



## SYSTEMATIC REVIEW

# Safety and efficacy of Azithromycin in prevention of chronic obstructive pulmonary disease exacerbation: systematic review and meta-analysis [version 1; peer review: 1 approved with reservations, 1 not approved]

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## Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) causes a major burden in terms of deaths and hospitalizations worldwide; it is associated with progressive lung function loss, and frequent exacerbations. Administration of macrolides has been considered beneficial in reducing the frequency of COPD exacerbations. The aim of this study is to assess the safety and efficacy of long-term administration of Azithromycin for patients with chronic obstructive pulmonary disease.

**Methods:** An extensive search was conducted on SCOPUS, and PubMed databases, CENTRAL, and ClinicalTrials.gov clinical trial registers for randomized clinical trials conducted on COPD patients and administered Azithromycin for more than two weeks. The selected studies underwent assessment for the risk of bias. We conducted random-effect model meta-analysis for the frequency of acute exacerbations during follow-up as a primary outcome.

**Results:** Out of 1021 screened records, 3 RCTs (Randomized controlled trials) involving 1264 patients were included in the final analysis. The pooled data of all 3 trials showed that administration of Azithromycin reduced the frequency of acute exacerbation of COPD [risk ratio (RR) = 0.69; 95% CI 0.53, 0.91,  $p = 0.01$ ]. Subgroup analysis indicated that 500 mg Azithromycin [risk ratio (RR) = 0.65; 95% CI 0.53-0.79,  $p = 0.01$ ] was found to be more beneficial than 250 mg Azithromycin [risk ratio (RR) = 0.60; 95% CI 0.27-1.33,  $p = 0.21$ ] in reducing acute exacerbation rate, however due to many limitations the analysis of the dosage was not conclusive.

**Conclusion:** Long-term Azithromycin administration for COPD patients is statistically not associated with increased risk of developing adverse events; in addition, it might be effective in reducing the

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frequency of acute exacerbations of COPD. However, dosage and duration of Azithromycin administration analysis was not conclusive and thus more RCTs are needed in these areas.

### Keywords

chronic obstructive pulmonary disease, acute exacerbation, macrolides, Azithromycin

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## Abbreviations

COPD: Chronic obstructive pulmonary disease.

FEV 1: Forced expiratory volume in 1 second.

FVC: Forced vital capacity.

RR: Risk ratio.

CI: Confidence interval.

SGRQ: St George Respiratory Questionnaire.

SF-36: Short-form 36 Health Survey.

SF-12: 12-Item Short-Form Health Survey.

## Introduction

Chronic obstructive pulmonary disease (COPD) is “a disease state characterized by airflow limitation that is not fully reversible”<sup>1</sup>. It is a progressive life threatening lung disease, with frequent symptoms that include: chronic cough, breathlessness, and sputum production<sup>2</sup>. It is the fourth leading cause of death worldwide affecting more than 60 million people and it is estimated to become the third by 2030. 3.2 million deaths occur due to COPD, with 90% of them occurring in middle and low income countries<sup>3–5</sup>. Until now, there is no definitive treatment for COPD and thus effective management of COPD relies on improving health status, reducing the mortality, as well as preventing and treating complications and exacerbations of the disease<sup>6</sup>.

COPD exacerbation is defined as “an acute worsening of respiratory symptoms that result in additional therapy”, and classified as mild (responsive to short acting bronchodilators), moderate (requiring antibiotics and/or oral corticosteroids in addition to short acting bronchodilators), or severe (requiring hospitalization)<sup>7</sup>. Numerous international guidelines have discussed recommendations about the benefits of antimicrobial agents in patients with acute exacerbation of COPD, as they are more prone to develop bacterial infections<sup>8–10</sup>. Among these antimicrobial agents, macrolides (such as Azithromycin) are especially favored as prophylactic antibiotics in COPD, mostly due to their potentially beneficial anti-inflammatory and immunomodulatory roles, in addition to their known antibacterial effect<sup>11</sup>.

