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Daniela Vitória Pereira da Silva

Reposicionando a Azitromicina para Infecções Respiratórias Virais Agudas: uma Revisão Sistemática de Ensaios Clínicos Randomizados

"Repositioning Azithromycin for Acute Respiratory Viral Infections: A Randomized Clinical Trials Systematic Review"

Florianópolis
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Orientadora: Profa. Dra. Thaís Cristine Marques Sincero
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Este Trabalho de Conclusão de Curso foi julgado adequado para obtenção do Título de Bacharel em Farmácia e aprovado em sua forma final pelo Curso de Graduação em Farmácia do Centro de Ciências da Saúde da Universidade Federal de Santa Catarina.

Local, 11 de dezembro de 2020.

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Este trabalho é dedicado aos meus queridos pais, meu irmão
e a todas as pessoas que estão lutando contra a COVID-19.

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RESUMO

O reposicionamento torna-se uma estratégia importante para o desenvolvimento rápido e econômico de medicamentos em situações de pandemia, como a causada pelo vírus SARS-CoV-2. A azitromicina (AZM) é um antibiótico que tem demonstrado efeitos anti-inflamatórios nas doenças respiratórias crônicas. Este estudo é uma revisão sistemática de ensaios clínicos randomizados e tem como objetivo avaliar a eficácia e segurança da AZM em infecções respiratórias virais agudas. Esta revisão sistemática foi conduzida seguindo as recomendações *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) e Cochrane nos bancos de dados PubMed, Scopus e Google Acadêmico nos últimos 10 anos. A busca foi realizada por meio da estratégia de combinação de descritores/palavras-chaves e operadores booleanos. Dois pesquisadores escolheram os estudos com base nos critérios de inclusão e exclusão e coletaram os dados de forma independente e cega. Todas as discrepâncias foram resolvidas por um especialista. Após essa etapa, foi realizada uma síntese qualitativa. 838 artigos foram recuperados, e 6 artigos foram incluídos nesta revisão. Um total de 553 pacientes foram analisados. Os estudos foram realizados em hospitais do Japão, China, Irã, Brasil e EUA. Três estudos usaram o placebo como controle, dois associaram a AZM ao oseltamivir (OS) e um avaliou os efeitos da combinação da AZM com a hidroxicloroquina (HCQ). Quatro estudos demonstraram alguns efeitos benéficos da administração de AZM em infecções virais, como tendência de reduzir o tempo dos sintomas e diminuir as citocinas, e nenhum dos pacientes apresentou efeitos colaterais graves. Três estudos foram classificados com baixo risco de viés e três moderados, de acordo com a análise feita pelo *Joanna Briggs Institute* (JBI). Considerando os poucos estudos incluídos nesta revisão, algumas inconsistências e outras limitações, as evidências disponíveis até o presente momento não suportam a indicação do uso de AZM para infecções virais agudas, devendo o uso do medicamento ser restrito apenas aos casos de infecções bacterianas.

Palavras-chave: Macrolídeos. Infecções do trato respiratório. Carga viral. Prognóstico. Agentes antivirais.

Title: Repositioning Azithromycin for Acute Respiratory Viral Infections: A Randomized Clinical Trials Systematic Review

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Abstract

Drug repositioning becomes an important strategy for rapid and economic development in pandemic situations, such as that caused by the SARS-CoV-2 virus. Azithromycin (AZM) is an antibiotic that has been demonstrating anti-inflammatory effects in chronic respiratory diseases. This study is a systematic review of randomized controlled trials and aims to evaluate the effectiveness and safety of AZM in acute viral respiratory infections. This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane recommendations in the PubMed, Scopus and Google Academics databases over the past 10 years. The search was carried out using the strategy of descriptors/words and boolean operators. Two researchers chose the studies based on inclusion and exclusion criteria and collected the data independently and blindly. All discrepancies were resolved by an expert. After this stage, a qualitative synthesis was performed. 838 articles were

recovered, and 6 articles were included in this review. A total of 553 patients were analyzed. The studies were carried out in hospitals in Japan, China, Iran, Brazil, and the USA. Three studies used placebo as a control, two associated AZM with oseltamivir (OS) and one evaluated the effects of combining AZM with hydroxychloroquine (HCQ). Four studies have shown some beneficial effects of AZM administration in viral infections, such as a tendency to reduce symptom time and decrease cytokines, and none of the patients had serious side effects. Three studies were classified to have low risk of bias and three moderated according to the analysis made by Joanna Briggs Institute (JBI). Considering the few studies included in this review, some inconsistency and other limitations, until the available evidence does not support the indication of the use of AZM for acute viral infections, and the use of the drug should be restricted only to cases of bacterial infections.

Keywords: Macrolides. Respiratory Tract Infections. Viral load. Prognosis. Antiviral agents.

Introduction

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 caused by the SARS-Cov-2 virus a pandemic situation[1]. Until December 5th, 2020, 63.965.092 cases were confirmed, including 1.488.120 deaths reported to WHO[2]. Despite this current scenario, acute respiratory diseases have an important history, occupying a place between the most frequent diseases over the years, mainly among the diseases that cause the most deaths or serious outcomes, demanding an immense burden of global health[3,4,5].

Viruses are the most isolated etiological agents in samples of acute respiratory infections, with influenza, rhinovirus, respiratory syncytial virus, adenovirus, and coronavirus[7]. Despite the potential of these infections, only infections by influenza have selective treatment (oseltamivir, peramivir, and zanamivir)[8,9]. The specific treatment absence for viral infections and the evolution to severe respiratory diseases is a worrying scenario[9], above all in Severe Acute Respiratory Syndrome (SARS) cases caused by MERS-CoV and SARS-CoV-2 virus[10].

Given the complexity of treatment and the clinical evolution of viral infections, a strategy of rapid and economical drug development has been adopted by the pharmaceutical industry. The search for different mechanisms from those drugs already registered and commercialized may lead to the discovery of new indications for use. This strategy is known as drug repositioning[11,12,13].

AZM is an antibacterial that has been studied for years as a treatment and/or a viral infection control that has been used in some cases of COVID-19[14,15,16,17]. In order to promote

rational medicines uses, providing a theoretical basis for future clinical practice decisions and new clinical research, we conducted a Randomized Clinical Trials (RCT) systematic review on AZM effectiveness and safety for the treatment of in patients with acute viral infections.

Methods

This systematic review was done adhering to PRISMA[18] and Cochrane Handbook[19]. The PRISMA protocols (PRISMA-P)[20] and checklist[21] method was also used for this systematic review development.

Research question

The review's first stage is the scientific question definition[22]. This search seeks to answer the question: What are the effectiveness and safety of AZM use for the treatment of hospitalized patients with acute viral respiratory diseases? After this definition, the research question was prepared based on the PICOS strategy[23] (Table 1) for better guidance and research results[24, 25].

Identification of relevant studies

The original articles published in the last 10 years (2010 Jan - 2020 Dec) in English, Portuguese (Brazil), and Spanish journals were retrieved from systematic searches in three databases: PubMed, Scopus, and Academic Google. The search strategy included keywords/descriptor use and the Medical Subject Headings (MeSH) terminology with the best results for each of the bases (Table S2).

All articles recovered from databases were transferred to a reference management software (My EndNote Web, Thomson Reuters) and all duplicates were removed. The remaining duplicates were also detected and excluded by the Rayyan QCRI mobile and web application[26].

