**South African National Department of Health**
**Brief Report of Rapid Review**
**Component: COVID-19**

## TITLE: AZITHROMYCIN FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

**Date: 9 April 2021** *(update of initial review of 11 May 2020)*

### Key findings

- We conducted a rapid review of clinical evidence for azithromycin in the management of COVID-19. The search for this update focused specifically on studies in which azithromycin was tested as a single agent, and not combined with other repurposed medicines (such as hydroxychloroquine or chloroquine).
- We found two randomised controlled studies which assessed the efficacy and safety of azithromycin for COVID-19, one in hospitalised patients, the other in ambulatory patients, both compared to standard of care.
- In the PRINCIPLE trial, a Bayesian platform study in ambulatory patients (n= 2265), there was no difference in progression to hospitalisation between the two groups (16/500 (3%) in the azithromycin arm vs 28/823 (3%) in the usual care arm). There were no deaths in either study arm.
- Horby et al. (RECOVERY trial; n=7363), found that azithromycin administered intravenously or by nasogastric tube to hospitalised patients with COVID-19 did not reduce mortality (absolute risk reduction 0.70%; 95% CI -1.25% to 2.66%), compared to standard of care (high certainty evidence). There was also no significant difference in the duration of hospital stay or progression to invasive mechanical ventilation. One serious adverse event of pseudomembranous colitis associated with azithromycin was reported.
- We did not identify any reports on the use of azithromycin in children and pregnant women with COVID-19.
- The use of azithromycin is not recommended for the treatment of COVID-19, except where indicated for other reasons (e.g. to treat bacterial co-infections).

**NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:**

| | We recommend against the option and for the alternative **(strong)** | We suggest not to use the option or to use the alternative **(conditional)** | We suggest using either the option or the alternative **(conditional)** | We suggest using the option **(conditional)** | We recommend the option **(strong)** |
|---|---|---|---|---|---|
| **Type of recommendation** | X | | | | |

**Recommendation:** We do not recommend routine use of azithromycin for the treatment of COVID-19 in either ambulatory or hospital settings. Azithromycin use should be restricted to patients in whom there is a clear antibacterial indication.
*Rationale:* There is no evidence of benefit for routine use of azithromycin for the treatment of COVID-19.
**Level of Evidence: I to II moderate to high certainty evidence**

**Therapeutic Guidelines Sub-Committee for COVID-19:** Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair).

| Version | Date | Reviewer(s) | Recommendation and Rationale |
|---|---|---|---|
| First | 11 May 2020 | AG, KC, GM | Currently insufficient evidence to recommend routine use of azithromycin in children or adults with COVID-19, except in approved clinical trials. |
| Second | 9 April 2021 | TL, MR, AG, KC | Evidence synthesis updated with data from 2 RCTs and recommendation not to use azithromycin routinely, except where there is a clear antibacterial indication. |

## BACKGROUND

In patients infected with SARS-CoV-2, disease severity and outcomes are believed to be related to characteristics of the immune response.[1,2] The inclusion of an immunomodulant macrolide antimicrobial such as azithromycin in the treatment of COVID-19 has therefore been suggested.[3,4,5] Macrolides have shown some antiviral activity against rhinovirus, influenza virus, respiratory syncytial virus, Zika virus, and Ebola virus.

Azithromycin is currently included in many South African standard treatment guidelines, including for the treatment of bacterial infections in penicillin-allergic patients, for rickettsial infections in patients unable to take tetracyclines, and specifically for the management of atypical bacterial infections, including nosocomial pneumonia. However, azithromycin is associated with a number of adverse effects, including QTc prolongation, which can result in ventricular arrythmias.[6] Concomitant administration with other QTc-prolonging drugs, such as chloroquine or hydroxychloroquine, may increase the risk of significant QTc prolongation. Studies suggest that some of these predicted safety concerns have been encountered when azithromycin has been used in COVID-19, alone or with other repurposed medicines.[7]

Current published evidence of the efficacy and safety of azithromycin in patients with COVID-19 was reviewed.

