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Efficacy and Safety of Quinolones as Potential First-Line Therapy for Pulmonary Tuberculosis: A Meta-Analysis

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Abstract

Introduction: Tuberculosis is an infectious disease that continues to plague the world today, causing concerns due to its high mortality rate. The therapy regimens used for the treatment of tuberculosis today have demonstrated high efficacy and safety, potentially reducing the disease's burden, but the use of some standardized medications has caused many resistances to emerge. Over the last decade, researchers have been looking for suitable alternatives, with quinolones emerging as the most promising candidate due to their efficacy, safety, and availability. However, their efficacy as a first-line treatment remains debatable.

Aim: This study is focused on assessing the efficacy and safety of quinolone therapy combined with other regimens for pulmonary TB first-line treatment.

Materials and methods: Literature search was conducted in the databases of Cochrane, PubMed, ScienceDirect, and Google Scholar using the Boolean keywords of "tuberculosis", "treatment", and "quinolone". Statistical analyses were performed using ReviewManager 5.4.1 and shown as forest plots of odds ratios.

Results: We analyzed 13 studies in this study. There were no significant differences between the study group and controls in the conversion rate ≤8 weeks (p=0.07, 95% CI 0.9–13.01), the success rate (p=0.80, 95% CI 0.57–1.54), adverse events (p=0.13, 95% CI 0.91–2.13), mortality rate (p=0.25, 95% CI 0.68–1.11), and recurrence rate (p=0.39, 95% CI [0.74–2.12]) .

Conclusions: According to the forest plot analysis, each of the results is non-significant. This concludes that the efficacy and safety of quinolone tended to be used as the second-line of choice of pulmonary tuberculosis treatment compared to the control group.

Keywords

INTRODUCTION

Tuberculosis (TB) is an infectious disease that keeps negatively affecting global health due to its high fatality rate.[1] According to the World Health Organization (WHO), there were an estimated 10.6 million people suffering from tuberculosis (TB) in 2021, accounting for 1.6 million deaths due to the disease's progression. According to the statistics, TB care is still inadequate around the world, both in terms of facilities and public awareness.[2]

Nowadays, the therapeutic regimens used in the treatment of tuberculosis have been proven to be so efficacious and safe that they might prevent the disease's burden; however, when the standardized drugs were introduced in the management of the disease, they caused many resistances to emerge and became a challenge. Therefore, there was an extensive search for an applicable alternative in the past decade, with quinolone as the most potential candidate due to its efficacy, safety, and availability. Gatifloxacin, moxifloxacin, and levofloxacin are the most numerous quinolones combined with the standard regimen of rifampin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E).[3] There were many preceding meta-analyses showing the promising efficacy and safety of the use of these drugs in TB treatment. However, its potency as the first-line treatment is still debatable. As an instance to this, a study has shown that the quinolone-containing regimen had a higher rate of sputum culture conversion in 2 months of treatment but had less favorable outcome.[4]

AIM

Due to its vagueness, we performed a meta-analysis to unveil the efficacy and safety of quinolone in TB treatment, especially if the drugs were combined with first-line standardized regimen.

MATERIALS AND METHODS

Eligibility criteria

We applied PICO strategies in this review to evaluate the efficacy and safety of quinolones as potential first line therapy in patients with pulmonary tuberculosis. Therefore, the PICO strategies for this meta-analysis were created as follows in **Table 1**:

Table 1. PICO strategies

Aspects	Criteria
Population	All patients with pulmonary tuberculosis
Intervention	Moxifloxacin or another quinolone
Comparison	Conventional FDC (RHZE)
Outcome	Conversion rate ≤8 weeks
	Success rate
	Adverse events
	Mortality rate
	Recurrence rate

RHZE: rifampin, isoniazid, pyrazinamide, and ethambutol

Database search and systematic literature screening

Five authors conducted a literature search in three medical electronic databases, including PubMed, ScienceDirect, and Cochrane Library, from August to September 2023. We used the PICO strategy to facilitate study tracing and identify the suitability of the studies we found. The literature search was performed using the following strategic keywords: tuberculosis OR TB AND treatment OR therapy AND moxifloxacin OR quinolone, which were based on the specification of each search engine. We also manually screened the article references and did not find from the previous systematic-reviews and meta-analysis studies related to our objective to secure every possible literature and include as "studies from other source or review source".

