroquine as standard care does not reflect current standard practice. Outcomes that were informed by evidence mainly from studies using hydroxychloroquine as standard care have therefore been downgraded for indirectness.

The certainty of the evidence ranges from moderate to low for the critical outcomes and very low for important outcomes for azithromycin for COVID-19 in the community setting. This is generally because of serious risk of bias (for concerns about missing data and incomplete reporting in 1 study, and lack of blinding for more subjective outcomes) and serious imprecision (for few events or only 1 study contributing to the outcome).

Values and preferences

The panel were not aware of any systematically collected data on preferences and values but they identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical

ventilation and serious adverse events. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes including less serious adverse events, discharge from hospital, duration of hospital stay and longer-term outcomes such as functional independence are likely to be of particular importance to patients. These outcomes were not as commonly reported in studies.

The panel inferred that, in view of the lack of meaningful benefit for people with COVID-19, the potential for harm and the risk of causing antimicrobial resistance, most would not choose azithromycin.

Resources

Cost effectiveness was not assessed as part of the evidence review.

Equity

The panel were not aware of any evidence for azithromycin use in children or pregnancy. However, because the overall recommendation is not to offer azithromycin to anyone, it is not expected to cause inequity among any subgroups.

Acceptability

The panel were not aware of any systematically collected evidence about acceptability. However, considering the important antibiotic stewardship implications and no evidence of effectiveness to treat COVID-19, use of azithromycin would not be acceptable unless there are other licensed indications for which its use remains appropriate.

Feasibility

The panel were not aware of any systematically collected evidence about feasibility.

Azithromycin is not used for treating COVID-19 in the UK, so the recommendation supports current practice.

Appendices

Appendix A: PICO table

PICO table

What is the effectiveness and safety of pharmacological and non-pharmacological treatments for acute symptoms and complications of COVID-19?

Criteria	Notes
Population	Adults, young people and children with suspected or confirmed COVID-19.
Interventions	Pharmacological and non-pharmacological treatments that has the potential to be used to treat COVID-19
Comparators	• Standard care alone, standard care plus placebo, placebo or active comparator Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone, remdesivir).
Outcomes	Those marked with an * are critical outcomes • All-cause mortality (n/N)* • Duration of invasive mechanical ventilation (IMV) (days)* • IMV or death (composite) (n/N)* • IMV (number of patients requiring IMV who were not already receiving IMV at randomisation) (n/N)* • Number of patients experiencing one or more serious adverse events (n/N)* • Reduction in hospitalisation* • Duration of supplemental oxygen (days) • NIC/HFNO (number of patients requiring NIV/HFNO who were not already receiving NIV/HFNO at randomisation) (n/N) • Supplemental oxygen (number of patients requiring supplemental oxygen who were not already receiving supplemental oxygen at randomisation) (n/N) • Number of patients experiencing one or more adverse events (n/N)

	• Number of patients who discontinued treatment due to an adverse event (n/N) • Number of patients experiencing septic shock (n/N) • Number of patients experiencing resolution of dyspnoea/breathlessness (n/N) • Number of patients requiring hospitalization (n/N) • Number of patients requiring admission to intensive care (n/N) • Duration of hospital stay (days) • Number of patients discharged from hospital (n/N) • Virological clearance (number of patients returning a negative PCR) (n/N) • Number of patients who experienced clinical recovery (resolution of symptoms or number of patients within category 1 of an ordinal scale [non-hospitalised and returned to normal life]) • Time to recovery (days) • Number of patients who experienced clinical improvement (measured by a one or two point decrease on a 6-8 point ordinal scale, or defined as a reduction in disease severity [e.g. 'severe' to 'mild' illness]) (n/N) • Time to improvement (days) • Number of patients who experienced clinical deterioration (measured by a one or two point increase on a 6-8 point ordinal scale, or defined as an increase in disease severity [e.g. 'mild' to 'severe' illness]) (n/N) • Time to deterioration (days) • Longer-term outcomes reported in the study such as functional independence The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or

	tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above.
Settings	All settings
Subgroups	• Adults > 50 years • Children <12 years of age • Disease severity (moderate/severe/critical) • Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • Time from symptom onset • Treatment with other therapeutics used for COVID-19
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies • before and after studies • interrupted time series studies Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards

Other exclusions	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Included studies

PRINCIPLE Trial Collaborative Group (2021) Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet (London, England) 397(10279): 1063-1074

Horby (2021) Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet

Cavalcanti, A. B., Zampieri, F. G., Rosa, R. G. et al. (2020) Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med

Furtado, R. H. M., Berwanger, O., Fonseca, H. A. et al. (2020) Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet 396(10256): 959-967

Hinks TS, Cureton L, Knight R EA (2021) A randomised clinical trial of azithromycin versus standard care in ambulatory COVID-19 – the ATOMIC2 trial. medRxiv