Studies selection

The selection of articles was conducted in two phases by two independent and blinding reviewers (DVPS and CF). In the first phase, titles and abstracts were read to eligibility, following a full PDF lecture. The disagreement cases were resolved by two other reviewers (one subject specialist and the other in review, TCMS and IGD, respectively) who determined the final study inclusion or exclusion. Exclusion reasons for the articles were added according

to the PICOS strategy: population, intervention, comparator, outcome, and study design. A PICOS structure was used to establish the eligibility criteria (Table 1)[24,25].

Inclusion: (P) only in patients (immunocompetent) with viral respiratory infections confirmed by viral diagnosis (culture, serology, or molecular methods); (I) AZM or AZM and association administration with posology; (C) placebo or other medication; (O) effectiveness assessment or safety assessment or both; (S) a prospective randomized clinical trial. Only articles with abstract and full text were included.

Exclusion: (P) outpatients, only clinical diagnosis, without laboratory tests, immunocompromised patients (HIV or transplantation); (I) other macrolides or immunomodulators (corticoids, chemotherapy); (C) without control group; (O) studies without evaluation of effectiveness and safety; (S) non-randomized clinical trial, cohort study, cross-sectional studies, case-control studies, experimental studies on animals or cells, reviews studies, expert opinion, guidelines, comments and other articles there not randomized clinical trial. Articles without abstract and/or full text not available were excluded.

Data extraction and qualitative synthesis

For all articles included the following information was recorded for the standard form: author (year), country, study design, treatment and comparison, study period, the aim of the study, therapeutic scheme (medication and control), sample, recruitment, and allocation, patients who completed the trial, cause of exclusion, gender, age (mean), use of combination immunosuppressants or steroids and dose, clinical and laboratory findings of effectiveness (significant or non-significant), safety results, conclusion and risk of bias/limitation reported by the article authors. The data will be extracted into spreadsheets and text documents stored on the Google Drive.

The articles were blinded and randomly distributed by the Research Randomizer® program (https://www.randomizer.org/) for two authors (DVPS, CF) to independently collect the data and checked the information in pairs. The articles were also blinded and randomly distributed for experts (TCMS, IGD, IFK) to remove the discrepancies. Finally, a qualitative synthesis was performed describing the findings and critically discussing the included studies.

Results

A total of 838 studies were recovered in all databases (Pubmed: 253, Scopus: 485, Academic Google: 100). After duplicates removing, 785 articles remained were evaluated by the eligibility criteria. In the first selection phase (title and abstract reading), 18 articles were

included and 767 were excluded. In the second phase (PDF reading), only six randomized clinical trials were included for data extraction (Figure 1, Flow Diagram PRISMA) (File S3).

Characteristics of included studies

Three studies were conducted in Asia (Japan China and Iran)[27,28,29], two in South America (Brazil),[30,31] and one in North America (USA)[32] (Table 2). The studies were conducted from 2012 to 2020[27,28,29,30,31,32]. Three clinical trials used placebo as the control group;[30,31,32] two an association between AZM and OS and one associated AZM with HCQ and Lopinavir/ritonavir (Kaletra®) (LPV/r)[27,28,29]. Three studies were double-masked[30,31,32] and three open-label[27,28,29]; one of which was a blocked open-label[29]. Four studies were multicenter[27,28,30,31] (Table 2).

The total number of patients recruited in all studies was 553 (AZM: 272 and control: 281), of which 301 were male and 252 female (AZM: 154/118; Control: 147/134)[27,28,29,30,31,32] (Table 2). Three studies were conducted out with babies[30,31,32] (AZM: newborns to six months; Control: one to six months) and three with adults[27,28, 29] (AZM: 33 to 68 years old; Control: 37 to 71 years old).

The studies objectives were to evaluate the AZM effectiveness in the wheezing[30,31] or hospital readmissions recurrence after the viral bronchiolitis first case[31], pro-inflammatory cytokines decrease production related to viral respiratory infections and consequent decrease in complications and symptoms related to the disease[27,28]. The effect on viral clearance[28], length of hospital stay and required oxygen was also assessed[30]. One study aimed to evaluate the effect of the combination of AZM and HCQ in the COVID-19 treatment[29].

Four studies have demonstrated some beneficial effect on the AZM administration[28,29,31,32]. One study obtained unfavorable results with the AZM use in acute viral bronchiolitis,[30] and one found unfavorable results in decreasing pro-inflammatory cytokine production but showed a potential resolution of symptoms such as fever and sore throat[27]. Four studies assessed the AZM administration adverse effects (gastrointestinal effects, dizziness, and QT[1] interval prolongation)[27,28,29,32] (Table 3).

Azithromycin versus Placebo

[1] parameter measured by the surface electrocardiogram corresponding to the period from the beginning of depolarization to the end of ventricular repolarization. Corrects for heart rate and assesses irregularities in electrical conduction and heart function.

Three double-masked studies tested AZM versus placebo in children[30,31,32]. Two were multicenter studies conducted out in Brazil for two years[30,31] (one[30] between 2009 and 2011 and another with an unspecified period[31]). One study was conducted in the USA for two consecutive winters (2011 - 2013)[32]. The three studies used an AZM oral suspension[30,31,32] and two described the placebo as a solution with AZM similar taste and appearance[31,32]. One study did not describe the placebo characteristics[30]. Both studies in Brazil used 10 mg/kg/day once a day for 7 days[30,31]. The dose used by the study conducted in the USA was 10 mg/kg once daily for 7 days, followed by 5 mg/kg once daily for an additional 5 days[32]. The children total number who completed the studies was 286 (AZM: 141 and control: 145)[30,31,32]. In the AZM group, 85 children were male and 56 female[30,31,32]. In the control group, 88 children were male and 57 female[30,31,32]. The three studies aimed to assess the AZM effects on clinical outcomes after the first acute viral bronchiolitis episode[30,31,32].

One study evaluated patients at a children's hospital who had positive nasal swabs for Respiratory Syncytial Virus (RSV)[32]. The evaluated parameters were IL-8 levels in the serum (at day 8) and in the nasal lavage (at days 8 and 15) during the hospitalization by human cytometric bead array (CBA) and wheezing recurrence or new hospitalizations/visits to emergency departments by respiratory symptoms during 50 weeks of follow-up after the AZM treatment[32]. Only the nasal lavage collected on day 15 showed a significant reduction in IL-8 levels (AZM: 2.217 pg/mL – 865 pg/mL; Control: 4.395 pg/mL - 2.318 pg/mL, on the days 8th and 15th, respectively)[32]. Significantly fewer days with respiratory symptoms (cough, wheeze, or shortness of breath) over the ensuing 50 weeks was demonstrated (AZM: 36.7 (28) vs Placebo: 70.1 (43.1) days[32]. The results showed no significant reduction in serum IL-8 levels on day 8 between the AZM and control groups (AZM: 6.971 fg/mL vs Placebo: 5.050 fg/mL)[32]. The wheezing recurrence (AZM: 39% vs Placebo: 50%), total number of episodes (AZM: 22% vs Placebo: 50%), and subsequent asthma diagnosis (AZM: 11% vs Placebo: 25%) did not show statistically significant differences between the groups during the 50-week follow-up[32]. Gastrointestinal effects (diarrhea, vomiting, or abdominal pain) were presented by 7 patients in the AZM group and 8 patients in the placebo group[32].