Study selection

Our systematic review is based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statements. The inclusion criteria for this study were as follows:

1. Full-text articles
2. Published in the last 10 years
3. English language
4. Free-full access/open access
5. PICO criteria

We excluded from the study systematic reviews, meta-analyses, literature reviews, case reports, case series, editorial letters, studies of animals, in vivo or in vitro studies, guidelines, books or book sections, abstracts only, and pilot studies.

The obtained studies in the literature search and screening process are compiled in a database. After removing duplicated articles, we screened articles in the required form and sought full-text articles retrieval, each author conducting an eligibility assessment for all articles based on their titles and abstracts. Each author reviewed articles that pass this selection stage by reading the entire manuscript. Any discrepancies were resolved in a discussion.

Risk of bias and data extraction

This systematic meta-analysis review is an observational study. The quality of these studies was assessed by the Jadad Scale. The authors obtained with respective study design, participants' inclusion criteria, intervention, and comparison arm details, analyzed outcomes within its treatment duration of follow-up are some of the basic characteristics' variables of our studies. The main investigated data of our meta-analysis was conversion rate under 8 weeks. The data was extracted in number of events of patients compared to the total included patients by using the Microsoft Excel software and Review Manager (RevMan) 5.4 statistical software.

Statistical analysis

This review focused on the comparison of control and experimental groups in which the results are expressed in number of events and total between the two groups. All meta-analyses were performed using the Review Manager (RevMan) 5.4. statistical software. The outcomes are presented in odds ratio (OR) values. Overall heterogeneity of the outcomes was concluded by the I^2 value where <30.0% represented 'low heterogeneity', and the value of between 30.0-50.0% and >50.0% showed 'moderate or some concern' and 'high or substantial heterogeneity', respectively.

RESULTS

A total of 717 papers were obtained in the literature search, 706 of which were excluded due to various reasons referred to in **Fig. 1**. Thus, a total of 11 eligible studies were included in the meta-analysis.

All data in these studies are associated with the effects of any of the quinolones used as first-line therapy, whether it is moxifloxacin, gatifloxacin, or even a standardized levofloxacin usually used in second-line treatment of pulmonary tuberculosis in nowadays guidelines. All studies were reported as RCT, and the outcomes of adverse events,
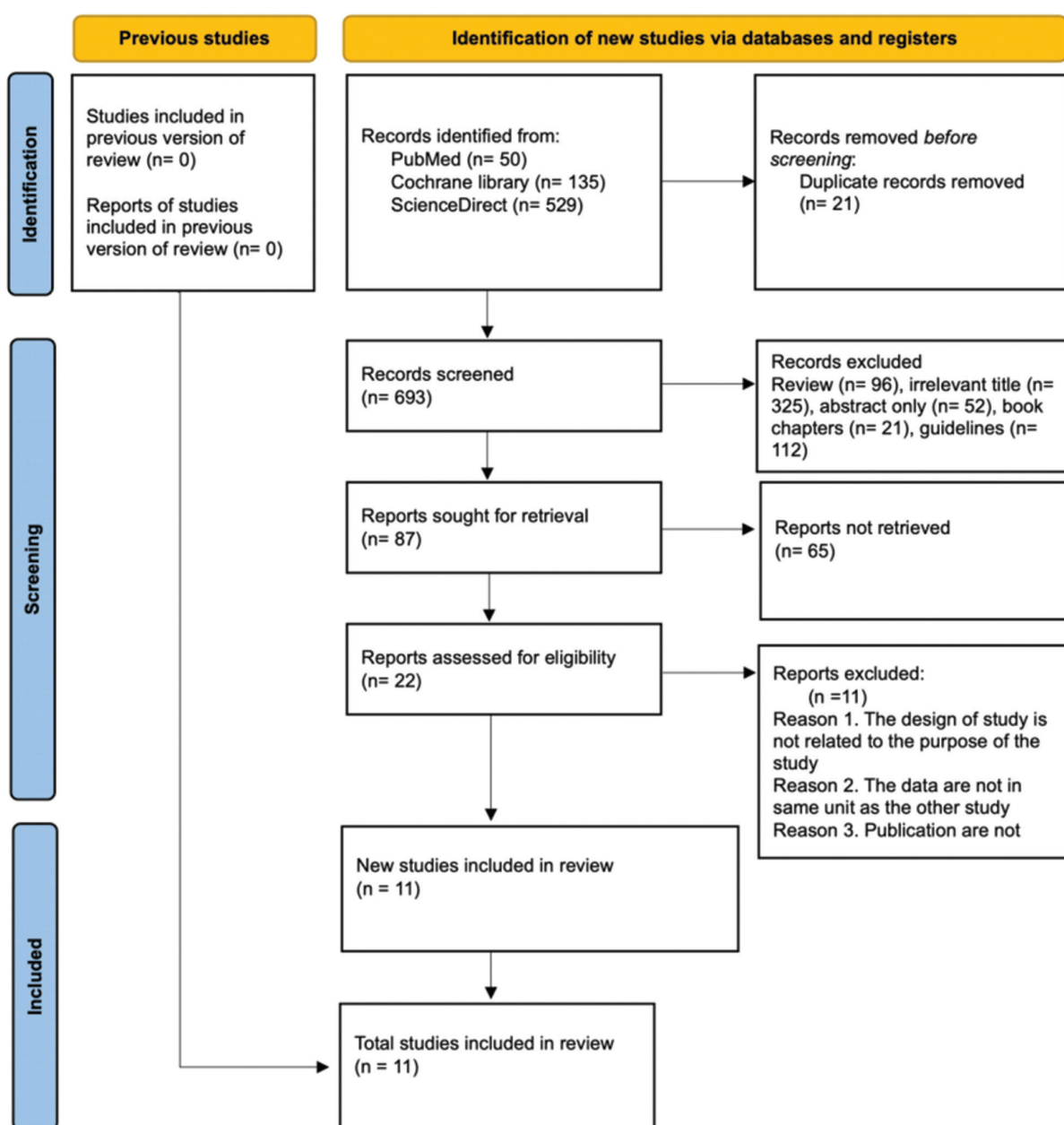