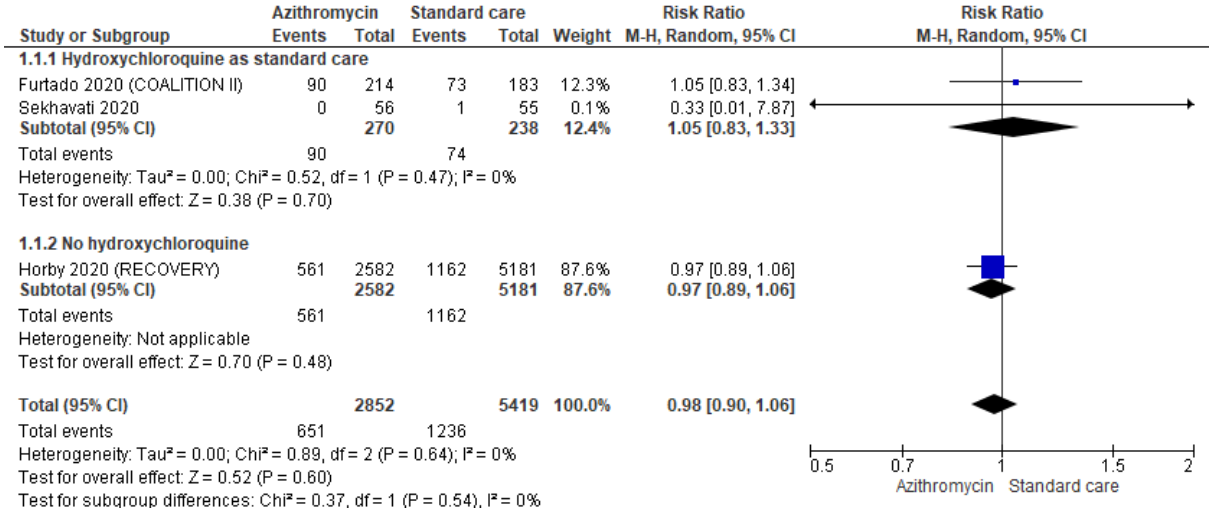
Omrani AS, Pathan SA, Thomas SA et al. (2020) Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. EClinicalMedicine 29: 100645

Sekhavati, E., Jafari, F., SeyedAlinaghi, S. et al. (2020) Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial. Int J Antimicrob Agents 56(4): 106143

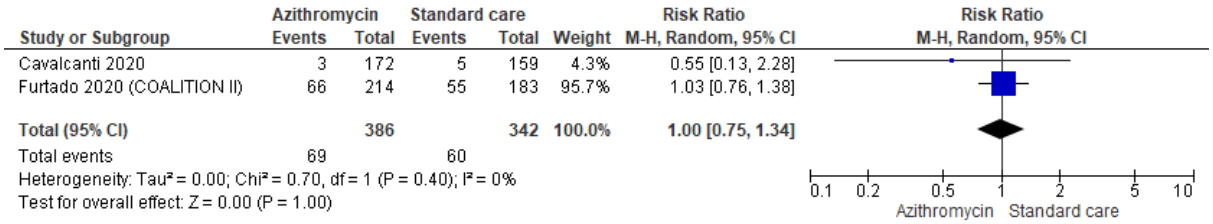
Appendix C: Forest Plots

People who are hospitalised with COVID-19

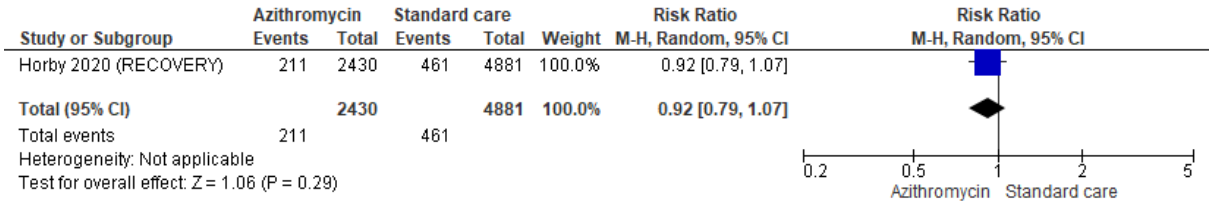
All-cause mortality (28-30 days)



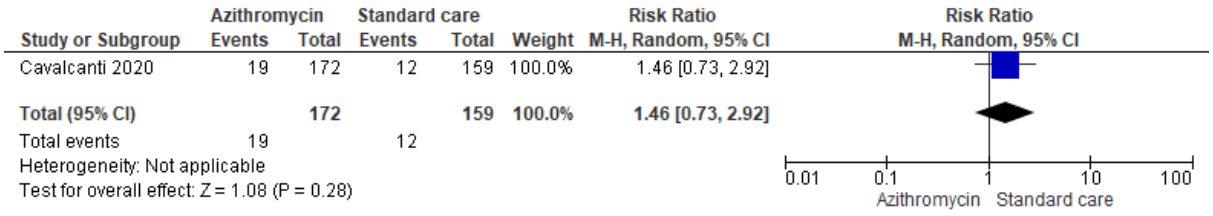
All-cause mortality (day 15)



