Original Article

Moxifloxacin is a safe and effective candidate agent for tuberculosis treatment: a meta-analysis of randomized controlled trials

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Background: Moxifloxacin is a fourth-generation fluoroquinolone that has shown good antibacterial activity against both gram-positive cocci and gram-negative bacteria. The purpose of this study was to evaluate the safety and efficacy of moxifloxacin in the drug treatment regimen of patients with tuberculosis.

Methods: We conducted an electronic database search of the PubMed, Embase, the Cochrane Controlled Center Register of Controlled Trials (CENTRAL), Web of Science, Baidu Scholar, and Google Scholar for literature related to clinical randomized controlled trials (RCTs) of tuberculosis patients (from the date of inception of the database to September 25, 2020). The experimental group received moxifloxacin while the control group did not use moxifloxacin. After literature screening, data extraction, and literature quality evaluation, the included studies were meta-analyzed using RevMan software 5.1.

Results: In total, 13 RCTs involving 7,774 patients were included in this meta-analysis. The negative rate of sputum culture in the experimental group (which received moxifloxacin) was significantly higher than that of the control group after 2 months of treatment [relative risk (RR) =1.12, 95% confidence interval (CI): 1.06–1.18, P<0.0001]. Treatment-related complications in the experimental group were significantly greater than those in the control group (RR =1.34, 95% CI: 1.07–1.67, P=0.01). There was no significant difference in the incidence of serious complications between the two groups (RR =1.09, 95% CI: 0.90–1.33, P=0.38). In addition, there were no significant differences in mortality and recurrence rate between the two groups (RR =0.79, 95% CI: 0.51–1.21, P=0.28; RR =1.41, 95% CI: 0.61–3.25, P=0.42).

Conclusions: This meta-analysis found that the addition of moxifloxacin to the treatment regimen of pulmonary tuberculosis patients could significantly increase the negative rate of sputum culture after treatment; however, it has no significant effect on the recurrence rate. Also, the addition of moxifloxacin was found to increase the incidence of complications, but did not increase the incidence of mortality or serious complications.

Keywords: Tuberculosis; moxifloxacin; effectiveness; adverse effects; meta-analysis

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Introduction

At present, the incidence of tuberculosis is slowly declining globally, but the total number of cases is still enormous and poses a significant challenge to the capacity of healthcare systems in many countries (1,2). Therefore, tuberculosis is still one of the major threats to global health, and greater efforts are needed to improve the effectiveness of treatment. At present, anti-tuberculosis therapy primarily relies on a

combination of medications to reduce drug resistance (3).

Currently, the implementation of tuberculosis treatment programs involves the combined administration of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by combined treatment with isoniazid and rifampin for 4 months. To reduce drug resistance, a combination of two drugs (isoniazid and rifampin) and three drugs (isoniazid, rifampin, and pyrazinamide) are often recommended in clinical practice (4,5). However, due to long-term use, compliance is poor in many patients (6). Therefore, new drugs that shorten the treatment time for tuberculosis can greatly reduce the possibility of disease recurrence and death due to insufficient treatment.

The fluoroquinolone drug moxifloxacin has shown antibacterial activity against Mycobacterium tuberculosis *in vitro* and *in vivo* (7,8). Early studies of moxifloxacin in mouse models have demonstrated that moxifloxacin has good bactericidal activity and can replace isoniazid (9). Although the use of moxifloxacin as a supplement in the treatment of tuberculosis has shown good results, the results of many clinical randomized controlled trials (RCTs) published in recent years are not completely consistent with each other. In order to determine the role of moxifloxacin in the treatment of tuberculosis, a meta-analysis of all available studies was conducted to comprehensively evaluate the efficacy and safety of adding moxifloxacin for the treatment of tuberculosis.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2612).

Methods

Literature search

We searched numerous databases, including PubMed, Embase, the Cochrane Controlled Center Register of Controlled Trials (CENTRAL), Web of Science, Baidu Scholar, and Google Scholar, from the date of inception of the database to September 25, 2020, without language restrictions. The search strategy was formulated with reference to the Cochrane Handbook. The English keywords were moxifloxacin and tuberculosis.

Inclusion and exclusion criteria

Inclusion criteria: (I) study type was RCT; (II) subjects were pulmonary tuberculosis patients over 18 years of age; (III) moxifloxacin was included in the treatment plan of the experimental group, and the treatment plan of the control group did not contain moxifloxacin; and (IV) the outcome indicators of the study were: (i) rate of sputum culture conversion, (ii) incidence of adverse reactions, (iii) incidence of serious adverse reactions, (iv) mortality, and (v) recurrence rate.