Figure 1. PRISMA chart of the study.

mortality rate, and recurrence rate or treatment failure were also recorded. The characteristics of each study are presented in **Table 2**.

Conversion rate ≤8 weeks

The sputum conversion is defined as a negative status of the mycobacterial content in the sputum at the time it was examined. The analysis was assessed within the 2 months or 8 weeks span after treatment initiation. Nine studies were

included in this analysis with random-effects model used to calculate the overall OR in 95% CI, since there was a significant heterogeneity (I^2: 98%). The overall effect OR in this outcome was 3.43 (95% CI 0.90–13.1, p=0.07), showing that the use of quinolones combined with other regimens improve the time of sputum conversion rate to negative. However, this was nonsignificant, concluding that there were no notable differences in sputum conversion time compared to the control group. The forest plot is shown in **Fig. 2**.

Table 2. Study characteristics

Study, authors	Population	Type of study	Mean age	Dose of quinolone used	Duration	Number of controls/ cases	Combination of drugs controls/cases
Jawahar et al.[5]	South India	RCT	N/A	400 mg	24 mos	165/115 165/136	(2EHRZ3/4HR3)/(2MHRZ3/2 MHR3) (2EHRZ3/4HR3)/(2GHRZ3/2 GHR3)
Gillespie et al.[6]	South Africa, India, Tanzania, Kenya, Thailand, Malaysia, Zambia, China, and Mexico	RCT	N/A	400 mg	18 mos	510/514 510/524	2HRZE/2HRZM 2EHRZ/2ERZM
Jindani et al.[7]	Africa, United Kingdom	RCT	N/A	400 mg	12-18 mos	188/139 188/221	(2RHZE/4RH)/(2MREZ/2MR) (2RHZE/4RH)/(2MREZ/4MR)
Velayutham et al.[8]	India	RCT	N/A	400 mg	2 mos	164/616	2RHZE/2HRZEM
Conde et al.[9]	Brazil	RCT	32	400 mg	2 mos	59/62	2REHZ/2PMHZ
Tweed et al.[10]	Africa	RCT	N/A	400 mg	26 mos	59/38	2RHZE/2BPaMZ
Perumal et al.[11]	Africa	RCT	N/A	400 mg	18 mos	98/98	2RHZE/2RHZM
Velayutham et al.[12]	India	RCT	N/A	400 mg	24 mos	212/99 212/299 212/308 212/305	(2RHZE3/4RH3)/(3MRHZE) (2RHZE3/4RH3)/(2MRHZE/2MRH) (2RHZE3/4RH3)/(2MRHZE/2MRH3) (2RHZE3/4RH3)/(2MRHZE/2MRHE3)
Dorman et al.[13]	USA, China, Africa, Vietnam, France, and Spain	RCT	31	400 mg	18 mos	829/849	2RHZE/2RHZM
Tweed et al.[14]	South Africa, Tanzania, the Philippines, Kenya, Malaysia, Uganda, Thailand, and Ukraine.	RCT	34	400 mg	24 mos	60/56 60/61 60/57	(2HRZE/4HR)/(6Pa200MZ) (2HRZE/4HR)/(4Pa200MZ) (2HRZE/4HR)/(4Pa100MZ)
Nyang'wa et al.[15]	Belarus, South Africa, Uzbekistan	RCT	N/A	400 mg	72 weeks	73/72	2RHZE/BPaLM