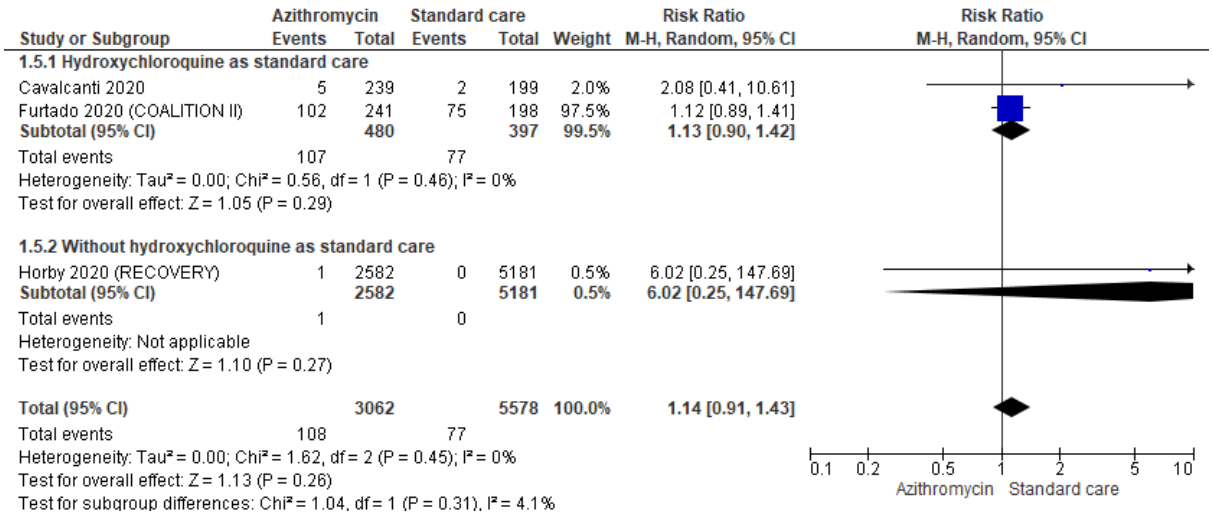
Invasive mechanical ventilation (day 28)



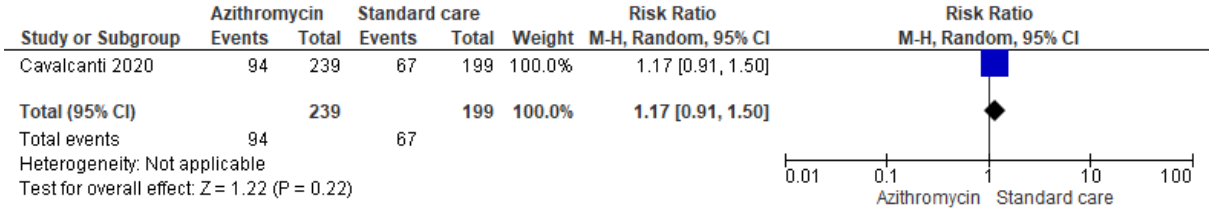
Invasive mechanical ventilation (day 15)