Exclusion criteria: (I) articles that did not meet the inclusion criteria; (II) the main outcomes of the article could not be obtained, including those cases where we did not receive a response from the author; and (III) repeatedly published articles.

Information and data extraction

We obtained the general characteristics of the included studies by reading the full texts, as well as by examining the inclusion criteria, basic data of the research subjects, intervention measures, follow-up time, main results, etc. For data that could not be obtained, we contacted the author/s as much as possible through email. The data was read and extracted by two authors independently. Any inconsistencies or disagreements were resolved through discussion between the reviewers. If these still could not be resolved, the third author was consulted and made the final decision.

Literature quality evaluation

Two researchers independently evaluated the included literature in accordance with the Cochrane Handbook 5.1.0 quality evaluation standard. The quality evaluation standard includes the following seven aspects: (I) generation of random sequence; (II) hidden grouping; (III) blinding of investigators and participants; (IV) blinding of outcome measurers; (V) incomplete report of patients and outcome events; (VI) selective result report; (VII) other limitations. Each item is divided into three levels: low risk of bias, unclear, and high risk of bias.

Statistical method

Meta-analysis was performed using RevMan5.1 software officially provided by Cochrane. First, the chi-square test and I^2 test were used to analyze the heterogeneity among the studies. If the homogeneity between studies was good (I^2<50%, P>0.1), the fixed effects model was used; otherwise, the random effects model was employed. If the clinical data could not be meta-analyzed, a descriptive

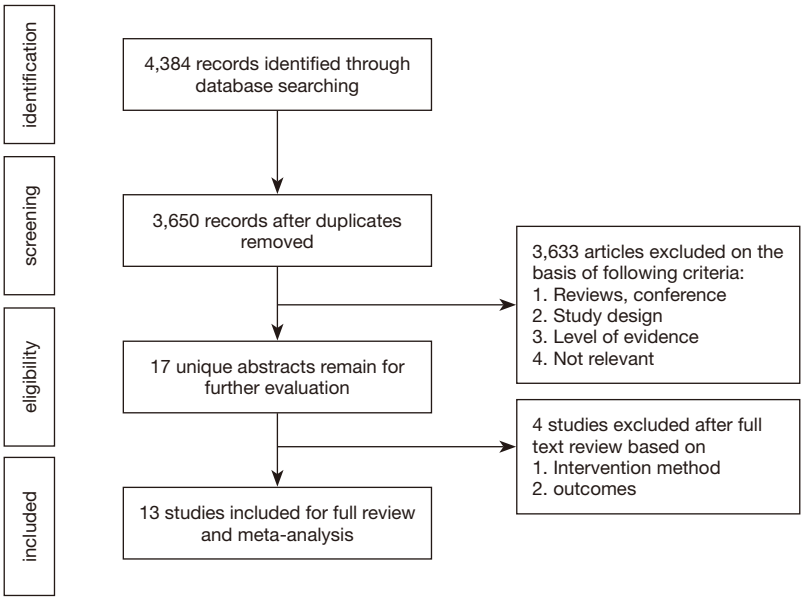

Figure 1 Literature screening process.

analysis was performed.

Results

Literature search results

In total, 4,384 articles were initially retrieved. Of these, 3,650 articles remained after using EndNote software (Thomson Corporation, Connecticut, USA) to eliminate duplicate articles. After reading the titles, abstracts, and full texts, 13 articles were finally included in the meta-analysis. The literature screening flow chart is shown in *Figure 1*.

General characteristics of included articles

A total of 13 studies (10-22) were included in this meta-analysis, all of which were designed as RCTs and involved 7,774 patients. The articles were published between 2006 and 2020. Patients in the articles mainly came from Africa, North America, and South America, mostly from Brazil, Uganda, India, Tanzania, Kenya, Thailand, Malaysia, Zambia, Spain, and China. The details of these studies are shown in *Table 1*.

Quality evaluation

Figure 2 shows the risk of bias of the included RCTs, and the results were acceptable.

Meta-analysis results

Rate of sputum culture conversion

Thirteen studies analyzed the rate of sputum culture conversion in pulmonary tuberculosis patients 2 months after treatment with and without moxifloxacin. The results showed that the rate of sputum culture conversion of the experimental group was significantly better than that of the control group, and the difference was statistically significant [relative risk (RR) =1.12, 95% confidence interval (CI): 1.06–1.18, P<0.0001, see *Figure 3*).