G: gatifloxacin; R: rifampin, H: isoniazid, Z: pyrazinamide, E: ethambutol; BPaLM: bedaquiline, pretomanid, linezolid, and moxifloxacin
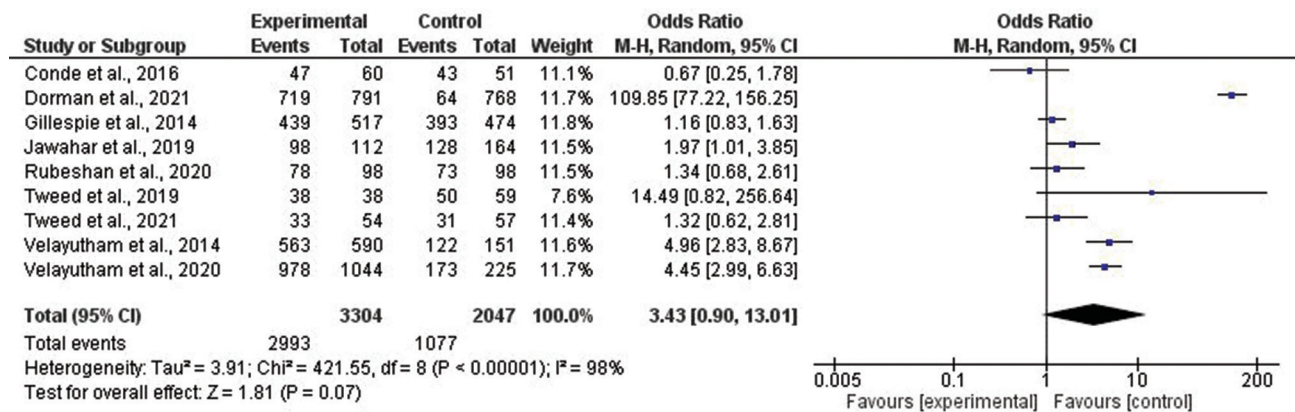
Figure 2. Forest plot of conversion rate analysis.

Success rate

Success rate was considered as completing treatment or stated as being cured by physicians. Eight studies were included in this analysis with random-effects model used to calculate the overall OR in 95% CI, since there was a significant heterogeneity (I^2: 74%). An OR of 0.94 was obtained (95% CI 0.57–1.54, p=0.80), suggesting that the use of quinolone addition to other drugs combination decrease the success of treatment compared to the standardized fixed-dose combination control. Nevertheless, this was insignificant, concluding that there were no notable differences in treatment completion or outcome compared to the control group. The forest plot analysis of success rate is shown in **Fig. 3**.

Adverse events

Adverse events were defined as any of unexpectable outcomes found during the treatment period. This may be skin rashes, elevated liver enzymes, QT interval prolongation, and many other clinical manifestations or laboratory anomalies. Eleven studies included in this analysis with random-effects model used to calculate the overall OR in 95% CI, since there was a significant heterogeneity (I^2: 85%). The analysis's OR was 1.39 (95% CI 0.91–2.13, p=0.13), suggesting that using quinolones in combination causes more adverse events to occur. The p-value in

the analysis, however, inferred that there were no significant differences in the outcome of adverse events in both groups. The forest plot is shown in **Fig. 4**.