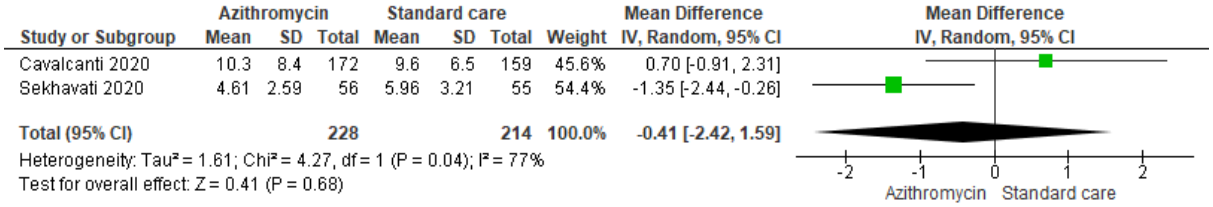
Serious adverse events



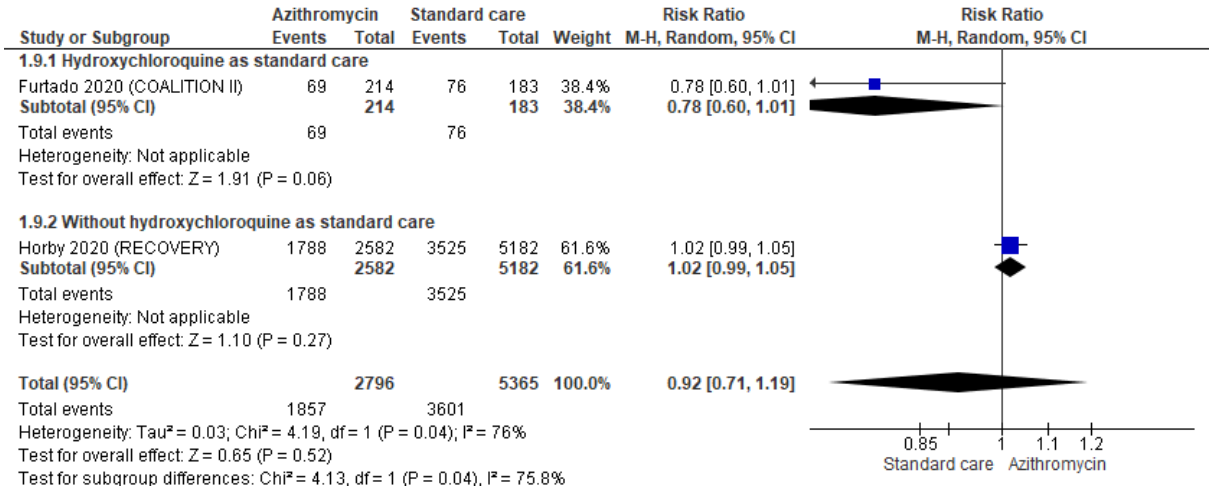
Adverse events



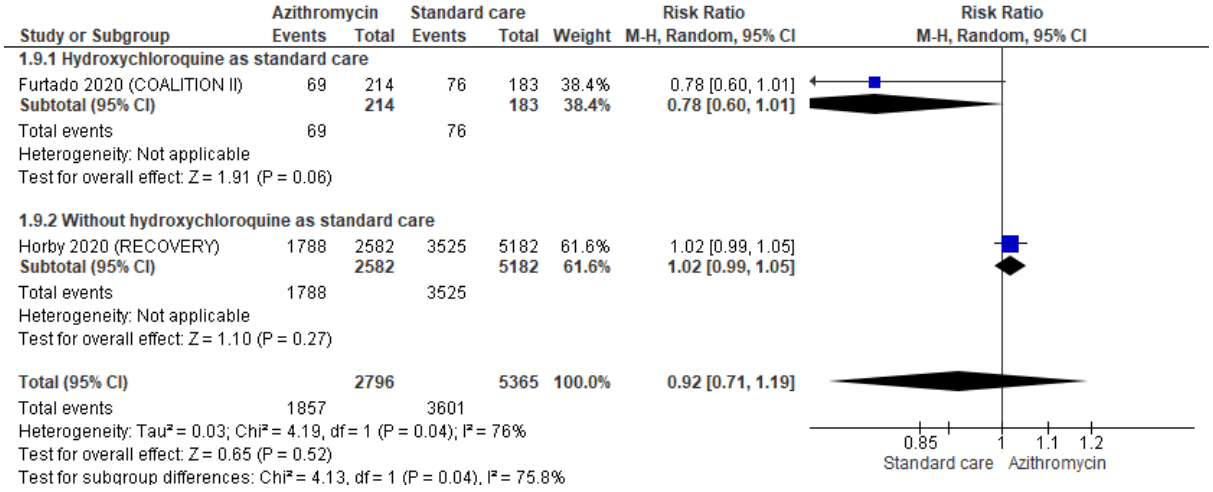
Duration of hospital stay (days)



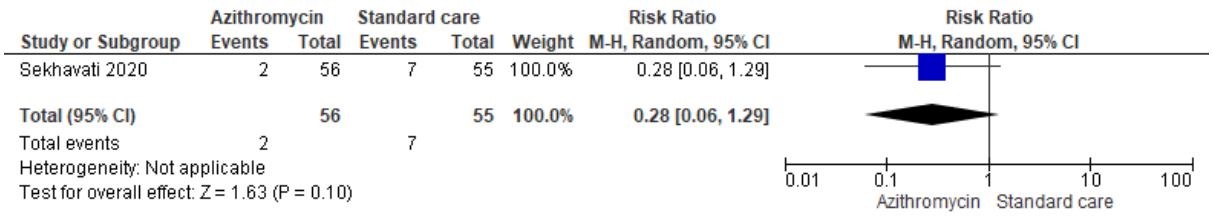
Discharge from hospital (29 days)



Discharge from hospital (day 15)