Rate of adverse reactions

Twelve studies analyzed the incidence of adverse reactions in the treatment of tuberculosis patients with and without moxifloxacin. The results showed that the incidence of adverse reactions in the experimental group was significantly higher than that in the control group, and the difference was statistically significant (RR =1.34, 95% CI: 1.07–1.67, P=0.01, see *Figure 4*).

Incidence of serious adverse reactions

Twelve studies analyzed the incidence of serious adverse reactions in patients with pulmonary tuberculosis treated with and without moxifloxacin. The results showed that there was no significant difference in the incidence of serious adverse reactions between the experimental group and the control group (RR =1.09, 95% CI: 0.90–1.33,

Table 1 Characteristics of included studies

Studies	Intervention		Population	Mean age (year) (case/control)	Number (case/control)	Percent Male (%)	Follow-up (month)	Type of study
	Experimental group	Control group						
Burman *et al.* (2006)	2HRZM/4HR	2HRZE/4HR	Africa and North America	31 [24–40]	169 /167	67.0%	2	RCT
Rustomjee *et al.* (2008)	2HRZM/4HR 2HRZG/4HR	2HRZE/4HR	South Africa	31.5 (9.1)	53/54	66.8%	4	RCT
Dorman *et al.* (2009)	2RZEM/4HR	2HRZE/4HR	North America, Brazil, South Africa, Spain, and Uganda	30 [25–38]	214/205	72.0%	2	RCT
Conde *et al.* (2009)	2HRZM/4HR	2HRZE/4HR	Brazil	34.1 (11.9)	74/72	62.0%	2	RCT
Jawahar *et al.* (2013)	2HRZM/2HRM 2HRZG/2HRG	2HRZE/4HR	South India	NA	251/165	73.0%	30	RCT
Velayutham *et al.* (2014)	2HRZEM	2RHZE	South India	NA	616/164	74.6%	2	RCT
Jindani *et al.* (2014)	2R(high-dose) ZEM/2M 2R(high-dose) ZEM/4M	2HRZE/4HR	Africa	NA	188/139 188/221	63.9%	18	RCT RCT
Gillespie *et al.* (2014)	2HRZM 2ERZM	2HRZE 2HERZ	South Africa, India, Tanzania, Kenya, Thailand, Malaysia, Zambia, China, and Mexico	NA	510/514 510/524	70.0%	18	RCT
Dawson (2015)	M(PR)Z	HRZE	South Africa and Tanzania	29.5 [11]/30.4 [10]	60/59 62/59	63%; 65%, 70%	2	RCT
Boeree (2016)	RMHZ	RHZE	South Africa and Tanzania	31 [24–38]/34 [26–41]	63/123	62%; 76%	3	RCT
Conde (2016)	PMHZ	REHZ	Brazil	33 [25–48]/30 [24–45]	62/59	76%, 61%	2	RCT
Yan (2018)	M(PA)REZ	2HREZS/6HRE	China	41 [11]/42 [12]	626/291	70%; 82.8%	>5	RCT
Velayutham (2020)	MHRZE	2HRZE/4RH	South India	NA	1118/253	79%; 76%	3–4	RCT

SD, standard deviation; Median (interquartile range). RCT, randomized controlled trial; E, ethambutol; H, isoniazid; M, moxifloxacin; P, rifapentine; PA, pasiniazid; PR, pretomanid; R, rifampicin; Z, pyrazinamide; NA, not available.

P=0.38, see *Figure 5*).

Mortality and recurrence rate

Nine studies analyzed the mortality of tuberculosis patients treated with and without moxifloxacin. The results showed that there was no statistically significant difference in mortality between the experimental group and the control group (RR =0.79, 95% CI: 0.51–1.21, P=0.28, *Figure 6*). Seven studies analyzed the recurrence rate of tuberculosis patients treated with and without moxifloxacin treatment regimens. There was no significant difference in the recurrence rate between the two groups (RR =1.41, 95%

Figure 2 Risk of bias in the included RCTs. RCTs, randomized controlled trials.

CI: 0.61–3.25, P=0.42, *Figure* 7).