Children with an acute bronchiolitis clinical diagnosis were recruited in another study[31]. A nasopharyngeal sample was collected for viral identification[31]. The evaluated parameters were the patient’s clinical results during the hospitalization (length of hospital stay, and identification of respiratory viruses), recurrence of wheezing episodes or hospital admissions during 3 and 6 months after the AZM treatment[31]. The only statistically significant difference presented by the study was the decrease in wheezing recurrence in 3 months (AZM:

19.1% and Placebo: 39.5%; RR: 0.48; CI: 0.24 – 0.98)[31]. The results did not show any statistically significant differences between the AZM group and the control group concerning the length of hospital stay (AZM: 3 – 8 vs Placebo: 3 – 9 days), wheezing episodes recurrence in 6 months (AZM: 25.6% vs Placebo: 27.3%) or hospital readmission in 3 and 6 months (AZM: 8.5% and 9.3% vs Placebo: 10.5% and 3.0%, respectively)[31]. Positivity for virus detection was not statistically significant (AZM: 54.1% for any virus or 45.9% for RSV vs Placebo: 66.7% for any virus and 63.9% for the RSV)[31]. Adverse effects were not reported by the study[31].

The last study that compared AZM to placebo was a multicenter study carried out with children clinically diagnosed with acute bronchiolitis[30]. Nasopharyngeal samples were collected for viral etiology tests[28]. The parameters evaluated were the decrease in hospitalization time, the time required for supplemental oxygen, the need to use antibiotics or bronchodilators, and the admission to the pediatric intensive care unit[30]. Data showed none statistically relevant result between the group treated with AZM and the control group[30]. The length of stay was the same for both groups (5 days), and there was no age difference or virus detection. The same result was found for the required oxygen time between both groups (4 days), with no difference by age or virus detection. Adverse effects were not reported by the study[30].

The only inflammatory marker tested that showed a significant result was the IL-8 nasal level[32]. Wheezing episodes were reduced only during the first three months after treatment[31], with no sustained protection over the months[30,31]. AZM extended the time between the second and third wheezing episodes[31].

Azithromycin Combinations (OS, HCQ, LPV/r (Kaletra®)

Two multicenter open-label studies evaluated the OS and AZM combination effectiveness in adults[27,28]. One study was carried out in China during two Influenza seasons (2013 - 2016)[28] and another in Japan from Dec 2010 to Mar 2011 (during the winter)[27]. One study administered 75 mg of OS alone every 12 hours or the same scheme in association with an extended release formulation of AZM 2,000 mg once daily[27]. Duration and dose/frequency used by the other study was the same for OS but differed in the AZM dosage (500 mg once daily)[28]. The total number of adults who completed the studies was 156 (OS: 81 and OS + AZM: 75)[27,28]. In the group that received AZM, 40 patients were men and 35 women[27,28]. In the group that received OS alone, 37 patients were men and 44 were women[27,28]. The studies aimed was

to evaluate the AZM effectiveness in respiratory infections caused by Influenza through the reducing symptoms evaluation, complications incidence, and viral clearance[27,28].

One study evaluated adults admitted with Influenza A or B diagnosis confirmed by antigen testing[27]. The parameters evaluated were the levels of inflammatory markers in the serum using the cytokine bead array (IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TGF-β, IFN-γ, and TNF-α), symptoms duration, reported complications (sinusitis, otitis media, bronchitis, and pneumonia), infection duration and adverse effects[27]. Hematological measurements, biochemical, and immunological tests were also evaluated[27]. The maximum temperature between days 3 and 5 was lower in the OS + AZM group than in the OS group alone (*p-value:* 0.048), with a greater decrease on day 4 in the AZM treated group (*p-value:* 0.037)[27]. The comparison between groups showed a tendency for early fever resolution in the group treated with OS + AZM (*p-value:* 0.05 on day 2 and 0.06 on day 5)[27]. The OS + AZM group showed significant increases in red blood cell count, hemoglobin, and hematocrit values on days 2 and 5 and a significant decrease in albumin and total protein levels on day 2 (*p-value:* <0.05 and <0.01, respectively)[27]. The OS + AZM group had a potential early Influenza related symptoms resolution (such as sore throat) on days 2 and 5 (*p-value:* 0.0323 and 0.2138, respectively)[27]. Not any statistically significant difference was observed between the two groups in the inflammatory cytokines or chemokines expression after 2 or 5 treatment days[27]. No serious adverse effects occurred and no patient discontinued treatment[27]. In the OS + AZM group the number of patients who had adverse effects was 11/56 (19.6%) and in the OS alone group was 9/51 (17.6%)[30]. Adverse effects were diarrhea (3 patients in the OS + AZM group) and a decrease in leukocytes (five in the OS + AZM group and three in the OS group)[27]. One patient in the OS group developed secondary pneumonia[27].

The second study that compared the OS with AZM association was conducted in adults with severe Influenza infection manifestations, and who had an Influenza A or B confirmed diagnosis by PCR or immunofluorescence[28]. The parameters evaluated were the levels of inflammatory mediators in plasma (IL-6, CXCL8/IL-8, IL-10, IL-1b, IL-12p70, TNF-α, CCL2/MCP-1, CXCL-9/MIG, CXCL10/IP-10, and CCL3/MIP-1a by a cytometric bead assay), viral clearance (decline in RNA concentration and culture), and symptom resolution (changes in symptom scores and length of hospital stay)[28]. Chest radiography, electrocardiogram, and liver function tests were also performed[28]. The results found were a rapid decrease in levels[2] of

[2] The *p-value* was defined in two different ways (presented respectively): (A) Unadjusted between-group: comparisons by GEE (OS, OS alone; OS+AZM, OS plus AZM); (B) Between-group: comparisons by GEE, adjusted for potential confounders (comorbidity, and severity indicated by hypoxemia).

IL-6 (*p-value:* 0.016 or 0.017; AZM: 83.4% and AZM + OS: 59.5%), CXCL8/IL-8 (*p-value:* 0.056[2] or 0.081[3]; AZM: 80.5% and AZM + OS: 58.0%), IL-17 (*p-value:* 0.015 or 0.017; AZM: 74.0% and AZM + OS: 34.3%), CXCL9/MIG (*p-value:* 0.043 or 0.031; AZM: 71.3% and AZM + OS: 56.0%), TNF-α (*p-value:* 0.084[2] or 0.090[2]; AZM: 40.1% and AZM + OS: 24.8%), IL-18 (*p-value:* 0.197 or 0.201; AZM: 29.1% and AZM + OS: 30.2%) and CRP (*p-value:* 0.173 or 0.171; AZM: 77.5% and AZM + OS 48.2%)[28]. There was a trend toward faster symptom resolution in the OS plus AZM group however the symptoms resolution score was not significant (*p-value:* >0.05; AZM: 79.0% and AZM + OS: 70%). The adverse effects incidence found between the two groups was similar[28]. Only one patient stopped AZM administration after 3 days due to dizziness[28].