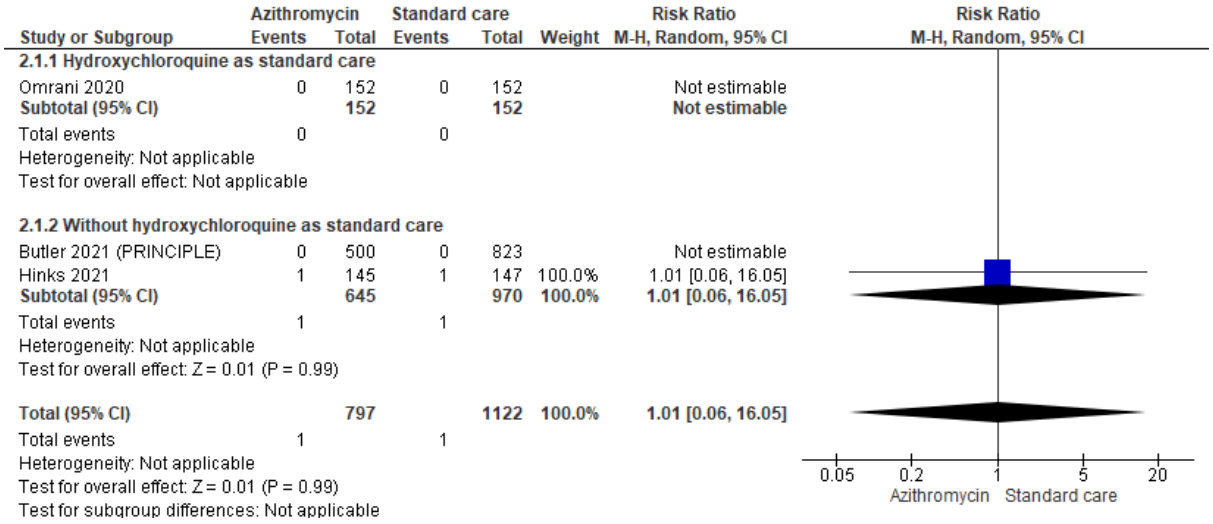


ICU admission

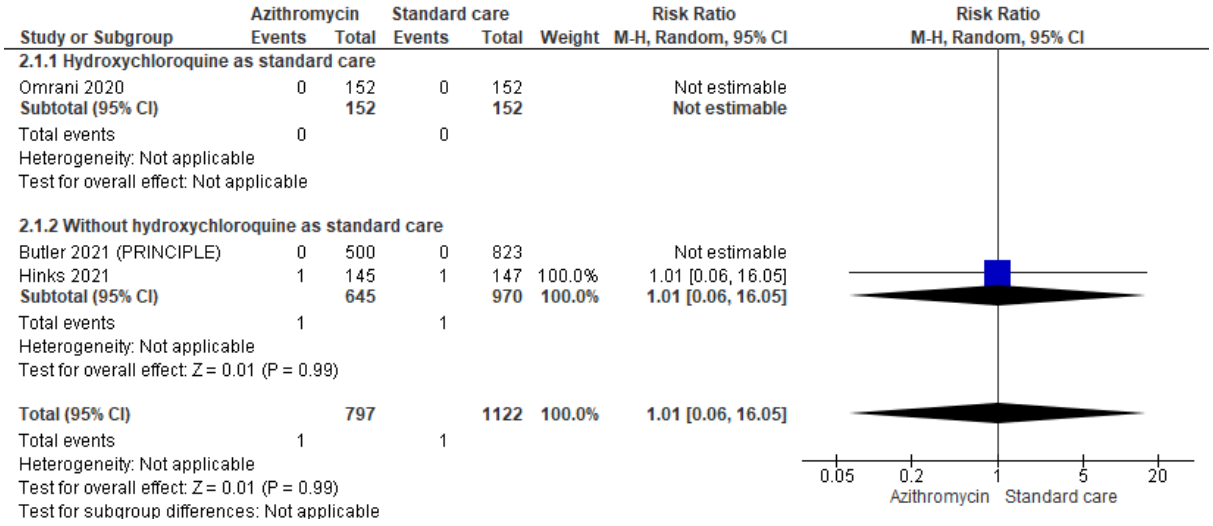


Non-hospitalised people with COVID-19

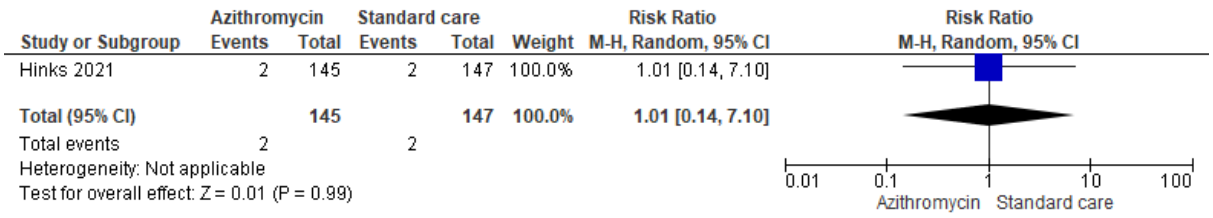
All-cause mortality



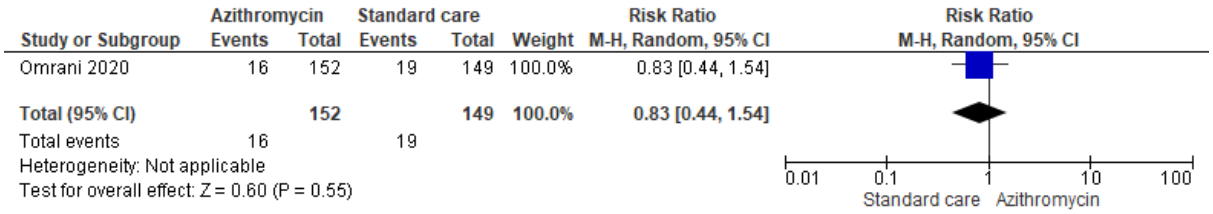
Hospitalisation or death (composite)