Mortality rate

Mortality rate was considered as death related to treatment. Nine studies were analyzed with fixed-effects model to calculate the overall OR in 95% CI due to insignificant heterogeneity (I^2: 14%). An OR of 0.87 (95% CI 0.68–1.11, p=0.25) simply showed that the mortality rate of subjects using quinolones as part of their regimens was lower compared to that of the control group but still failed to reach statistical significance. Thus, the mortality rates in both groups were about just the same. The forest plot analysis is shown in **Fig. 5**.

Recurrence rate

Tuberculosis treatment is prone to recurrence after completion. In this study, we analyzed a total of 5 studies with fixed-effects model to calculate the overall OR in 95% CI due to insignificant heterogeneity (I^2: 10%). The OR was 1.26 (95% CI 0.74–2.12, p=0.39), suggesting that the experimental group tended to have recurrences of the disease more often than the control group. Nonetheless, there were
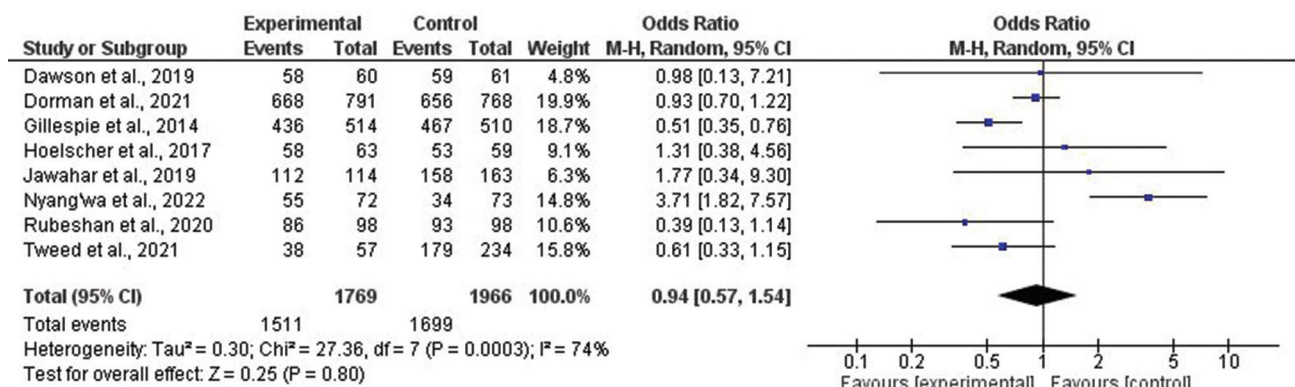

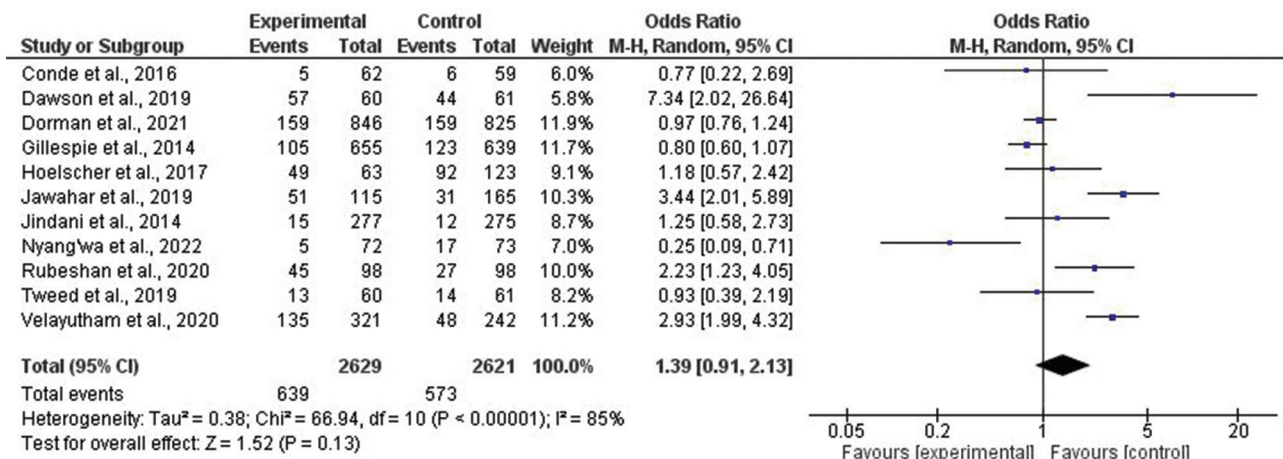**Figure 3.** Forest plot of success rate.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Conde et al., 2016	5	62	6	59	6.0%	0.77 [0.22, 2.69]
Dawson et al., 2019	57	60	44	61	5.8%	7.34 [2.02, 26.64]
Dorman et al., 2021	159	846	159	825	11.9%	0.97 [0.76, 1.24]
Gillespie et al., 2014	105	655	123	639	11.7%	0.80 [0.60, 1.07]
Hoelscher et al., 2017	49	63	92	123	9.1%	1.18 [0.57, 2.42]
Jawahar et al., 2019	51	115	31	165	10.3%	3.44 [2.01, 5.89]
Jindani et al., 2014	15	277	12	275	8.7%	1.25 [0.58, 2.73]
Nyangwa et al., 2022	5	72	17	73	7.0%	0.25 [0.09, 0.71]
Rubeshan et al., 2020	45	98	27	98	10.0%	2.23 [1.23, 4.05]
Tweed et al., 2019	13	60	14	61	8.2%	0.93 [0.39, 2.19]
Velayutham et al., 2020	135	321	48	242	11.2%	2.93 [1.99, 4.32]
Total (95% CI)		2629		2621	100.0%	1.39 [0.91, 2.13]
Total events	639		573			