HCQ + LPV/r (Kaletra®)

A single open and blocked study carried out in adults for 15 days in a hospital compared the AZM association with other drugs[29]. The study aim was to evaluate the AZM benefits added to HCQ in patients with a QT prolongation low risk and arrhythmia diagnosed with COVID-19[29]. The dose administered in the AZM + HCQ + LPV/r (Kaletra®) group was 500 mg of AZM oral once daily, LPV/r 400/100 mg orally twice daily, and oral HCQ 400 mg once daily for 5 days[29]. The control group received only the HCQ and LPV/r combination in the same posology[29]. The number of patients who completed the survey was 111 (56 in the AZM + HCQ + LPV/r group and 56 in the LPV/r + HCQ group)[29]. In the group treated with the AZM association, 28 patients were male and 28 female[29]. In the group treated only with HCQ + LPV/r, 23 patients were men and 33 women[29]. The parameters evaluated were vital signs (body temperature, respiratory rate, heart rate, and SpO_2), hospitalization duration, admission to the intensive care unit (ICU) need and duration, mortality rate, and follow-up results after 30 days of discharge[29]. The statistically significant differences found were regarding myalgia (AZM: 18 or 32.14% vs without AZM: 22 or 74.55%), weakness (AZM: 10 or 17.86% vs without AZM: 3 or 5.45%), headache (AZM: 6 or 10.71% vs without AZM: 18 or 32.7%), vomiting (AZM: 7 or 12.5% vs without AZM: 16 or 29.09%), length of hospital stay (AZM: 5 ± 2.59 vs without AZM: 6 ± 3.21), high SpO_2 levels at discharge (AZM: 93.95% ± 2.14 vs without AZM: 92.40% ± 4.58), and respiratory rate lower (AZM: 15.85 ± 1.99 vs without AZM:17.42 ± 2.42 breaths/min) in the AZM treated group[29]. No statistically significant results were found in SpO_2 (between admission and day 3 89.36% vs 88.75% with or without

[3] *p-value*:<0.10

AZM, respectively), mortality (with AZM: 0 vs without AZM: 1), need for intubation (with AZM: 0 vs without AZM: 3), fever (with AZM: 38 vs without AZM: 33), dyspnea (with AZM: 41 vs without AZM: 43), chills (with AZM: 18 vs without AZM: 25), cough (with AZM: 34 vs without AZM: 41), sputum production (with AZM: 3 vs without AZM: 8), hemoptysis with (AZM: 3 vs without AZM: 0), chest pain with (AZM: 10 vs without AZM: 12), need for ICU admission (AZM: 2 vs without AZM: 7) or in the ICU hospitalization duration (AZM: 5.00 vs without AZM: 4.43)[29]. The study applied a scoring system before starting treatment to predict the QT prolongation risk[29]. The patient's QT interval was monitored, and none showed prolongation during treatment[29].

Risk of Bias

Three studies were classified to have low risk of bias and three moderated according to the analysis made by Joanna Briggs Institute (JBI)[33]. For three studies[27,28,29] the response to questions "Were participants blind to treatment assignment?" and "Were those delivering treatment blind to treatment assignments?" was scored as "high-risk of bias" because the participants and delivering were not concealed (Table 4). In this systematic review, five studies reported the small number of samples as a risk of bias[27,28,29,31,32].

Discussion

AZM is a significant macrolide antibacterial used to treat infections caused by some susceptible organisms. In the present review, we showed the AZM effectiveness on viral respiratory infections. Effectiveness is already well proven for the treatment of upper and lower respiratory tract infections, acute otitis media, skin/soft tissues, and in some sexually transmitted infections cases[34]. Some studies have shown the macrolides effectiveness, especially AZM, also relating to anti-inflammatory effects. It explains the current protocols for this drug recommendation to use in chronic lung diseases such as COPD and cystic fibrosis[35,36]. It use is well controlled by the protocols that are indicated only in last cases, after preferential therapy failure and also a great risk of respiratory exacerbations[35]. Recommendations reinforce the need for caution when prescribing AZM because it is related to the resistant microorganisms selection and side effects[35,36]. In 2013, the Food and Drug Administration (FDA) agency has included AZM in the list of drugs that can cause QT interval prolongation[36,37]. Despite the main research being carried out in chronic use cases in diseases with an important inflammatory response, some researchers have used these results to investigate the beneficial

immunomodulation effects of AZM on the immune system response in cases of acute infections[14,15,16,17,39-40].

The lung is extensively exposed to contaminants in the air[5]. For lung defense, a system formed by secretory epithelial cells and immune cells (macrophages and dendritic cells) is present in the tissue[35]. Damage to host cells occurs during viral infection through the process of internalization and replication, activating the cell apoptosis mechanism[35,38]. The apoptosis process has some role in the pathophysiology, but the main complications are caused by the host's unbalanced response to surviving viruses and infected cells. These observations explain why different virions can cause similar clinical syndromes and sequels. The recognized viral infection leads to cytokines and chemokines release for the recruitment and activation of more defense cells at the infection site[38,41,42]. The major objective of the immune system is to eliminate infection, restore injured tissue and prevent tissue destruction during the process[42,45]. The hyperresponsiveness of the innate system that occurs in some cases leads to uncontrolled anti-inflammatory regulatory mechanisms and host cells are also affected. The tissue is infiltrated by defense cells attracted by chemotaxis; the increase in monocytes/macrophages and neutrophils was observed in lung samples from patients with respiratory viral infections[43,44,47]. As a consequence of cytokine/chemokine contact occurs host cell involvement and apoptosis. The death of normal host cells has several consequences for example, the death of pulmonary epithelial and endothelial cells that lead to increased vascular permeability and alveolar edema, with impaired blood oxygenation and maintenance of homeostasis. The extensive infiltration of macrophages can lead to fibrosis and pulmonary involvement with severe outcomes for the patient[44]. Pro-inflammatory cytokines, such as IL 6, IL-8, IL-1B, GM-CSF, reactive oxygen species and chemokines such as CCL2, IP-10 and CCL3 contribute to this condition[44]. Increased immune cells and cytokines and chemokines are associated with more severe forms of acute viral respiratory infections (pneumonia and SARS); and increased need for admission to an ICU or administration of supplemental oxygen[43,45,46,47].

Based on these findings, we conducted a systematic review to assess the anti-inflammatory AZM effects in acute viral infections. Our results demonstrate that the number of randomized clinical trials on this subject is limited and significant differences were found between study designs. The different clinical parameters evaluated, as well as differences in dosage, frequency, inclusion criteria, and even the controls used make meta-analysis impossible, decreasing the quality of the evidence in this study. Some studies have similar evaluation parameters, and although collected on different days, the results differ each other. Only one study showed significant decreases concerning to myalgia, weakness, headache,

vomiting, length of hospital stay, and differences in SpO_2 (at discharge)[29]. The other studies did not show a decrease in hospital stay[30,31]. Some studies have shown a tendency to resolve symptoms earlier compared to control, although some of the values presented were not statistically significant[27,28]. The reduction in serum IL-8 demonstrated by Lee et al (2017)[28] was not observed by Kakeya et al (2014)[27], and Beigelmand et al (2015)[32]. The levels of IL-6 and TNF-alpha were also not compatible between the studies[27,28]. However, the *p-value* found by Lee et al (2017)[28] was higher than 0.05, and the authors used a *p-value* of 0.10 to consider the significance of the results, which implies an increase in the study bias. Another study also considered a p-value greater than 0.05 for the analysis of symptom resolution on day 5[27]. In the three studies carried out, the use of AZM during the first case of acute viral infection did not present a protective factor during the following months[30,31,32], only protection in 3 months to wheezing episodes[31].

Strengths and limitations

This systematic review was developed through PRISMA and Cochrane recommendations, which ensures the quality of the methodology used. The type of study used for the review (randomized clinical trial) is a strong point of this review because the most reliable results in humans are derived from this type of research. These studies are also used to develop treatment protocols. All selection, data extraction and analysis and bias were performed blindly and the extracted data was checked by specialists. The articles were randomly distributed (through a computer program) for the extraction and data validation stages by a specialist. The risk of minimal bias found in the studies was moderate.