**Note:** As of 5 April 2021, 69 clinical trials investigating the role of azithromycin in the treatment of COVID-19 are registered on various clinical trial registries (accessed from the COVID-NMA initiative platform: https://covid-nma.com/).

## RESEARCH QUESTION:

Should azithromycin be used to treat suspected or confirmed COVID-19, with or without other medicines used as standard of care?

## METHODS

For the initial rapid review four electronic databases (PubMed, Cochrane COVID Study Register, Clinicaltrials.gov and WHO ICTRP) were screened on 24 April 2020, and records of observational data were extracted and reviewed to inform the initial recommendation that there was insufficient evidence to routinely recommend azithromycin in children or adults with COVID-19.

The search strategy for this update focuses on randomised controlled trials or systematic reviews of randomised controlled trials that have been published since the initial review. The Epistemonikos L*OVE evidence platform (https://app.iloveevidence.com/) was searched for randomised controlled trials and systemic reviews on 5 April 2021. Screening of records and data extraction was conducted by one reviewer (TL) and relevant records were checked and extracted in a narrative table of results (TL and MR). The final report was reviewed by AG and KC.

The search strategies for both reviews are shown in Appendix 1.

### Eligibility criteria for review

**Population:** Patients with suspected or confirmed COVID-19, no restriction to age or disease severity.

**Intervention:** Azithromycin either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

**Comparators:** Any (standard of care/placebo or active comparator)

**Outcomes:** Mortality; progression to hospitalisation (for ambulant patients); duration of hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV2 PCR on nasopharyngeal swab; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse events, adverse reactions.

**Study designs:** Systematic reviews of randomised controlled studies or randomised controlled trials.

## RESULTS

The Epistemonikos L*OVE evidence platform (https://app.iloveevidence.com/) was searched on 5 April 2021. One reviewer screened 18 records, excluded two duplicates and identified two eligible articles.[8,9] Records that were excluded include two press release statements and randomised controlled studies where additional agents that have been shown not to be effective for COVID-19 were included in the treatment groups (i.e. chloroquine or hydroxychloroquine[10,11,12,13,14,15], lopinavir/ritonavir[16,17] or ivermectin[18]).

Data in **Table 1** reports the main characteristics and outcomes of the two included studies - one study investigating azithromycin in ambulatory care, the other in hospitalised patients.

**AMBULATORY CARE:**

The PRINCIPLE trial[8] was a UK based, primary care, open label, multi-arm, adaptive platform randomized trial (n=2265 in total, of which 2120 were included in the published analysis). The analysis included 500 patients randomized to azithromycin 500mg daily for three days plus usual care, compared with 823 randomized to usual care alone. (The balance of participants (n= 797) received other interventions.) Outcomes up to 28 days post- randomisation were reported. The primary outcomes included hospitalisation or death at 28-days.

- **Mortality:**
  There were no deaths in either study arm.

- **Hospitalisation:**
  There was no difference in COVID-19-related hospitalisations between the two arms (16/500 (3%) in the azithromycin arm vs 28/823 (3%) in usual care arm).
  2/455 (1%) in the azithromycin arm and 4/668 (1%) in usual care arm were admitted to hospital during the trial for non-COVID-19 related reasons.

- **Adverse effects:**
  A study participant withdrew from the study due to adverse effects associated with azithromycin, but no details are described. No serious adverse events were reported.

**HOSPITAL SETTING:**

The RECOVERY trial[9] was a large (n= 7763) open-label multicentre study performed at 176 hospitals in the United Kingdom that compared azithromycin (administered intravenously or by nasogastric tube) to standard of care. The primary outcome was all-cause mortality at day 28.