Azithromycin belongs to macrolides family; it is a semi-synthetic antibiotic derived from another macrolide, erythromycin. Azithromycin has bactericidal and bacteriostatic properties, hence it is used in treating certain bacterial infections<sup>12</sup>. Azithromycin acts by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of the targeted bacteria, thereby inhibiting the translocation step of protein synthesis stopping bacterial growth<sup>13</sup>.

Several studies have discussed the beneficial role of macrolides for COPD patients<sup>14–19</sup>, some of them suggested that long-term Azithromycin therapy has been shown to decrease the rate of recurrence and severity of exacerbations of COPD<sup>20,21</sup>. However, there is little evidence as to whether Azithromycin is safe and efficacious for management of COPD; thus our study aims to evaluate the efficacy and safety of long-term administration of

Azithromycin therapy for chronic obstructive pulmonary disease by accumulating the evidence from randomized control trials that studied the efficacy and safety of Azithromycin administration for COPD patients.

## Methods

### Search strategy

We systematically searched the literature on PubMed and Scopus databases, as well as the Cochrane central register of controlled trials (CENTRAL) and ClinicalTrials.gov register clinical trial registers. We searched using the terms; chronic obstructive pulmonary disease, exacerbation, chronic bronchitis, emphysema, Azithromycin. The electronic search string used for PubMed was as follows: (((chronic obstructive pulmonary disease OR chronic bronchitis) OR emphysema) AND exacerbation) AND Azithromycin. Our search was limited to human studies only. Our last search was on January 24, 2018. Moreover, hand searching was done by screening the reference lists of all included studies (Figure 1).

### Inclusion criteria

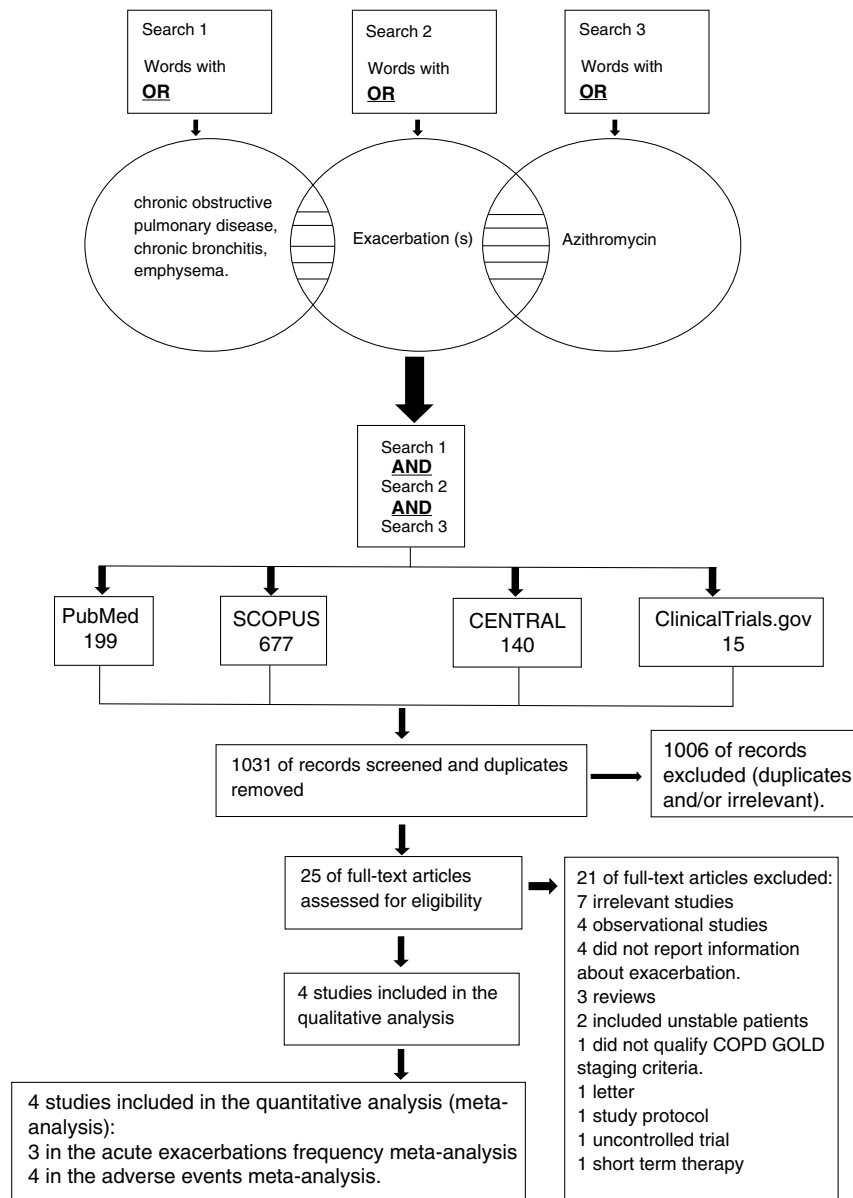
Our eligibility criteria for studies to be included in our meta-analysis were: (1) Randomized controlled trials that included only stable COPD patients in any stage of the disease. (2) COPD is defined clinically as [forced expiratory volume in 1 second (FEV 1) /forced vital capacity (FVC)] <70%, FEV 1 <80% predicted, and an increase in FEV 1 <12% (or 200 ml) after inhaling bronchodilators, according to Tiffeneau-Pinelli Index<sup>22</sup>. (3) Studies that used Azithromycin. (4) The drug was administered orally and the therapy lasted more than two weeks. (5) Information about clinical efficacy or the safety of the drug were reported.