Discussion

In addition to the new drugs recommended by the World Health Organization for the treatment of multidrug-resistant tuberculosis such as linezolid, bedaquinoline and dramanib, there are also about 17 new compounds targeting Mycobacterium tuberculosis that are currently undergoing different experimental phase of clinical trials. Moxifloxacin has demonstrated antibacterial activity against both gram-positive cocci and gram-negative bacteria, and especially against respiratory pathogens (23). Studies have shown that moxifloxacin is effective in the treatment of chronic bronchitis, skin infections, community-acquired pneumonia, and bacterial infections (24,25). In recent years, an increasing number of high-quality clinical studies have focused on the application of moxifloxacin in the treatment of tuberculosis (18,20). However, the latest evidence-based medicine research has not yet been updated.

This meta-analysis included a total of 13 qualified RCTs to evaluate the safety and efficacy of adding moxifloxacin to the treatment regimen of tuberculosis patients. The results showed that the RR value for the rate of sputum culture conversion was 1.12, and the difference was significant (P<0.0001), which indicates that the addition of moxifloxacin could improve the bactericidal activity of the treatment. In terms of overall adverse reactions, the addition of moxifloxacin could also significantly increase the incidence of adverse reactions. The RR value was 1.34, which is a significant difference (P=0.01), indicating that the introduction of moxifloxacin may increase adverse reactions during treatment. However, it did not increase the incidence of serious adverse reactions. In addition, the addition of moxifloxacin did not increase the mortality rate, and could not reduce the recurrence rate in the later period.

An earlier meta-analysis evaluated the clinical outcomes of moxifloxacin plus standard first-line treatment for tuberculosis (26). Patients in the control group were given a combination of pyrazinamide (Z), isoniazid (H), and rifampin (R), with or without ethambutol (Ethambutol, E). This was called standard therapy. Patients in the study group were given the standard regimen plus moxifloxacin. Six eligible studies were included. The results showed that compared with the control group, the addition of moxifloxacin did not increase the rate of sputum culture conversion in the study group, which is inconsistent with the results of our study. Moreover, the meta-analysis of Xu *et al*. (27) included nine appropriate studies, and the results showed that the introduction of moxifloxacin could improve the clinical efficacy by increasing the sputum culture conversion rate and reducing the recurrence rate. The ability of moxifloxacin to increase the sputum culture conversion rate is consistent with the results of our study. Earlier studies by Ruan *et al*. and Guan *et al*. also revealed similar results (28,29), however their results were mostly based on fewer studies or non-RCTs. Our present study

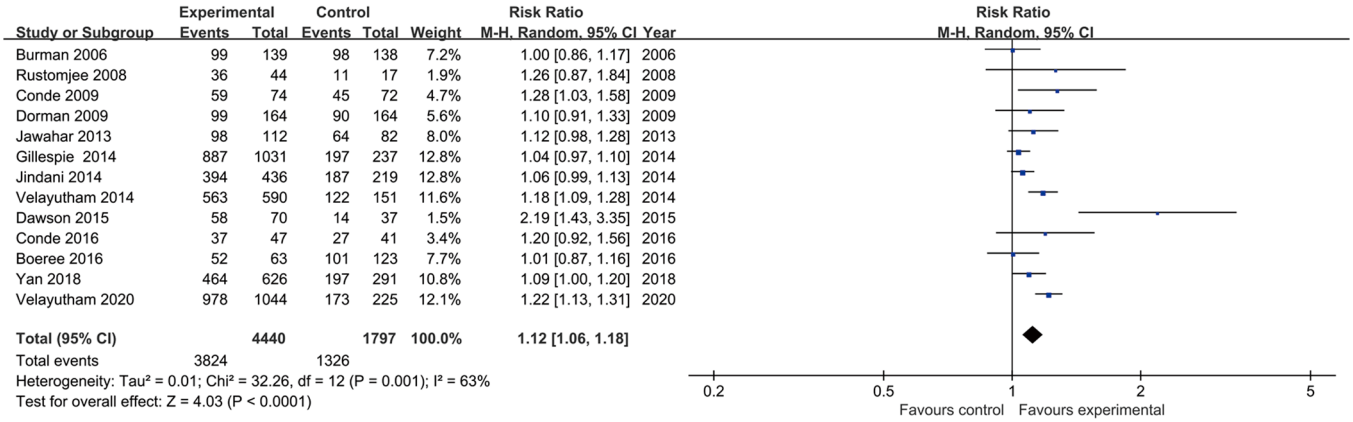

Figure 3 Rate of sputum culture conversion.