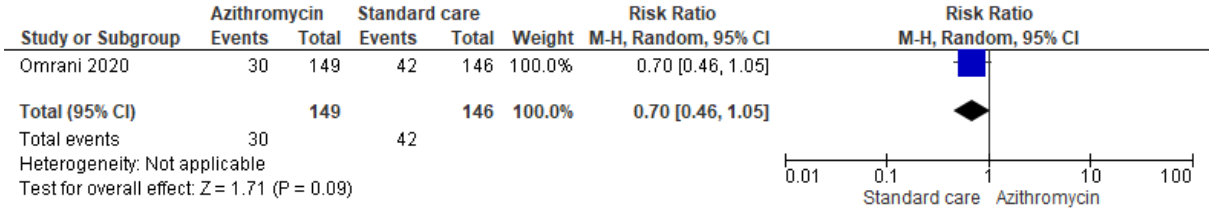
Non-invasive/invasive mechanical ventilation (composite)



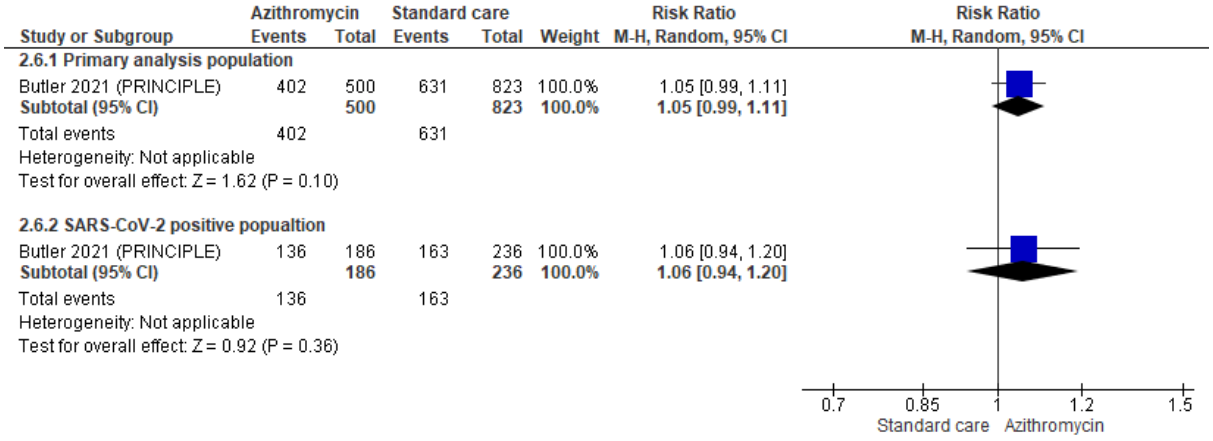
Virologic clearance at day 6



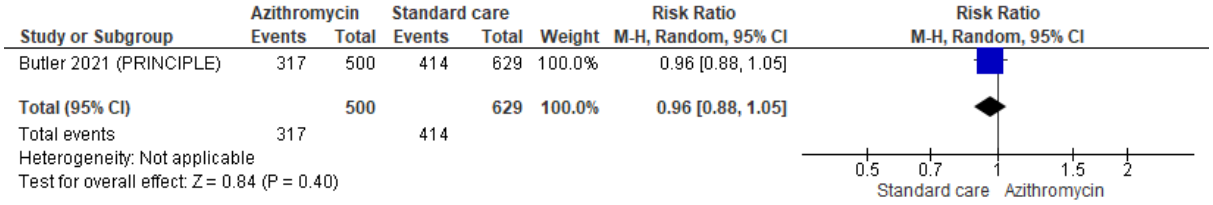
Virologic clearance at day 14



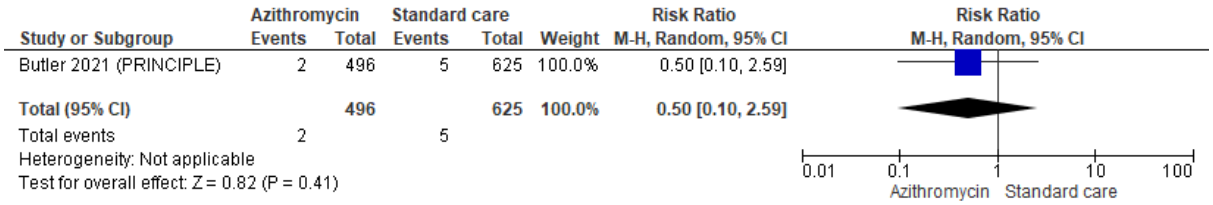
Patient reported clinical recovery (28 days)