### Studies selection

Four reviewers, AA, KA, AA, and HA screened the titles and abstracts of the search results independently for potentially eligible studies. After removing duplicates and irrelevant records, they independently reviewed the full-text of potentially eligible studies using the previously mentioned inclusion criteria. Any differences between the reviewers were solved through consensus. There were no disagreements that needed to be resolved by the senior author.

### Data extraction and quality assessment

We measured the risk of bias for all studies that fulfilled our inclusions criteria using RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) risk of bias assessment tool using: allocation concealment, random sequence generation, blinding of participants and personnel, incomplete outcome data, blinding of outcome assessment, selective reporting as the main parameters for bias. The information that we extracted from the selected studies were study setting information, patients' characteristics information, treatment information (dosage, therapy strategy, course of therapy, concomitant medication to treat COPD), frequency of exacerbations, and adverse events reports. The reviewers extracted this information independently. Output RevMan file used for analysis is available as Underlying data<sup>23</sup>.



**Figure 1.** PRISMA flowchart illustrating the search strategy and the process of studies selection.

### Statistical analyses

We used random-effects models to pool treatment effects and to calculate the risk ratios (RR) with 95% CI for all clinical end-points, which were the frequencies of exacerbations. All types of exacerbations (mild, moderate, and severe) were included in the pooled analysis with no distinction between them, because some of the included studies reported severe exacerbations while others reported non severe exacerbations. To examine the robustness of the effect we performed a sensitivity analysis by removing the trials with the highest weights and computing the overall estimates for the remaining studies. Regarding statistical heterogeneity, we used the I<sup>2</sup> statistic on a scale of 0–100% (>50% indicated a statistical between-study inconsistency, and >75% represented a very large degree of

heterogeneity). Subgroup analysis were performed for two strata of data, dosage of Azithromycin used (250 mg Azithromycin or 500 mg Azithromycin) and the duration of the administration (3 months or 12 months). Funnel plot method was used to assess the publication bias.  $P < 0.05$  was considered statistically significant. RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) was used to perform the pooling analyses of the data.