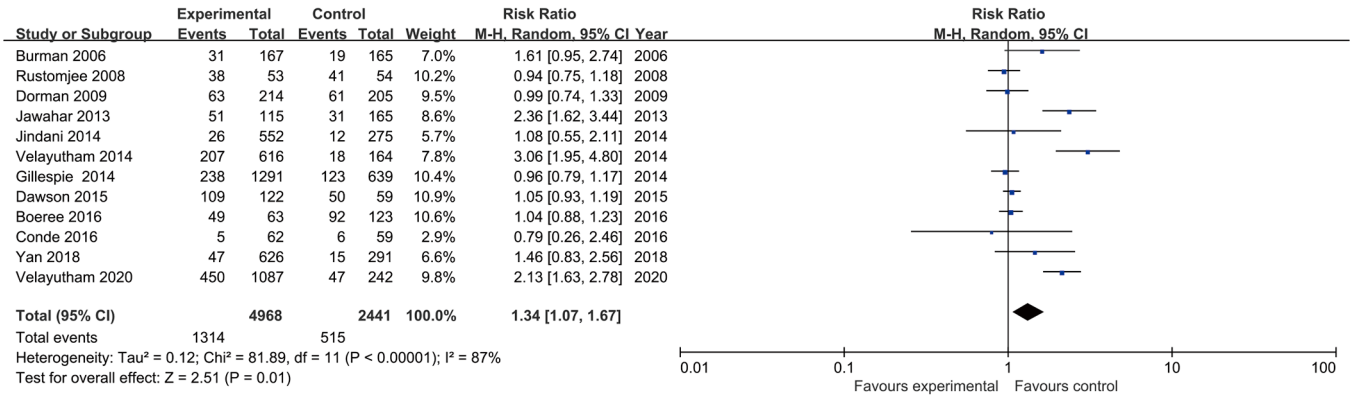

Figure 4 Incidence of adverse reactions.

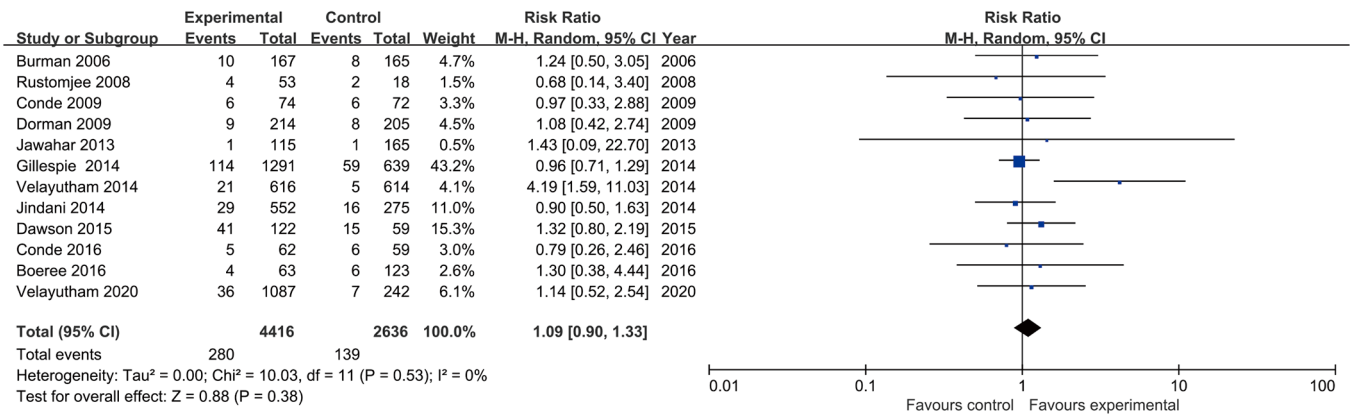

Figure 5 Incidence of serious adverse reactions.