- **Mortality at day 28:**
  There was no difference between the azithromycin (561/2585; 22%) and comparator (1162/5181; 22%) study groups; absolute risk reduction (ARR) 0.70%; 95% CI -1.25% to 2.66% (high certainty evidence).

- **Duration of hospital stay:**
  No difference in duration of hospital stay; median 10 days for azithromycin [IQR 5 to >28] vs 11 days [5 to >28] for standard of care (moderate certainty evidence).

- **Progression to invasive mechanical ventilation:**
  No significant difference in progression to invasive mechanical ventilation; azithromycin 211/2430 (9%) vs standard of care 461/4881 (9%); ARR 0.76%, 95% CI -0.63% to 2.15%).

- **Adverse effects:**
  No significant difference was observed in the frequency of new cardiac arrhythmias [101/2314 (4.4%) vs 224/4670 (4.8%)]. There was one serious adverse effect of pseudomembranous colitis associated with azithromycin.

## CONCLUSION

For ambulatory care of COVID-19 patients, azithromycin did not reduce risk of hospitalisation. In hospitalised patients with COVID-19, azithromycin did not improve survival or the number of participants progressing to mechanical ventilation. Azithromycin did not reduce the duration of hospital stay. Azithromycin may cause serious adverse reactions, as described in regulatory authority labelling of azithromycin products. Inappropriate use of antibiotics is associated with increased antimicrobial resistance, which is a serious public health concern. Routine use of azithromycin is therefore not recommended in ambulant or hospitalised COVID-19 patients, and its use should be restricted to patients in whom there is a clear antimicrobial indication.

**Reviewers:** Trudy Leong (TL): Essential Drugs Programme, National Department of Health; Milli Reddy (MR): Better Health Programme – South Africa; Andy Gray (AG): Division of Pharmacology, University of KwaZulu-Natal; Karen Cohen (KC): Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town.

**Declaration of interests:** TL, MR, AG and KC have no interests to declare in respect of azithromycin therapy for COVID-19.