### Results

#### Studies identification and selection

Initially 1031 published records were identified (677 from SCOPUS, 199 from PubMed, 15 from ClinicalTrials.gov register, and 140 from CENTRAL) (Figure 1). 4 studies<sup>24–27</sup>

meet the inclusion criteria. 1348 participants were included in the four trials, the follow-up duration varied among the studies: 3 months<sup>25</sup>, 6 months<sup>27</sup>, and 12 months<sup>24,26</sup>. Of the total number of participants in the included trials, 674 participants were randomly assigned to receive Azithromycin, while 674 were allocated to receive Placebo; in addition both groups continued receiving their concomitant medications (long acting  $\beta_2$  agonists, long acting anticholinergics, inhaled corticosteroids, short acting  $\beta_2$  agonists, oral Prednisolone) (Table 1), Azithromycin dosages used were 250 mg Azithromycin<sup>24,25,27</sup> and 500 mg Azithromycin<sup>26</sup>.

The duration of Azithromycin therapy was for 3 months<sup>25,27</sup> and 12 months<sup>24,26</sup>, the total number of withdrawals among the selected studies was 66. Three studies<sup>24,26,27</sup> compared the frequency of acute exacerbation difference that occurred during the follow-up period between the Azithromycin group and the Placebo group using Poisson regression model. One study<sup>25</sup> reported acute exacerbations as percentages for both of the study groups. All four studies reported the adverse events that occurred during the follow-up period. In addition to acute exacerbations rate and the adverse events, other outcomes like health related quality of life<sup>24-27</sup>, bacterial culture, macrolides resistance<sup>24,26,27</sup>, and pulmonary functions test<sup>25-27</sup> were also reported.

### Qualitative data synthesis

The time to the first acute exacerbation of COPD in days was higher among patients who received Azithromycin compared patients who received the Placebo<sup>24-26</sup>. Uzun *et al.* revealed that hospital admission odds ratio did not differ between the two groups<sup>26</sup>, however, according to the other studies hospital admissions were reported more amongst the Placebo group<sup>24,25,27</sup>. Furthermore, chest computed tomography symptom score did

not show any difference between the two groups<sup>27</sup>, and after 12 weeks of Azithromycin therapy a significant increase in the Leicester Cough Questionnaire total score was reported in the Azithromycin group compared with the Placebo. Pulmonary function test was conducted in all four studies<sup>24-27</sup>, with the exception of Albert *et al.*, all indicated that no significant difference in the test results were reported between Azithromycin and Placebo groups.

Nasopharyngeal colonization was assessed in three studies<sup>24,26,27</sup>, two of them<sup>24,26</sup> reported that fewer patients in the Azithromycin group had positive culture during the course of the study (p value < 0.001, p value= 0.044 respectively) while the other<sup>27</sup> reported no difference between the Azithromycin and Placebo group. Macrolide-resistant bacteria were detected more in the Azithromycin group of Simpson *et al.*, in which the incidence of resistance was 81% among Azithromycin group, and 41% in the placebo (p value < 0.001)<sup>27</sup>, however it was detected more among the Placebo group with 24%, in contrast to 6% among Azithromycin group (p value = 0.036) from Uzun *et al.*<sup>26</sup>. Nasopharyngeal colonization was not associated with the occurrence of acute exacerbations in either group (p value 0.31)<sup>24</sup>.

Quality of life was recorded using different tools: St George Respiratory Questionnaire (SGRQ)<sup>24-27</sup>, Short-form 36 Health Survey (SF-36)<sup>24,25</sup>, and the 12-Item Short Form Health Survey (SF-12)<sup>26</sup>. Three studies<sup>24-26</sup> reported a decrease in SGRQ total scores in the Azithromycin group compared with the Placebo group, however one study<sup>27</sup> reported no decrease in the total score among Azithromycin group. The results of the SF-36 scores varies among studies as one study<sup>24</sup> stated that no changes were seen in the scores while the other study<sup>25</sup> reported a significant difference in the scores between Azithromycin and Placebo