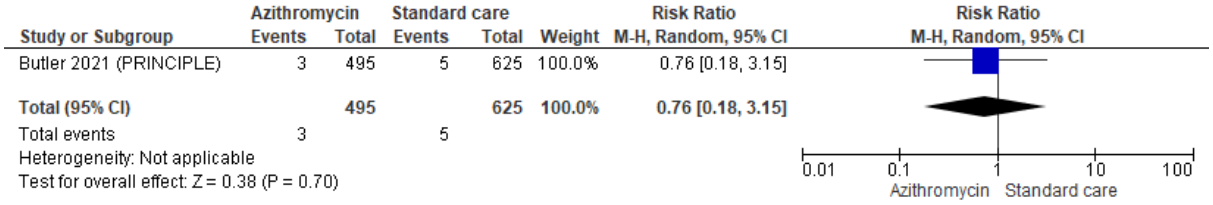
Sustained clinical recovery (28 days)



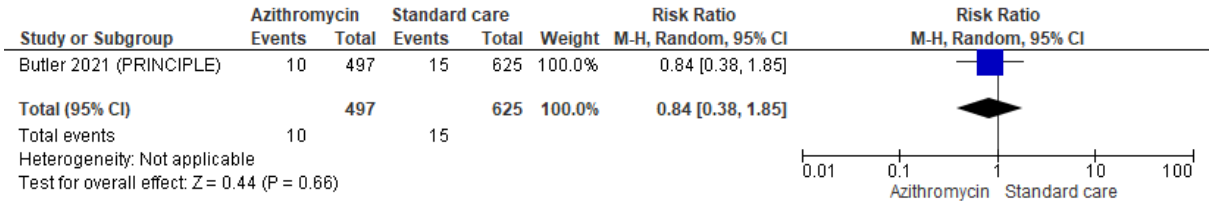
Mechanical ventilation or ECMO (day 28)



ICU admission



Supplemental oxygen



Appendix D: GRADE tables

Azithromycin compared to standard care for COVID-19: People hospitalised with COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard care	With azithromycin		Risk with standard care	Risk difference with azithromycin
All-cause mortality (follow-up: range 28 days to 30 days)											
8271 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	Moderate	1236/5419 (22.8%)	651/2852 (22.8%)	**RR 0.98** (0.90 to 1.06)	228 per 1,000	**5 fewer per 1,000** (from 23 fewer to 14 more)
All-cause mortality (follow-up: 15 days)											
728 (2 RCTs)	not serious	not serious	serious[b]	serious[c]	none	Low	60/342 (17.5%)	69/386 (17.9%)	**RR 1.00** (0.75 to 1.34)	175 per 1,000	**0 fewer per 1,000** (from 44 fewer to 60 more)
Invasive mechanical ventilation (follow-up: range 28 days to 30 days)											
7311 (1 RCT)	not serious	not serious	not serious	serious[d]	none	Moderate	461/4881 (9.4%)	211/2430 (8.7%)	**RR 0.92** (0.79 to 1.07)	94 per 1,000	**8 fewer per 1,000** (from 20 fewer to 7 more)
Invasive mechanical ventilation (follow-up: 15 days)											
331 (1 RCT)	serious[e]	not serious	serious[b]	serious[d]	none	Very low	12/159 (7.5%)	19/172 (11.0%)	**RR 1.46** (0.73 to 2.92)	75 per 1,000	**35 more per 1,000** (from 20 fewer to 145 more)
Serious adverse events											

Certainty assessment							Summary of findings				
8640 (3 RCTs)	serious[e]	not serious	not serious	serious[f]	none	Low	77/5578 (1.4%)	108/3062 (3.5%)	**RR 1.14** (0.91 to 1.43)	14 per 1,000	**2 more per 1,000** (from 1 fewer to 6 more)

Discharge from hospital (follow-up: 29 days)

728 (2 RCTs)	serious[e]	not serious	serious[b]	serious[g]	none	Very low	178/342 (52.0%)	176/386 (45.6%)	**RR 0.92** (0.82 to 1.02)	520 per 1,000	**42 fewer per 1,000** (from 94 fewer to 10 more)

ICU admission

111 (1 RCT)	not serious	not serious	serious[b]	serious[d]	none	Low	7/55 (12.7%)	2/56 (3.6%)	**RR 0.28** (0.06 to 1.29)	127 per 1,000	**92 fewer per 1,000** (from 120 fewer to 37 more)

Adverse events

438 (1 RCT)	serious[e]	not serious	serious[b]	serious[d]	none	Very low	67/199 (33.7%)	94/239 (39.3%)	**RR 1.17** (0.91 to 1.50)	337 per 1,000	**57 more per 1,000** (from 30 fewer to 168 more)

Duration of hospital stay (assessed with: Number of days)

442 (2 RCTs)	serious[e]	serious[h]	serious[b]	serious[a]	none	Very low	214	228	-	The mean duration of hospital stay was 0 days	MD 0.41 days fewer (2.42 fewer to 1.59 more)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 95% CI crosses the line of no effect
b. due to use of hydroxychloroquine as standard care.
c. due to 95% CI crosses the line of no effect, Only data from one study
d. Only data from one study
e. due to minor deviation from intervention
f. due to few events
g. 95% CI crosses line of no effect
h. The magnitude of statistical heterogeneity was high, with I^2 77%.