Heterogeneity: Tau² = 0.38; Chi² = 66.94, df = 10 (P < 0.00001); I² = 85%
Test for overall effect: Z = 1.52 (P = 0.13)

Figure 4. Forest plot of adverse events analysis.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dawson et al., 2019	4	60	2	61	1.4%	2.11 [0.37, 11.96]
Dorman et al., 2021	3	846	7	825	5.2%	0.42 [0.11, 1.61]
Gillespie et al., 2014	105	655	123	639	77.2%	0.80 [0.60, 1.07]
Jindani et al., 2014	7	277	6	275	4.3%	1.16 [0.39, 3.50]
Nyangwa et al., 2022	0	72	2	73	1.8%	0.20 [0.01, 4.18]
Rubeshan et al., 2020	8	98	3	98	2.0%	2.81 [0.72, 10.94]
Tweed et al., 2019	4	60	2	61	1.4%	2.11 [0.37, 11.96]
Tweed et al., 2021	4	65	12	271	3.2%	1.42 [0.44, 4.54]
Velayutham et al., 2020	2	268	4	187	3.5%	0.34 [0.06, 1.90]
Total (95% CI)		2401		2490	100.0%	0.87 [0.68, 1.11]
Total events	137		161			

Heterogeneity: Chi² = 9.30, df = 8 (P = 0.32); I² = 14%
Test for overall effect: Z = 1.14 (P = 0.25)

Figure 5. Forest plot of mortality rate.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dorman et al., 2021	8	791	2	768	8.0%	3.91 [0.83, 18.49]
Jawahar et al., 2019	11	108	10	155	29.4%	1.64 [0.67, 4.02]
Jindani et al., 2014	5	186	5	163	20.7%	0.87 [0.25, 3.07]
Tweed et al., 2021	0	60	2	157	5.5%	0.51 [0.02, 10.86]
Velayutham et al., 2020	8	268	8	187	36.4%	0.69 [0.25, 1.87]
Total (95% CI)		1413		1430	100.0%	1.26 [0.74, 2.12]
Total events	32		27			

Heterogeneity: Chi² = 4.45, df = 4 (P = 0.35); I² = 10%
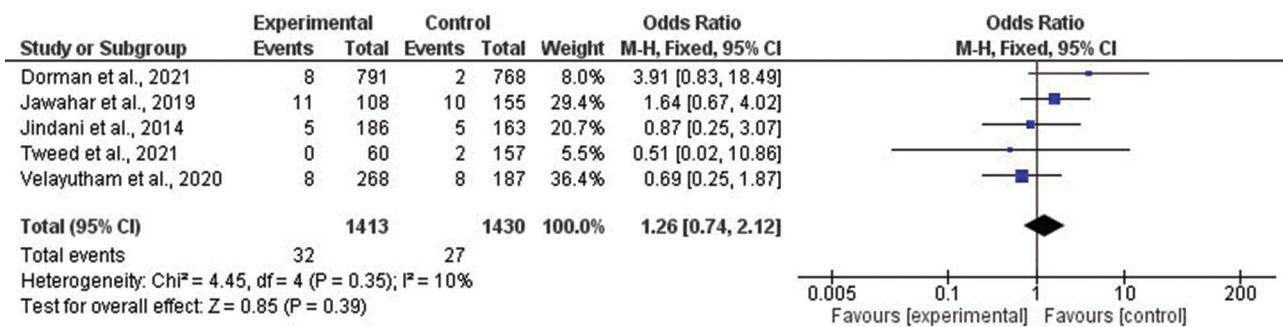Test for overall effect: Z = 0.85 (P = 0.39)