**Table 1. characteristics of the included studies.**

Literature Source	Total subjects N	Azithromycin group N	Placebo Group N	Males N	Females N	Therapy strategy	Concomitant medications To treat COPD	Course of therapy/month	age mean Yrs.
Albert <i>et al.</i>	1142	570	572	661	456	Azithromycin 250 mg/day compared with placebo	Inhaled glucocorticoids, LAMAs, LABAs	12 months	66 $\pm$ 9
Berkhof <i>et al.</i>	84	42	42	63	21	Azithromycin 250 three times/week compared with placebo	Inhaled glucocorticoids, LAMAs, LABAs	3 months	68 $\pm$ 10
Simpson <i>et al.</i>	30	15	15	19	11	Azithromycin 250 mg/day compared with placebo	inhaled corticosteroids	3 months	70.8 $\pm$ 7.6
Uzun <i>et al.</i>	92	47	45	40	52	azithromycin dihydrate 500 mg three times/week compared with placebo	Inhaled glucocorticoids, LAMAs, LABAs	12 months	64.8 $\pm$ 10.2

N: number, Yrs: years, COPD: chronic obstructive pulmonary disease, LAMAs: long acting anticholinergics, LABAs: long acting  $\beta_2$  agonists.

groups. In addition, the mean change differed significantly between the Placebo group and the Azithromycin group in the mental component score of SF-12<sup>26</sup>. The most commonly reported adverse event was hearing decrement which was reported in 18% (252) of the participants, an audiogram-confirmed hearing decrement occurred more frequently in participants receiving Azithromycin compared to those receiving Placebo (P=0.04), however, audiogram-confirmed hearing decrement was used in only one study<sup>24</sup>. Table 2 demonstrates the side effects that occurred among the patients.

**Table 2. adverse events reported among the patients.**

Adverse events	Azithromycin group 674 patients % (n) 18	Placebo group Patients % (n)
Gastrointestinal*	5 (37)	4 (31)
Cardiovascular #	4 (32)	5 (36)
Hearing decrement	21 (142)	16 (110)
Respiratory &	4 (33)	7 (49)
Others \$	25 (174)	26 (178)

\* = diarrhea, nausea, vomiting and gastric ulcer...etc.

# = QTc prolongation, myocardial infarction, supraventricular tachycardia, heart failure...etc.

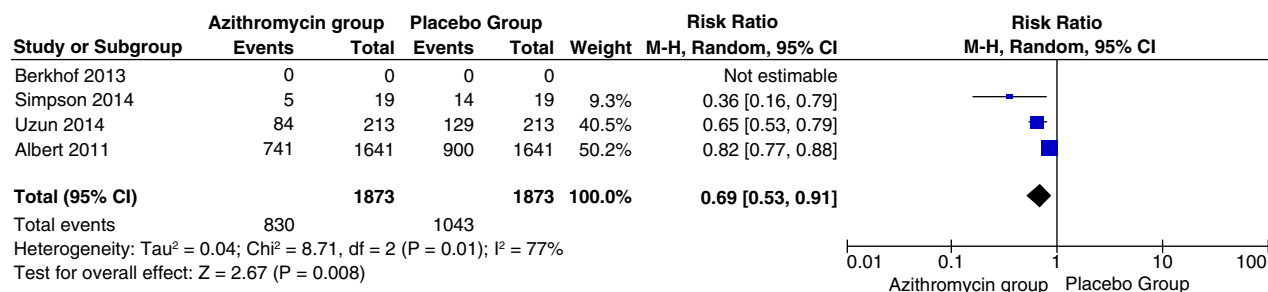
& = common cold, dyspnea and cough, Pneumonia...etc.

\$ = Neoplasm, Tinnitus, Allergic reactions, abnormal lab tests...etc.