Azithromycin compared to standard care for COVID-19: People not hospitalised for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard care	With azithromycin		Risk with standard care	Risk difference with azithromycin
All-cause mortality (follow-up: range 28 days to 30 days)											
1919 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	Low	1/1122 (0.1%)	1/797 (0.1%)	**RR 1.01** (0.06 to 16.05)	1 per 1,000	**0 fewer per 1,000** (from 1 fewer to 13 more)
Supplemental oxygen (follow-up: 28 days)											
1122 (1 RCT)	very serious[c]	not serious	not serious	serious[d]	none	Very low	15/625 (2.4%)	10/497 (2.0%)	**RR 0.84** (0.38 to 1.85)	24 per 1,000	**4 fewer per 1,000** (from 15 fewer to 20 more)
ICU admission (follow-up: 28 days)											
1120 (1 RCT)	very serious[c]	not serious	serious[e]	serious[d]	none	Very low	5/625 (0.8%)	3/495 (0.6%)	**RR 0.76** (0.18 to 3.15)	8 per 1,000	**2 fewer per 1,000** (from 7 fewer to 17 more)
Sustained clinical recovery (follow-up: 28 days)											
1129 (1 RCT)	very serious[c]	not serious	not serious	serious[d]	none	Very low	414/629 (65.8%)	317/500 (63.4%)	**RR 0.96** (0.88 to 1.05)	658 per 1,000	**26 fewer per 1,000** (from 79 fewer to 33 more)
Hospitalisation or death (composite) - All patients (follow-up: 28 days)											

Certainty assessment							Summary of findings				
1615 (2 RCTs)	serious[a]	not serious	not serious	serious[f]	none	Low	45/970 (4.6%)	31/645 (4.8%)	**RR 0.92** (0.59 to 1.43)	46 per 1,000	**4 fewer per 1,000** (from 19 fewer to 20 more)

Hospitalisation or death (composite) - SARS-CoV-2 positive population (follow-up: 28 days)

422 (1 RCT)	serious[a]	not serious	not serious	serious[f]	none	Low	17/236 (7.2%)	11/186 (5.9%)	**RR 0.82** (0.39 to 1.71)	72 per 1,000	**13 fewer per 1,000** (from 44 fewer to 51 more)

NIV/IMV or death (composite) (follow-up: 28 days)

292 (1 RCT)	not serious	not serious	not serious	serious[d]	none	Moderate	2/147 (1.4%)	2/145 (1.4%)	**RR 1.01** (0.14 to 7.10)	14 per 1,000	**0 fewer per 1,000** (from 12 fewer to 83 more)

Invasive mechanical ventilation or ECMO (follow-up: 28 days)

1121 (1 RCT)	serious[a]	not serious	not serious	serious[d]	none	Low	5/625 (0.8%)	2/496 (0.4%)	**RR 0.50** (0.10 to 2.59)	8 per 1,000	**4 fewer per 1,000** (from 7 fewer to 13 more)

Virologic clearance (follow-up: 6 days)

301 (1 RCT)	not serious	not serious	serious[e]	serious[d]	none	Low	19/149 (12.8%)	16/152 (10.5%)	**RR 0.83** (0.44 to 1.54)	128 per 1,000	**22 fewer per 1,000** (from 71 fewer to 69 more)

Virologic clearance (follow-up: 14 days)

295 (1 RCT)	not serious	not serious	serious[e]	serious[f]	none	Low	42/146 (28.8%)	30/149 (20.1%)	**RR 0.70** (0.46 to 1.05)	288 per 1,000	**86 fewer per 1,000** (from 155 fewer to 14 more)

Patient reported clinical recovery - All patients (follow-up: 28 days)

Certainty assessment							Summary of findings				
1323 (1 RCT)	very serious[c]	not serious	not serious	serious[d]	none	Very low	631/823 (76.7%)	402/500 (80.4%)	**RR 1.05** (0.99 to 1.11)	767 per 1,000	**38 more per 1,000** (from 8 fewer to 84 more)

Patient reported clinical recovery - SARS-CoV-2 positive population

422 (1 RCT)	very serious[c]	not serious	not serious	serious[d]	none	Very low	163/236 (69.1%)	136/186 (73.1%)	**RR 1.06** (0.94 to 1.20)	691 per 1,000	**41 more per 1,000** (from 41 fewer to 138 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. Incomplete data and/or large loss to follow up
b. due to few events
c. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up
d. Only data from one study
e. due to use of hydroxychloroquine as standard care.
f. 95% CI crosses line of no effect