**Table 1. Characteristics of included studies**

| Citation | Study design | Population (n) | Treatment | Main findings |
|---|---|---|---|---|
| PRINCIPLE Trial Collaborative Group[8] | Open-label, multi-group, prospective, adaptive platform RCT*<br><br>Setting: Primary level – general practitioner practices | N=2120 (n=500 randomised to azithromycin, oral + usual care, n=823 to usual care alone & n=797 to other interventions)<br><br>Mean age: 60.7 years (SD 7.8)<br>Severity: Mild cases - ambulatory patients<br><br>Patient inclusion criteria: ≥ 65 years, or ≥ 50 years with comorbidities, and ongoing symptoms from PCR-confirmed or suspected COVID-19 (in accordance with the UK National Health Service [NHS] syndromic case definition of high temperature, a new, continuous cough, or a change in sense of smell or taste). Symptoms must have started within the past 14 days. | Azithromycin 500 mg, oral once daily for 3 days + usual care VS usual care alone VS other interventions.<br><br>Usual care in the NHS for suspected COVID-19 in the community is supportive and focused on managing symptoms.<br><br>Antibiotics only recommended if bacterial pneumonia suspected; guidelines recommend doxycycline. | 402/500 (80%) in the azithromycin + usual care vs 631/823 (77%) in the usual care alone group reported feeling recovered within 28 days.<br><br>Median time to first reported recovery for patients in the azithromycin + usual care was 7 days (IQR = 3 to 17) and in the usual care group was 8 days (IQR = 2 to 23). No meaningful benefit in the azithromycin + usual care group in time to first reported recovery vs usual care alone (HR1.08, 95% Bayesian credibility interval (BCI) 0.95 to 1.23)<br><br>16/500 (3%) in the azithromycin + usual care and 28/823 (3%) in the usual care group were hospitalised.<br><br>No difference in groups of how participants felt after 28 days, in time to first alleviation of symptoms, in hospitalisations, and time to reduction of severity of symptoms<br><br>No deaths in either study group.<br><br>A study participant withdrew from the study due to adverse effects associated with azithromycin, but no details are described. |
| RECOVERY Collaborative Group; Horby et al, Lancet, February 2021[9]<br><br>NCT04381936<br>ISRCTN (50189673) | Open label, multi-centre, United Kingdom, adaptive platform RCT*<br><br>Setting: 176 NHS Hospitals<br><br>Follow up: 28 days | N=7763 (n=2582 randomised to azithromycin IV/NGT, n= 5181 to SOC)<br><br>Mean age: 65.3<br>4819 males/2944 females<br>Severity: Not reported, but critical patients on invasive mechanical ventilation n=452<br><br>Patients admitted to hospital were eligible for the study if they had clinically suspected or PCR-confirmed SARS-CoV-2 infection; initially recruitment was limited ≥18 years but from 9 May 2020, the age limit was removed. | Azithromycin 500 mg once a day orally, IV/NGT for 10 days or until discharge (if sooner)<br>*vs*<br>SOC (Usual standard of care for the local hospital –expected to evolve over time)<br><br>Duration : 10 days | **Primary outcome:** All-cause mortality at day 28.<br>*Azithromycin vs SOC:* 561/2582 (22%) vs 1162/5181 (22%); RR 0·97, 95% CI 0·87 to 1·07 – no difference<br><br>**Secondary outcomes:**<br>-Discharged from hospital within 28 days: *Azithromycin vs SOC:* 1788/2582 (69%) vs 3525/5181 (68%); RR 1.04, 95 % CI 0.98 to 1.10 – no difference<br>- Time to being discharged: *Azithromycin vs SOC:* 10 (5 to >28) vs 11 (5 to >28) days – no difference<br>- Composite endpoint (Receipt of invasive mechanical ventilation or death): *Azithromycin vs SOC:* 603/2430 (25%) vs 1273/4881 (26%); RR 0·95 (0·87 to 1·03) – no difference<br><br>**Adverse effects:** |

| Citation | Study design | Population (n) | Treatment | Main findings |
|---|---|---|---|---|
| | | Patients with known prolonged QTc interval; hypersensitivity to macrolides; already on chloroquine/ hydroxychloroquine, were excluded.<br><br>Pregnant and paediatric patients were excluded. | | - Frequency of new cardiac arrhythmias: 101 (4.4%) vs 224 (4.8%) – no difference.<br>- One serious adverse effect of pseudomembranous colitis associated with azithromycin.<br><br>**Risk of bias:** Overall assessment – **Moderate** risk with some concerns.<br>There were no substantive differences in study procedures, population, interventions and outcomes between the pre-print article and the trial registries, study protocol and statistical analysis plan. The study achieved its pre-stated sample size. Adequate randomisation and allocation sequence was concealed. Intention-to-treat analysis, and although unblinded, the risk of bias for outcome of mortality considered to be low. As measurement of discharge from hospital alive (i.e. clinical improvement) requires clinical judgement, risk assessed to be of some concern as study was unblinded. Trial was analysed as pre-specified. |

* Platform trial = adaptive clinical trial in which multiple treatments for the same disease can be tested simultaneously.

## Appendix 1: Search strategy

### 24 April 2020

**PubMed**

#3: Search ((#1 AND #2) NOT (animals[mh] NOT humans[mh]))

#2: Search (coronavir*[tiab] OR coronovirus*[tiab] OR corona virus[tiab] OR virus corona[tiab] OR corono virus[tiab] OR virus corono[tiab] OR COVID-19[tiab] OR COVID19[tiab] OR 2019-nCov[tiab] OR 2019nCov[tiab] OR cv-19[tiab] OR n-cov[tiab] OR ncov*[tiab] OR hCOV*[tiab] OR SARS cov-2[tiab] OR SARS-coronavirus[tiab] OR SARS-cov[tiab] OR (wuhan*[tiab] AND (virus[tiab] OR viruses[tiab] OR viral[tiab])) OR (COVID*[tiab] AND (virus[tiab] OR viruses[tiab] OR viral[tiab])) OR MERS-cov[tiab] OR MERS cov[tiab] OR COVID-19[NM] OR severe acute respiratory syndrome coronavirus 2[nm])