### Quantitative data synthesis

The final analysis of the pooled data of the all three trials showed that administration of Azithromycin reduced the frequency of acute exacerbation of COPD [risk ratio (RR) = 0.69; 95% CI 0.53, 0.91, p = 0.008] (Figure 2). Subgroup analysis of Azithromycin dosage (Table 3) revealed that 500 mg Azithromycin [risk ratio (RR) = 0.65; 95% CI 0.53–0.79, p=0.01] is more beneficial than 250 mg Azithromycin [risk ratio (RR) = 0.60; 95% CI 0.27–1.33, p=0.21] in reducing acute exacerbation rate. Moreover, administration of Azithromycin for 12 months [risk ratio (RR) = 0.75; 95% CI 0.59–0.94, p=0.01] was more effective than 3 months. [risk ratio (RR) = 0.36; 95% CI 0.16–0.79, p=0.01]. Additionally, long-term administration of Azithromycin to COPD patients was not associated with increased risk of developing adverse events [risk ratio (RR) = 0.94; 95% CI 0.81, 1.11, p = 0.48] (Figure 3), subgroup analysis of Azithromycin dosage and therapy duration (Table 4) reported no significant difference between Azithromycin and Placebo groups in developing adverse events.

Regarding the risk of bias assessment, the included studies had low risk of bias. Additionally, sensitivity analysis and publication bias sensitivity analysis on the frequency of acute exacerbation performed by deleting the highest weight trial<sup>24</sup> revealed no significant difference on the results (p value changed to 0.03). In addition, sensitivity analysis on the adverse events performed by deleting the highest weight trials<sup>24,27</sup> also revealed no

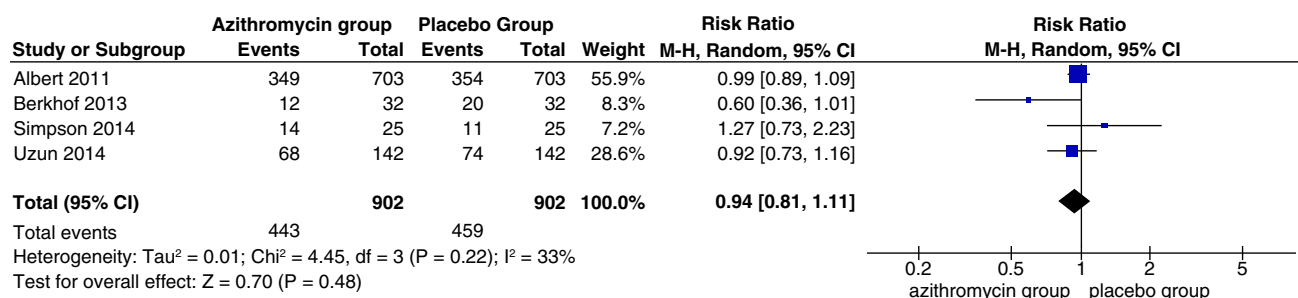


**Figure 2. Forest plot of risk ratios of the frequency of acute exacerbations of chronic obstructive pulmonary disorder (COPD) in patients treated with Azithromycin compared to those who received the placebo.** The size of the square is proportional to the weight of the individual studies. M-H = Mantel-Haenszel method.

**Table 3. subgroup analysis for the frequency of acute exacerbation of chronic obstructive pulmonary disorder (COPD) based on the therapy duration and azithromycin dosage.**

Subgroup	Acute exacerbation frequency of COPD		
	studies, n	RR (95% CI)	P value
250 mg azithromycin	2	0.60 [0.27, 1.33]	0.21
500 mg azithromycin	1	0.65 [0.53, 0.79]	< 0.001
3 months therapy	1	0.36 [0.16, 0.79]	0.01
12 months therapy	2	0.75 [0.59, 0.94]	0.01





**Figure 3. Forest plot of risk ratios of developing adverse events in patients treated with Azithromycin compared to those who received the placebo.** The size of the square is proportional to the weight of the individual studies. M-H = Mantel-Haenszel method.

significant difference on the results (p value changed to 0.36). Furthermore, regarding publication bias analysis, funnel plots of both acute exacerbation frequency and adverse events were symmetrical. In regard to heterogeneity among the studies, 77% heterogeneity was found among the frequency of acute exacerbation meta-analysis studies, while 33% was found among adverse events meta-analysis studies.