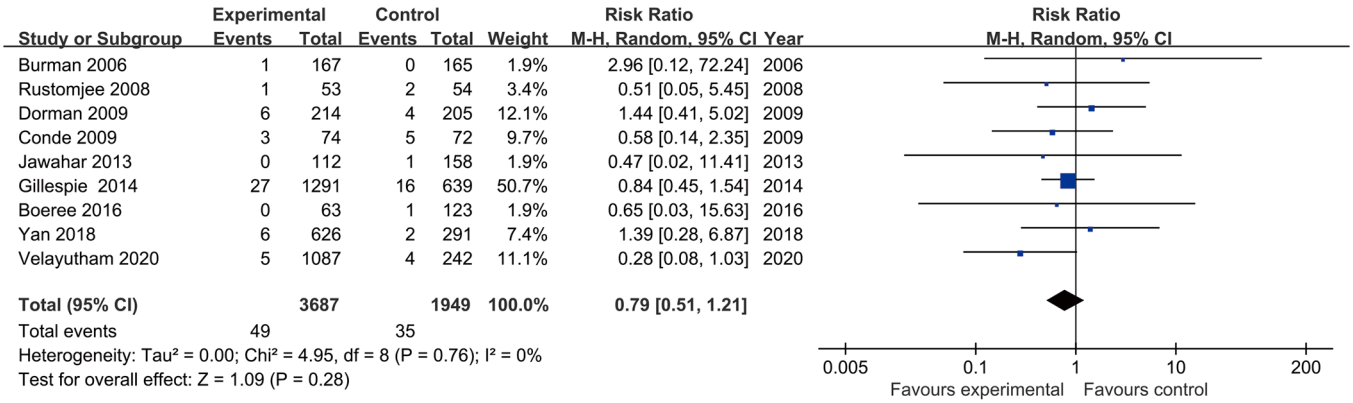

Figure 6 Mortality.

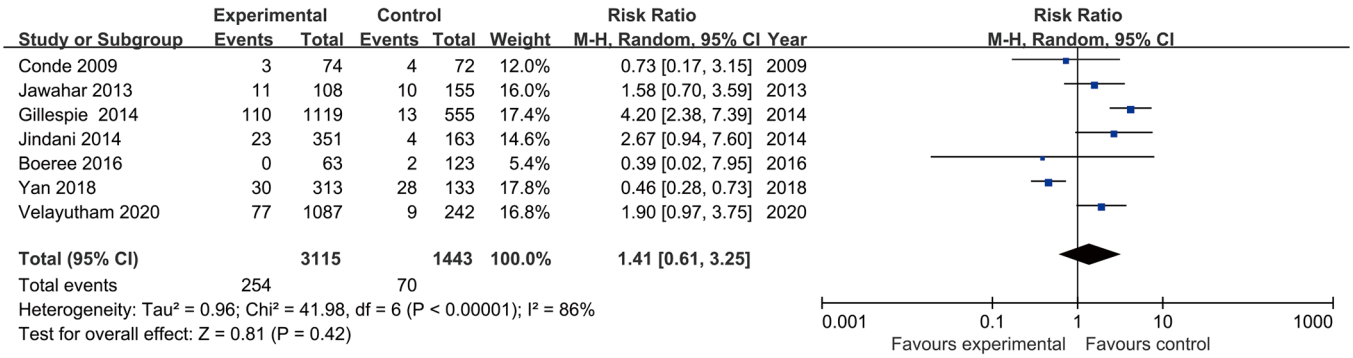

Figure 7 Recurrence rate.

included 13 qualified RCTs involving a greater number of patients than the aforementioned studies, and the results showed that the introduction of moxifloxacin into the treatment regimen did not reduce the recurrence rate of tuberculosis patients. The 13 RCTs included in this study all reported the rate of sputum culture conversion after 2 months of treatment. The overall data showed that the introduction of moxifloxacin in the early treatment regimen could significantly increase the bacteriostasis of the treatment regimen. Furthermore, the previous meta-analysis of Xu *et al*. involved only three studies that reported results related to the recurrence rate (27), and found that moxifloxacin could significantly reduce the recurrence rate. Meanwhile, in our meta-analysis, seven of the 13 RCTs included reported recurrence of sputum culture, and the results demonstrated that the introduction of moxifloxacin cannot reduce the recurrence rate. According to Chen *et al*., Whole Genome Sequencing (WGS) is a promising approach to predict resistance to H, R, Z, Levofloxacin with satisfactory accuracy, sensitivity, and specificity of over 85.0%. The specificity of WGS in diagnosing anti-tuberculosis drug resistance, and high-level resistance to moxifloxacine (2.0 mg/L) needs to be improved (30).

This study had some limitations that should be noted. Firstly, the follow-up time of the studies included in this meta-analysis varied, and the experimental group's medication regimen was not completely consistent, which may have affected the validity of our results. Also, due to the limited number of included studies, subgroup analysis was not performed.

Conclusions

This meta-analysis found that adding moxifloxacin to the treatment plan of tuberculosis patients could significantly increase the rate of sputum culture conversion after

treatment; however, it has no significant effect on the recurrence rate. Also, the addition of moxifloxacin was found to increase the incidence of adverse reactions, but did not increase the incidence of mortality or serious adverse reactions.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-2612

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2612). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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