Although this study was designed with high accuracy in systematization, our limitation was the small number of databases searched, and consequently few studies included. In the future, more randomized clinical studies need to be carried out to better assess the anti-inflammatory effects of AZM in acute viral respiratory infections. For this, the study protocols need to be well designed and standardized, allowing the comparison between the results and the performance of a meta-analysis (effect measures).

Conclusion

Considering the few studies included in this review, some inconsistency and other limitations, until the available evidence does not support the indication of the use of AZM for acute viral infections, and the use of the drug should be restricted only to cases of bacterial infections. The use of the drug should be performed only for the cases already indicated and

scientifically proven, to ensure the rational use of drugs and avoid selective pressure on bacteria. Although no study has shown severe adverse effects, the use of AZM presents a risk, and the patient's condition regarding risk/benefit should always be assessed, especially in patients who have a cardiovascular risk for prolongation of the QT interval.

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Transparency declaration

None to declare.

Contributors

DVPS, CF, IGD performed the literature research and designed the data extraction form. DVPS and CF performed data extraction, and IFK, IGD, TCMS. The data analysis and critical review was performed by DVPS, IGD and TCMS. All wrote the paper. TCMS critically reviewed subsequent drafts. All authors approved the final version of the manuscript for submission. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Supplementary data

Table S1. PRISMA-P 2015 Checklist.

Table S2. Search Strategy.

File S3. List of references of excluded (with reasons) and included studies.

Abbreviations

DVPS, CF, TCMS, IFK and IGD are the article authors initials.

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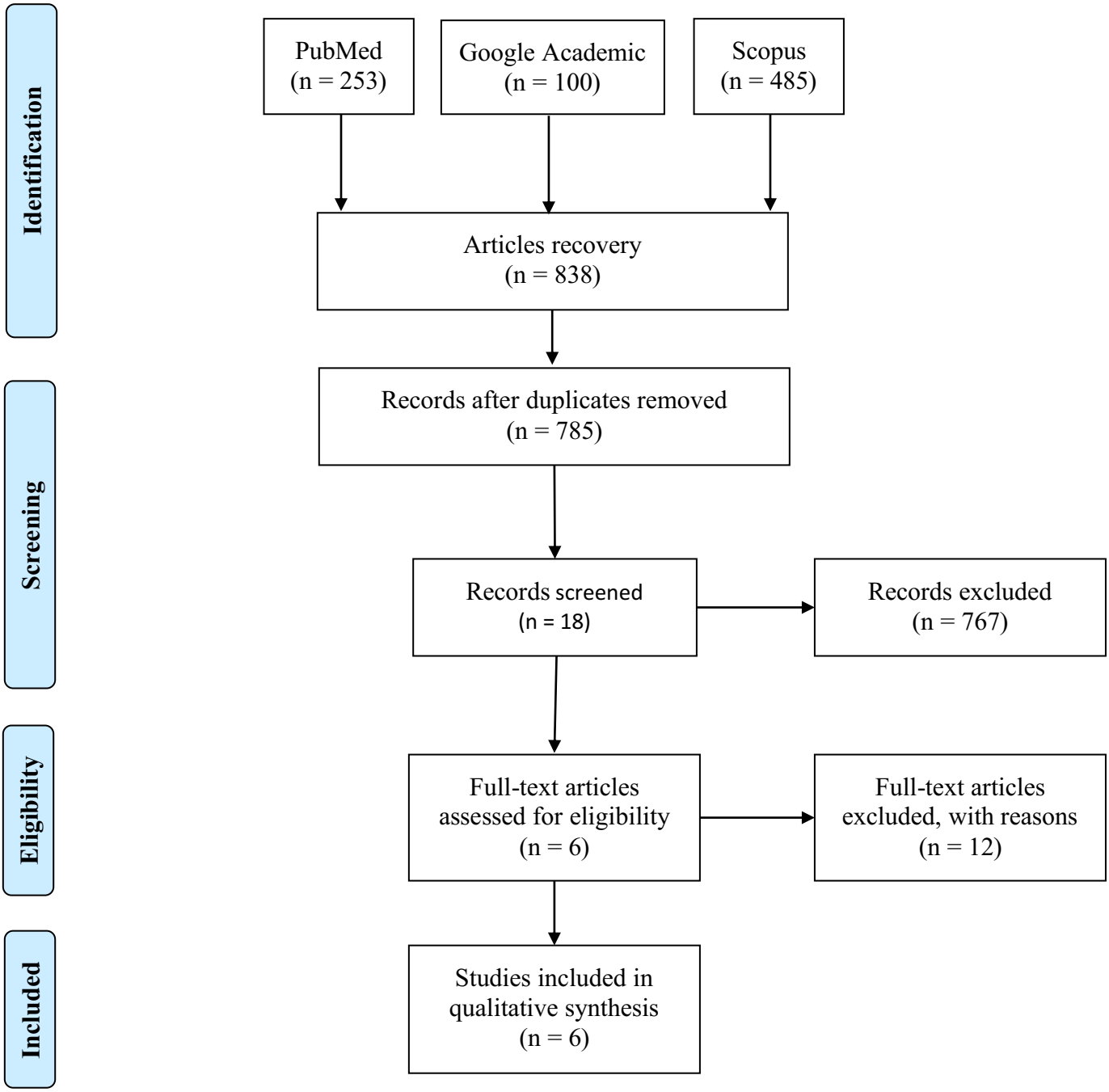
Figure 1: Research process PRISMA flowchart

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Table 1. PICOS and eligibility strategies

PICOS		INCLUSION	EXCLUSION
Population	Hospitalized patients diagnosed with viral respiratory infections (only confirmed diagnosis)	Only in patients (immunocompetent) with viral respiratory infections confirmed by diagnosis viral quantification (culture, serology or molecular methods)	Outpatients Only clinical diagnosis Without laboratory tests Immunocompromised patients (HIV or transplantation)
Intervention	Administration of azithromycin (AZM)	AZM or AZM and association with posology	Other macrolides or immunomodulators (corticoides, chemotherapy)
Comparison	Placebo or other, or combination with other medications	Placebo or other medication	Without control group
Outcomes	Effectiveness: incidence of disease-related complications, the time to alleviation of disease symptoms, viral quantification, culture-negativity, laboratorial parameters (inflammatory markers, i.e., cytokine, CPR and other), duration of influenza, duration of hospitalized/length of stay prognostic. Safety: complication, adverse drug reaction, interaction medication.	Effectiveness assessment or safety assessment or both	Studies without evaluation of effectiveness and safety
Types of Studies Included*	Clinical trial: randomized and non-randomized	Clinical trial: randomized prospective	Clinical trial non-randomized Cohort study Cross-sectional studies Case-control studies Experimental studies on animals or cells
Question	What are the effectiveness and safety of azithromycin use for the treatment of hospitalized patients with acute viral respiratory diseases?		

Based on PICO strategy for studies of intervention (Needleman IG, 2002; Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions.Version 5.1.0 [updated March 2011]. England: John Wiley & Sons, Ltd; 2011).