#1: Search (azithromycin[mh] OR azithromycin[tiab] OR sumamed[tiab] OR zithromax[tiab] OR azitrocin[tiab] OR azadose[tiab] OR zitromax[tiab] OR macrolide[tiab] OR macrolides[tiab] OR macrolides[mh])

**Records retrieved from search #3: 34 (5 relevant to PICO question)**

**WHO ICTRP**

Downloaded Excel file from their website (1528 trials in file) – searched for azithromycin and retrieved

**Records retrieved: 45**

**Cochrane COVID Study Register (https://covid-19.cochrane.org/)**

azithromycin OR azithromycin OR sumamed OR zithromax OR azitrocin OR azadose OR zitromax OR macrolides

**Records retrieved: 45**

**Clinical trials.gov**

azithromycin OR azithromycin OR sumamed OR zithromax OR azitrocin OR azadose OR zitromax OR macrolides | SARS-COV-2 OR COVID-19 OR 2019-nCOV OR 2019 NOVEL CORONAVIRUS OR SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

**Records retrieved: 53 (44 for treatment of Covid-19)**

### 5 April 2021

**Epistemonikos L*OVE evidence platform:** https://app.iloveevidence.com/

prevention or treatment AND pharmacological intervention/azithromycin AND RCTs reporting data

**Records retrieved: 18 (2 duplicates, 2 press releases, 2 relevant to PICO question)**

## Appendix 2: Evidence to decision framework

| | JUDGEMENT | EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| EVIDENCE OF BENEFIT | **What is the size of the effect for beneficial outcomes?**<br>Large ☐ Moderate ☐ Small ☐ None ☒ Uncertain ☐ | There are no benefits in terms of any clinically important outcomes. |
| EVIDENCE OF HARMS | **What is the size of the effect for harmful outcomes?**<br>Large ☐ Moderate ☒ Small ☐ None ☐ | Azithromycin is associated with an increased risk of adverse events (as described in regulatory authority labelling of azithromycin products) |
| BENEFITS & HARMS | **Do desirable effects outweigh undesirable harms?**<br>Favours intervention ☐ Favours control ☒ Intervention = Control *or* Uncertain ☐ | |
| QUALITY OF EVIDENCE | **What is the certainty/quality of evidence?**<br>High ☐ Moderate ☒ Low ☐ Very low ☐ | |
| FEASABILITY | **Is implementation of this recommendation feasible?**<br>Yes ☐ No ☐ Uncertain ☐ | N/A* |
| RESOURCE USE | **How large are the resource requirements?**<br>More intensive ☐ Less intensive ☐ Uncertain ☐ | **Price of medicines:** N/A* |
| VALUES, PREFERENCES, ACCEPTABILITY | **Is there important uncertainty or variability about how much people value the options?**<br>Minor ☐ Major ☐ Uncertain ☐<br>**Is the option acceptable to key stakeholders?**<br>Yes ☐ No ☐ Uncertain ☐ | N/A* |
| EQUITY | **Would there be an impact on health inequity?**<br>Yes ☐ No ☐ Uncertain ☐ | N/A* |

* Judgements for these domains are not applicable, given the strong recommendation not to support use of hydroxychloroquine for treatment of COVID-19 due to the lack of evidence (benefit or harm).

### Appendix 3: Updating of rapid report

| Date | Signal | Rationale |
|---|---|---|
| 8 February 2021 | RECOVERY trial results | The RECOVERY trial results for the azithromycin arm that was reported in preprint format reported has recently been published peer-review format in the Lancet. |

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