Figure 6. Forest plot of recurrence rate.

no significant differences in the recurrence rate between the two groups. The forest plot analysis is shown in **Fig. 6**.

DISCUSSION

This meta-analysis, which includes 11 eligible studies, was conducted to assess the efficacy and safety of quinolone combined with other regimens administered primarily in pulmonary tuberculosis. This therapy was meant to be administered as medications given without any preceding therapy after diagnosis had been made. The primary outcome of efficacy was measured with the conversion rate of sputum in less than 8 weeks with OR of 3.43 with non-significant difference (*p*=0.07), suggesting that addition of quinolones, such as moxifloxacin, gatifloxacin, or levofloxacin, may enhance the activity of bacterial elimination in comparison with the standardized FDC. However, this may not be an important finding because it was non-significant, suggesting that there was no difference in the bacterial

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elimination activity in both groups.

For secondary outcomes to assess safety, the success rate, adverse events, mortality rate, and recurrence rate were taken into account. Success rate showed OR about 0.94 (p=0.80) suggesting that the addition of quinolone into other first-line regimens lowering patients' adherence to therapy compared to the nowadays recommended regimens. This was non-significant, too, so there was no difference between the experimental group and control group in terms of patients' adherence or outcome. The OR was 1.39 (p=0.13) for adverse events implying that the use of quinolone added to other regimens may add other adverse events compared to the RHZE regimens alone, but this was non-significant for both groups. The mortality rate statistical analysis shown OR of 0.87 (p=0.25), meaning that the use of additional quinolone to other regimens may be safer or decrease the rate of death related to therapy compared to the standardized regimen group. However, this was also insignificant so the safety of both compared regimens were no different. In recurrence rate, the OR was 1.26 which shows that regimens including quinolones tend to recur after the therapy has been completed compared to the FDC-treated group. This suggests that quinolone may be more prone to develop resistance compared to RHZE. Nonetheless, this too, was also non-significant so there was no difference in resistance tendency between both groups.

Some previous similar studies of meta-analysis also compared groups of quinolone-combined regimens and RHZE. The results vary between studies. In a previous meta-analysis[16] assessing similar outcomes, with 9 eligible studies included, revealed that the use of moxifloxacin in the recommended regimen improved the rate of sputum culture conversion compared to the control group within 2 months of treatment, indicating that addition of moxifloxacin could enhance the antibacterial effect. The findings are inconsistent in the present study. The discrepancies in the outcome of this present meta-analysis may be due to the varying first-line treatment combined with varying quinolone regimens, where the experimental group drugs including other drugs of choices, such as bedaquiline or pretomanid, while the earlier study only used H, R, Z, or E with one of the drugs switched with moxifloxacin or the regimen alone was added with moxifloxacin directly. The difference in exclusion and inclusion criteria along with the sample size of eligible studies (nine in the present study versus six in the previous study) might also result in inconsistent findings.

An older review of literature made by Chen et al.[17], with 6 eligible studies, demonstrated that the addition of moxifloxacin did not significantly improve the rate of sputum culture conversion compared to the control group within 2 months of treatment. These findings are consistent with the current study, which found that adding moxifloxacin did not increase the rate of sputum culture conversion compared to the control group within two months of treatment.[17] This implies that the addition of any quinolone regimens to first-line agents is not as effective due to the high potency of the first-line drugs alone in bactericidal activity.