*Review studies, expert opinion, guidelines, comments and other articles there not randomized clinical trial

Table 2. Summary of characteristics of included studies

Author (year)	Country	Treatment and Comparision	Study completed (number of patients)	Gender M/F (%)	Mean Age (years or months)	Adherence (%)	Parameters evaluated
Beigelmand et al. (2015)	USA	AZM or placebo	39 AZM (19) Placebo (20)	59/41	AZM: 3.7 ± 3.7 Mo. Placebo: 3.9 ± 2.0 Mo.	AZM: 89 Placebo: 82	IL-8 serum and nasal lavage levels (on day 8, primary otucome, and 15 secondary) by CBA and clinical outcomes (effect on recurrent wheezing over the 50 weeks following the treatment).
Kakeya et al. (2014)	Japan	OS or OS + AZM	107 OS (56) OS + AZM (51)	46.7/53.3	OS + AZM: 42.9 ± 17.3 yr OS: 44.1 ± 17.3 yr	~ 100	Influenza duration; Influenza-related complications incidence (sinusitis, otitis media, bronchitis, and pneumonia); Influenza symptoms alleviation time; and adverse events and adverse drug reactions. Cytokines levels (IL-1b, IL-2, IL-4, IL-6, IL-8, IL -10, IL-12, TGF-b, IFN-c, and TNF-a) were measured in serum using the CBA Hematological measurements (RBC, Hb level, Ht level, platelet count, WBC, and WBC fraction); biochemical (levels measurement of AST, ALT, T-Bil, BUN, Cre, T-P, Alb, Na, Cl, and K) and immunological (CRP level) tests on days 1, 2, and 5. The differences in values on day 2 and day 5 from those observed on day 0 were evaluated.
Lee et al. (2017)	China	OS or OS + AZM	49 OS (25) OS + AZM (24)	62.0/38.0	OS + AZM: 54.7 ± 18.5 yr OS: 58.6 ± 18.1 yr	99	Plasma cytokine/chemokine and pro-inflammatory mediator changes ((IL)-6, CXCL8/IL-8, IL-10, IL-1b, IL-12p70, TNF-a, CCL2/MCP-1, CXCL-9/MIG, CXCL10/IP-10, and CCL3/MIP-1a by CBA), viral clearance (culture and RNA concentration), and symptom resolution were compared between the two arms. Electrocardiogram was monitored.
Luisi et al. (2020)	Brazil	AZM or placebo	63 AZM (34) Placebo (29)	61.4/38.6	AZM: 3.26 ± 2.49 Mo. Placebo: 3.14 ± 2.29 Mo.	NR	Clinical outcomes; required oxygen supplemental duration; respiratory viruses identification; identify recurrent wheezing and hospital adminissions.
Pinto et al. (2012)	Brazil	AZM or placebo	184 AZM (88) Placebo (96)	60.3/39.7	AZM: 3.08 ± 2.23 Mo. Placebo: 3.12 ± 2.29 Mo.	NR	Primary outcomes: LOS for AB and supplemental oxygen requirement duration. Other variables: antibiotic use; bronchodilators use; admission to the pediatric intensive care unit. Subgroups: age > or < 3 months; respiratory viruses identification; and positive for RSV.
Sekhavati et al. (2020)	Iran	AZM + HCQ + LPV/r (Kaletra ®) or HCQ + LPV/r (Kaletra®)	111 AZM + HCQ + LPV/r (Kaletra ®) (56) HCQ + LPV/r (Kaletra®) (55)	45.95/54.05	AZM + HCQ + LPV/r (Kaletra ®): 54.38 ± 15.92 HCQ + LPV/r (Kaletra®): 59.89 ± 15.55	100	Vital signs, SpO2 levels, hospitalisation duration, need and duration of intensive care unit admission, mortality rate and results of 30-day follow-up after discharge

Legend: **AB:** Acute Brchiolitis; **Alb:** albumin; **ALT:** Alanine Aminotransferase; **AST:** Aspartate Aminotransferase; **AZM:** Azithromycin; **BUN:** Blood Urea Nitrogen; **CBA:** Cytometric bead array**; CCL:** CC Chemokine Ligands; **CXCL:** CXC Chemokine Ligands; **Cl:** Chloride; **Crea:** Creatinine; **CRP:** C-Reactive Protein; **F:** Female; **Hb:** Hemoglobin levels; **HCQ:** Hydroxychloroquine; **Ht:** Hematocrit; **IFN-β:** Interferon Beta; **IL:** Interleukin; **K:** Potassium; **LPV/r (Kaletra®):** Lopinavir and Ritonavir; **LOS:** Length of Stay in Hospital; **M:** Male; **Mo:** Months; **Na:** Sodium; **OS:** Oseltamivir; **PUC- RS:** Pontifical Catholic University of Rio Grande do Sul**; RBC:** Red Blood Cell; **RSV**: Respiratory Syncytial Virus; **T-Bil:** Total Bilirubin; **TGF-β:** Transforming Growth Factor beta; **TNF-α:** Tumor Necrosis Factor Alpha; **T-P:** Total Protein; **UFRGS:** Federal University of Rio Grande do Sul**; WBC:** White Blood Cell; **Yr:** Years. (-) or NR: Not Reported or without complete information.

Table 3. Summary of results found from included articles

Author (year)	Clinical and laboratory findings	Experimental	Control	Adverse effects
Beigelmand et al. (2015)	No reduction in IL-8 serum levels between groups on day 8	Median serum IL-8: 6.971 fg/mL	Median serum IL-8: 5.050 fg/mL	7 children in the AZM group and 8 children in the placebo group with gastrointestinal adverse events (diarrhea, vomiting or abdominal pain) during the active treatmente phase.
	Significant reduction in nasal lavage IL-8 levels on day 15	Day 8 medium nasal IL-8 : 2,217 pg/mL Day 15 medium nasal IL-8 : 865 pg/mL	Day 8 medium nasal IL-8: 4,395 pg/mL Day 15 medium nasal IL-8: 2,318 pg/mL	
	No difference in recurrent wheezing and asthma between groups over the 50 weeks after the initial RSV bronchiolitis episode and also who experienced 3 or more subsequent wheezing episodes.	AZM: 39% AZM 3 or more episodes: 22%	Placebo: 50% Placebo 3 or more episodes: 50%	
	The participants proportion with a physician's asthma diagnosis did not differ between the AZM and placebo groups.	AZM: 11%	Placebo: 25%	
	Significantly fewer days with respiratory symptoms (cough, wheeze, or shortness of breath) over the ensuing 50 weeks.	36.7	70.0	
	The emergency department visits numbers for respiratory symptoms did not differ between the groups	-	-	
Kakeya et al. 2014	No statistically significant differences were observed between the 2 groups in the inflammatory cytokines or chemokines expression on baseline or days 2 and 5. Except for the baselineTNF-α values that were statistically significantly higher in the OS + AZM-group than in the OS-group.	-	-	OS + AZM: 11 of the 56 patients (19.6%) OS: 9 of the 51 patients (17.6%). It was not detected difference in the incidence of adverse events between the 2 groups. No severe adverse events occurred in either group and no patients discontinued treatment. The adverse events related were diarrhea (3 in the OS + AZM-group) and decreased WBC (5 in the OS + AZM-group and 3 in the OS-group). Only 1 patient in the OS-group developed secondary pneumonia.
	The maximum temperature on days 3 through 5 was significantly lower in the OS + AZM-group than in the OS-group.	-	-	
	Significant decrease in the maximum temperature was observed on day 4 between the OS + AZM-group and OS-group.	-	-	
	Compared to the OS-group, the OS + AZM-group showed a trend toward earlier resolution of fever.	-	-	
	OS + AZM-group showed statistically significant increases in the RBC and hemoglobin and Ht values on days 2 and 5 and a statistically significant decrease in the levels of Alb and T-P on day 2.	-	-	
	OS+AZM-group showed a potential early resolution of influenza-related symptoms such sore throat on days 2 and 5.	None = 10 (19.6%); Mild = 19 (37.3%); Moderate = 14 (27.5%); Severe 3 (5.9%)	None = 11 (19.6%); Mild = 26 (46.4%); Moderate = 13 (23.2%); Severe 4 (7.1%)	