## Discussion

Long-term administration of Azithromycin was associated with reduction in the frequency of acute exacerbation among COPD patients, similar findings have been detected among cystic fibrosis patients<sup>28</sup>, however Yao and colleagues deduced that Erythromycin was more effective than Azithromycin in decreasing acute exacerbation frequency<sup>29</sup>.

Many studies have investigated the immunomodulatory effects of macrolides, like decreasing the synthesis of pro-inflammatory cytokines in response to viral infections<sup>30</sup>, decreasing the hypersecretion of pro-inflammatory cytokines and chemokines<sup>31</sup>, enhancement of phagocytosis function of alveolar macrophages<sup>32</sup>, and preserving airway epithelial integrity<sup>33</sup>. Moreover, in addition to the immunomodulatory effects, the decrease in airway bacterial colonization in patients receiving Azithromycin might also be linked to the reduction in the systemic inflammation<sup>34</sup> since infections are the most common cause of acute exacerbation<sup>7</sup>.

The statistical pooling of the data revealed that 500 mg dose of Azithromycin is superior to 250 mg dose, however this results is not enough to draw a conclusion that it is more beneficial, since there is only one study included in the meta-analysis that used a 500 mg dose with only 92 patients in contrast to 1256 patients that were included in the studies that used a 250 mg dose.

Moreover, In the meta-analysis, no difference was found regarding the development of adverse events between the Azithromycin group and the Placebo group even at 500 mg dose and for 12 months' therapy duration, in contrast to a previous meta-analysis, which revealed that nonfatal adverse events (gastrointestinal reactions, ototoxicity, rash, and liver injury) were associated with the Placebo group. In addition, hearing decrement occurred more frequently in participants receiving Azithromycin compared to those receiving Placebo, but the

improvements in hearing that occurred on repeat testing, suggested that hearing decrements were overestimated in both groups. Gastrointestinal adverse events were the second most common encountered, conversely, they were the most common side effects reported in two previous studies<sup>28,29</sup>. nevertheless, the usage of serial audiometry was only in one study while the other included studies report no usage of audiometry in assessing hearing decrement among the participants, this might have led to underreporting of adverse events in these studies, which may in turn have led eventually to this result in the meta-analysis. Additionally, Albert *et al.* and Simpson *et al.* used a daily dose of 250mg Azithromycin, but Berkhof *et al.* used a three times a week dose of 250mg Azithromycin, while Uzun *et al.* used a three times a week dose of 500mg Azithromycin. The meta-analysis did not differentiate between intermittent and daily dosing, which might affect the results of the subgroup analysis of dosage and adverse events.

In summary, this study revealed that, long-term Azithromycin administration for COPD patients is not statistically associated with increased risk of developing adverse events, yet three studies did not perform serial audiometry which might have led to under reporting of the adverse events. Furthermore, there is a lack of differentiation between intermittent and daily dosing in the adverse events meta-analysis, these limitations might proscribe such a conclusion. In addition, the results of the pooled data suggest that Azithromycin is effective in reducing the frequency of acute exacerbation of COPD, and the use of Azithromycin may be beneficial for COPD patients. Only four studies were included in this review, more studies are required to confirm our findings especially regarding dosage and adverse events.

## Data availability

### Underlying data

Harvard Dataverse: Systematic Revman file. <https://doi.org/10.7910/DVN/EQMBCH><sup>23</sup>

### Reporting guidelines

Harvard dataverse, PRISMA checklist for 'Safety and efficacy of Azithromycin in prevention of chronic obstructive pulmonary disease exacerbation: systematic review and meta-analysis'. <https://doi.org/10.7910/DVN/3XMNFR><sup>35</sup>

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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# Open Peer Review

Current Peer Review Status: ? ✖

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## Version 1

Reviewer Report 14 July 2020

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**Miles Weinberger** 

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This submission by Ahmed *et al.* is an attempt at a systematic review and meta-analysis of azithromycin in prevention of exacerbations of chronic obstructive pulmonary disease (COPD). It should be noted that azithromycin should not be capitalized, nor should placebo. A primary limitation of this review includes only 4 studies that differ in the proportion of males and females. The largest of the studies, 1142 subjects, had 58% males, the next largest, 92 subjects, had 43% males. A study with 84 subjects had 75% males. This suggests that the 4 studies may not be looking at the same disease. The heterogeneity of COPD is well established<sup>1-3</sup>. Moreover, another meta-analysis that included 11 studies with 1910 subjects<sup>4</sup> was not included in the current submission.

The interest of macrolide antibiotics, particularly azithromycin, was the serendipitous discovery of the curative effect of these antibiotics in diffuse panbronchiolitis<sup>5</sup> through a mechanism not related to their antibiotic effect. The wide range of immunomodulator effect of azithromycin has resulted in studies of various obstructive lung disease including cystic fibrosis, an asthma phenotype, post-transplant bronchiolitis in addition to non-pulmonary inflammatory diseases<sup>6</sup>. However, no other disease has been associated with essentially absolute cure as seen with diffuse panbronchiolitis. As such, a report such as this by Ahmed *et al.* needs to consider the heterogeneity of COPD and whether the 4 studies are looking at subjects with the same COPD. With the number of subjects predominantly from one study and the failure to include a larger systematic review and meta-analysis further limit the relevance of this report. The authors need to expand their source of data and consider the complexity of COPD and whether azithromycin might best target a specific COPD phenotype.

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**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**

Partly

**Is the statistical analysis and its interpretation appropriate?**

I cannot comment. A qualified statistician is required.

**Are the conclusions drawn adequately supported by the results presented in the review?**

Partly

**Competing Interests:** No competing interests were disclosed.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.**

Reviewer Report 10 April 2019

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**Bruce K. Rubin**

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Noting that the macrolide antibiotics have immunomodulatory (and **not** anti-inflammatory)

properties, these authors have performed a limited systematic review and meta analysis of one of these medications, azithromycin, for the prevention of exacerbations of COPD. After a search of SCOPUS, PubMed, and ClinicalTrials.gov they identified three studies for the acute exacerbations frequency analysis and concluded that the use of azithromycin for three to six months reduces the frequency of exacerbations; but it is not clear if this is clinically significant, if the effect is greatest in severe or less severe exacerbations, or if the dosage or dosing frequency makes a difference. The authors refer to this as a “research study”. It is in fact a systematic review which not does not directly evaluate the safety or efficacy of long-term administration of azithromycin as the authors claim in the first paragraph of their Abstract.

The greatest shortcoming of this study is the authors’ failure to perform a complete literature search of clinical trials studying the use of macrolides in the prevention of COPD exacerbations. In October 2018 a Cochrane review by Herath et al.<sup>1</sup> on this exact subject, includes studies of all macrolide antibiotics for the prevention of COPD exacerbations. The Cochrane review is not only much more comprehensive and robust in terms of analysis and conclusions, but Ahmed et al., fail to cite this previously published systematic review. Furthermore, there was an additional complete systematic review on this subject published in the JAMA in 2014<sup>2</sup> also not cited by these authors; strongly suggesting that their literature review was superficial at best. Therefore, although, the current manuscript is a narrowly focused systematic review; given the published Cochrane review this paper adds little to the literature.

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## Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

## Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

## Is the statistical analysis and its interpretation appropriate?

Partly

## Are the conclusions drawn adequately supported by the results presented in the review?

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** airway biology, biomedical engineering, airway inflammation and immunity

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

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