Lee et al. 2017	Faster downregulation of IL-6	83.4% reduction	59.5% reduction	The treatments were generally well tolerated. Only 1 patient stopped AZM after 3 days because of dizziness. Incidence of adverse events was similar between the groups.
	Faster downregulation of CXCL8/IL-8	80.5% reduction	58.0% reduction	
	Faster downregulation of IL-17	74.0% reduction	34.3% reduction	
	Faster downregulation of CXCL9/MIG	71.3% reduction	56.0% reduction	
	Faster downregulation of likely reduction in TNF-a (indicated by sTNFR-1)	40.1% reduction	27.8% reduction	
	Faster downregulation of IL-18	29.1% reduction	30.2% reduction	
	Faster downregulation of CRP	77.5% reduction	48.2% reduction	
	There was a trend toward faster symptom resolution in oseltamivir plus AZM group; however the score of symptoms resolution was not significant	79.0% reduction	70.0% reduction	
Luisi et al. (2020)	No differences in LOS, days mean	5.32 ± 2.63*	5.85 ± 3.30*	Not reported
	No differences in β2 agonist use	24.3%*	33.3%*	
	Differences in wheezing in 3 months	19.1%	39.5%	
	No differences in hospital readmission in 3 months	8.5%	10.5%	
	Positive for any virus	54.1%	66.7%	
	RSV positive	45.9%	63.9%	
	No differences in wheezing in 6 months	25.6%	27.3%	
	No differences in hospital readmission in 6 months	9.3%	3.0%	
Pinto et al. (2012)	No differences in LOS, in days	5 (3 - 7)	5 (3 - 7)	Not reported
	No differences in LOS by age, in days	< 3 months 6 (4 - 7) > 3 months 3 (3 - 6)	< 3 months 5 (3 - 9) > 3 months 5 (3 - 6)	
	No differences in LOS by virus detection, in days	Positive for virus 5 (3 - 7) Negative for virus 4.5 (2.75 - 7)	Positive for virus 5 (3 - 8.75) Negative for virus 4 (3 - 7)	
	No differences in LOS by RSV detection, in days	Positive for RSV 5 (3 - 7) Negative for RSV 4 (3 - 7)	Positive for virus 5 (4 - 8.5) Negative for virus 4.5 (3 - 6.75)	
	No differences in LOO_2 requetiment, in days	4 (2 - 6)	4 (3 - 6)	
	No differences in LOO2 by age, in days	< 3 months 4 (3 - 7) > 3 months 3 (2 - 5)	< 3 months 4 (3 - 8) > 3 months 4 (2 - 6)	
	No differences in LOO2 by virus detection, in days	Positive for virus 4 (3 - 7) Negative for virus 3 (2 - 5)	Positive for virus 5 (3 - 7) Negative for virus 3 (2 - 5)	
	No differences in LOO2 by RSV detection, in days	Positive for RSV 4 (3 - 8) Negative for RSV 3 (2 - 5)	Positive for RSV 5 (3 - 7) Negative for RSV 3 (2 - 5)	
	Significant difference in respiratory rate/min, mean	46.8 ± 8.98	51 ± 12.97	

Sekhavati et al. 2020	No difference in day 3 SpO2, (%)	89.36 ± 4.29	88.75 ± 7.67	A baseline QTc interval was obtained and monitored during the treatment, along with the heart rate and serum electrolytes. A scoring system to predict the risk of QT interval prolongation of patients has been designed. The results were interpreted as low (<7), medium (7-10) and high risk (≥11) of QT interval prolongation. In this study, all patients had a risk score of <6 (low), and none of them experienced QTc interval prolongation, which would have warranted a halt in treatment with HCQ and AZM.
	No difference regarding fever, n (%)	38 (67.86)	33 (60.00)	
	No difference regarding dyspnoea, n (%)	41 (73.21)	43 (78.18)	
	No difference regarding chills, n (%)	18 (32.14)	25 (45.45)	
	No difference regarding cough, n (%)	34 (60.71)	41 (74.55)	
	No difference regarding sputum production, n (%)	3 (5.36)	8 (14.55)	
	No difference regarding haemoptysis, n (%)	3 (5.36)	0 (0.00)	
	No difference regarding chest pain, n (%)	10 (17.86)	12 (21.82)	
	Significant difference regarding myalgia, n (%)	18 (32.14)	22 (74.55)	
	Significant difference regarding weakness, n (%)	10 (17.86)	3 (5.45)	
	Significant difference regarding headache, n (%)	6 (10.71)	18 (32.7)	
	Significant difference regarding vomiting, n (%)	7 (12.50)	16 (29.09)	
	Significant difference regarding hospital stay, days	4.61 ± 2.59	5.96 ± 3.21	
	No difference regarding need for ICU admission, n (%)	2 (3.57)	7 (12.73)	
	No difference regarding death, n (%)	0 (0.00)	1 (1.82)	
	No differences in the dischard discharge body temperature, in ºC	36.88 ± 0.33	36.77 ± 0.53	
	No differences in the ICU length of stay, in days	5.00 ± 0.01	4.43 ± 2.99	
	Significant differences in the respiratory rate at discharge, breaths/min	15.85 ± 1.99	17.42 ± 2.42	
	Significant difference in the SpO2 at discharge, in %	93.95 ± 2.14	92.40 ± 4.58	
	No difference regarding in the need for intubation, n (%)	0 (0.00)	3 (5.45)	
	Difference in body temperature on admission (°C)	38.07 ± 0.69	37.72 ± 0.91	
	No difference in SpO2 on admission (%)	89.61 ± 2.98	89.51 ± 6.84	

Legend: **AZM:** Azithromycin; **CCL:** CC Chemokine Ligands; **CXCL:** CXC Chemokine Ligands; **CRP:** C-Reactive Protein; **HCQ:** Hydroxychloroquine; **Ht:** Hematocrit; **IL:** Interleukin; **K:** Potassium; **LOS:** Length of Stay in Hospital; OS: Oseltamivir; **RBC:** Red Blood Cell; **RSV**: Respiratory Syncytial Virus; **T-Bil:** Total Bilirubin; **TNF-α:** Tumor Necrosis Factor Alpha; **T-P:** Total Protein; **WBC:** White Blood Cell.
*Results demonstrated based on the patient's number who completed the follow-up 3 months (AZM group: 37 and placebo group: 33).
(-) or NR: Not Reported or without complete information.

Table 4 Results from Joanna Briggs Institute Critical Appraisal Checklist for Randomized Clinical Trials.

QUESTION/Author, year	Beigelman et al (2015)	Kakeya et al (2014)	Lee et al (2017)	Luisi et al (2020)	Pinto et al (2012)	Sekhavati et al (2020)
1. Was true randomization used for assignment of participants to treatment groups?	Y	N	N	N	Y	N
2. Was allocation to treatment groups concealed?	Y	N	N	Y	N	N
3. Were treatment groups similar at the baseline?	Y	Y	Y	Y	Y	Y
4. Were participants blind to treatment assignment?	Y	N	N	Y	Y	N
5. Were those delivering treatment blind to treatment assignments?	Y	N	N	Y	Y	N
6. Were outcomes assessors blind to treatment assignment?	Y	N	N	Y	Y	Y
7. Were treatment groups treated identically other than the intervention of interest?	N	N	Y	N	N	Y
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	N	Y	N	N	N	Y
9. Were participants analyzed in the groups to which they were randomized?	Y	Y	Y	Y	Y	Y
10. Were outcomes measured in the same way for treatment groups?	Y	Y	Y	Y	Y	Y
11. Were outcomes measured in a reliable way?	Y	Y	Y	Y	Y	Y
12. Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Y	Y	Y	Y	Y	Y
TOTAL (%)	85	54	54	77	77	69
Risk of Bias*	Low	Moderate	Moderate	Low	Low	Moderate

From: Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. *JBI*, 2020. Available from https://synthesismanual.jbi.global

Table S1. PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al**:** Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☒	NA
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	406 – 412
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	397
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	398 – 400
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	62
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	66

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	100 – 111
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	81 – 83
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	82 – 87; AND
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	120
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	93 – 99
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	122 – 126
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	617
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	114 – 120
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	302 – 307
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	NA
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	125 – 126
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	☐	☒	NA

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	16	reporting within studies)			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	NA

Table S2. Search strategy.

Search	Query/PubMed (Mesh)	Scopus
Block 1 Viral respiratory infection #1	Respiratory Tract Infections Viral load Viral diseases Hospitalization	Respiratory Tract Infections Viral load
Block 2 Azithromycin #2	Macrolides* Antiviral Agents	Macrolides Antiviral Agents Azithromycin
Block 3 Outcome #3	Prognosis	Prognosis Treatment outcome
Block 4 NOT	HIV or HIV infections hepatitis	HIV Hepatitis
Combo #3	#1 AND #2 AND #3 AND NOT #4 (N=253)	#1 AND #2 AND #3 AND NOT #4 (N=485)

*Major subject term

Google Scholar (Gray Literature):

(Respiratory tract infection OR viral diseases) AND (macrolides OR azithromycin) AND NOT (hiv and hepatitis) filetype:pdf (N=100)

File S3. Reference *list of included* studies (six).

1. Beigelman A, Isaacson-Schmid M, Sajol G, Baty J, Rodriguez OM, Leege E, et al. Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 levels, and recurrent wheezing in infants with RSV bronchiolitis. *J Allergy Clin Immunol* 2015;135(5):1171-1178.
2. Kakeya H, Seki M, Izumikawa K, Kosai K, Morinaga Y, Kurihara S, et al. Eficaccy of Combination Therapy with Oseltamivir Phosphate and Azithromycin for Influenza: A Multicenter, Open-Label, Randomized Study. *PLoS One.* 2014; 9(3):e91293.
3. Lee N, Wong CK, Chan MCW, Yeung ESL, Tam WWS, Tsang OTY, et al. Anti-inflammatory effects of adjunctive macrolide treatment in adults hospitalized with influenza: A randomized controlled trial. *Antiviral Res* 2017; 144(0):48-56.
4. Luisi F, Roza CA, Silveira VD, Machado CC, Rosa KM, Pitrez PM et al. Azithromycin administered for acute bronchiolitis may have a protective effect on subsequent wheezing. *J Bras Pneumol* 2020;46(3):e20180376.
5. Pinto LA, Pitrez PM, Luisi F, de Mello PP, Gerhardt M, Ferlini R, et al. Azithromycin therapy in hospitalized infants with acute bronchiolitis is not associated with better clinical outcomes: a randomized, double-blinded, and placebo-controlled clinical trial. *J Pediatr* 2012;161(6):1104-8.
6. Sekhavati E, Jafari F, SeyedAlinaghi S, Jamalimoghadamsiahkali S, Sadr S, Taberestani M et al. Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial. *Int J Antimicrob Agents* 2020; 56(4):106143.

Reference *list of excluded* studies (twelve), including the reasons for *exclusion*.

1. Ceccato A, Cilloniz C, Ranzani OT, Menendez R, Agusti C, Gabarrus A, et al. Treatment with macrolides and glucocorticosteroids in severe community-acquired pneumonia: A post-hoc exploratory analysis of a randomized controlled trial. *PLoS One* 2017;12(6):e0178022. Reason: Wrong Population.
2. Chang AB, Grimwood K, Robertson CF, Wilson AC, van Asperen PP, O'Grady KA, et al. Antibiotics for bronchiectasis exacerbations in children: rationale and study protocol for a randomised placebo-controlled trial. *Trials* 2012;13(0)156. Reason: Wrong Outcome.
3. Chang AB, Grimwood K, White AV, Maclennan C, Sloots TP, Sive A, et al. Randomized placebo-controlled trial on azithromycin to reduce the morbidity of bronchiolitis in Indigenous Australian infants: rationale and protocol. *Trials* 2011; 12(0):94. Reason: Wrong Outcome.
4. Gašparić cM, Penezić A, Kolumbić-Lakoš A, Kovačić D, Kukuruzović MM, Baršić B. Safety and effectiveness of azithromycin in the treatment of lower respiratory infections: An international, multicenter, non-comparative study. *Acta Clinica Croatica* 2015; 54(2):149-158. Reason: Wrong Population.
5. Izadi M, Dadsetan B, Najafi Z, Jafari S, Mazaheri E, Dadras O, et al. Levofloxacin Versus Ceftriaxone and Azithromycin Combination in the Treatment of Community Acquired Pneumonia in Hospitalized Patients. *Recent Pat Antiinfec Drug Discov* 2018; 13(3):228-239. Reason: No Free Full Text.
6. Legier K, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. *Travel Med Infect Dis* 2020; 36(0):101791. Reason: Wrong Population.

7. Liu S, Zheng Y, Wu X, Xu B, Liu X, Feng G, et al. Early target attainment of azithromycin therapy in children with lower respiratory tract infections. *J Antimicrob Chemother* 2018; 73(10):2846-2850. Reason: Wrong Population.
8. Million M, Lagier JC, Gautret P, Colson P, Fournier PE, Amrane S, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis* 2020; 35 (0): 101738. Reason: Wrong Study Design.
9. Mosquera RA, Gomez-Rubio AM, Harris T, Yadav A, McBeth K, Gonzales T, et al. Anti-inflammatory effect of prophylactic macrolides on children with chronic lung disease: a protocol for a double-blinded randomised controlled trial. *BMJ open* 2016; 6(9):e012060. Reason: Wrong Population.
10. Uranga A, Espana PP, Bilbao A, Quintana JM, Arriaga I, Intxausti M, et al. Duration of antibiotic treatment in community-acquired pneumonia: A multicenter randomized clinical trial. *JAMA Internal Medicine* 2016; 176(9):1257-1265. Reason: Wrong Population.
11. Uzun S, Djamin RS, Kluytmans J, Van't Veer NE, Ermens AAM, Pelle AJ, et al. Influence of macrolide maintenance therapy and bacterial colonisation on exacerbation frequency and progression of COPD (COLUMBUS): Study protocol for a randomised controlled trial. *Trials* 2012; 13(0): 82. Reason: Wrong Population.
12. Vermeesch K, Belmans A, Bogaests K, Gyselinck I, Cardinaels N, Gabrovska M, et al. Treatment failure and hospital readmissions in severe COPD exacerbations treated with azithromycin versus placebo - a post-hoc analysis of the BACE randomized controlled trial. *Respir Res* 2019; 20(1):237. Reason: Wrong Populat