Regarding adverse events, no significant differences were found in these studies, showing that the addition of any quinolone might not add adverse events during the launch of treatment. The recurrence rate in present study is also showing similar trend - no significant differences were found between the experimental group and the controls. On the other hand, the two previous studies have shown that the use of quinolone might reduce relapse cases. The most likely cause of this inconsistent finding, like in the outcome of efficacy, was the use of varying first-line treatments combined with varying quinolone regimens, regardless of the drug's potency in specific populations or settings where certain drugs are most potent. Furthermore, the difference in the study methodology may also yield this inconsistent finding.

Quinolones, known also as fluoroquinolones, are synthesized drugs made from structural modification of the 4-oxo-1,4-dihydroquinoline or 1,8-naphthyridine nucleus. The fluorination of these molecules at position 6 will usually omit the product of fluoroquinolone, such as levofloxacin, moxifloxacin, and gatifloxacin which have antituberculosis activity due to its C-8 methoxy moiety. In general, these drugs are used to treat MDR-TB. It has been approved that the use of quinolone (ofloxacin and ciprofloxacin) is effective with success rates of about 70% for MDR-TB cases. Furthermore, levofloxacin may substitute ofloxacin in some cases, showing superior efficacy. Also, moxifloxacin and gatifloxacin are effective in the MDR-TB treatment due to its lower mutant prevention concentrations for tuberculosis and should have greater potential to prevent the development of drugs resistances. In DS-TB, the most common reason to include quinolone in first-line treatment is due to standardized regimens-induced hepatotoxicity. In case of definitive treatment, ofloxacin or levofloxacin may be used in combination with R or H, or perhaps even pyrazinamide, depending on the liver function status. A study also stated a benefit of using quinolone, showing that there is no additional hepatic insult if levofloxacin and moxifloxacin are used. Aside from this, the lack of pharmacological interactions between drugs proved to be advantageous. However, random regimens could not be used.[18]

There are some limitations in this meta-analysis. Firstly, this study includes all drugs used primarily in tuberculosis treatment, which may distort the potency of the most effective combination regimen between quinolone and non-quinolone drugs. Secondly, this study does not differentiate the subjects with DS or MDR status. Lastly, this study is a retrospective study which means that this meta-analysis has methodological limitations.

CONCLUSIONS

In conclusion, the efficacy and safety of quinolone tended to be used as the second-line choice of pulmonary tuberculosis treatment compared to the control group. However, additional studies should be conducted in the future to define the clear capabilities of quinolone in tuberculosis therapy.

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Эффективность и безопасность хинолонов в качестве потенциальной терапии первой линии при лёгочном туберкулёзе: метаанализ

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Резюме

Введение: Туберкулёз – это инфекционное заболевание, которое продолжает поражать мир и сегодня, вызывая обеспокоенность из-за высокого уровня смертности. Схемы терапии, используемые сегодня для лечения туберкулёза, продемонстрировали высокую эффективность и безопасность, потенциально снижая тяжесть заболевания, но использование некоторых стандартизированных лекарств привело к появлению многих резистентностей. В течение последнего десятилетия исследователи искали подходящие альтернативы, причем хинолоны стали наиболее многообещающими кандидатами из-за их эффективности, безопасности и доступности. Однако их эффективность в качестве лечения первой линии остается дискуссионной.

Цель: Данное исследование сосредоточено на оценке эффективности и безопасности терапии хинолонами в сочетании с другими схемами лечения первой линии туберкулёза лёгких.

Материалы и методы: Поиск литературы проводился в базах данных Cochrane, PubMed, ScienceDirect и Google Scholar с использованием логических ключевых слов „туберкулёз", „лечение" и „хинолон". Статистический анализ проводился с использованием ReviewManager 5.4.1. и показаны в виде Лес графиков отношений шансов.

Результаты: В этом исследовании мы проанализировали 13 исследований. Не было существенных различий между основной группой и контрольной группой по коэффициенту конверсии < 8 недель ($p = 0.07$, 95 % CI 0.9–13.01), частоте успеха ($p = 0.80$, 95 % CI 0.57–1.54), нежелательным явлениям ($p = 0,13$, 95 % CI 0,91–2,13), уровню смертности ($p = 0,25$, 95 % CI 0,68–1,11) и частоте рецидивов ($p = 0.39$, 95 % CI [0.74–2.12]).

Выводы: Согласно анализу Лес участков, каждый из результатов является незначимым. Это позволяет сделать вывод, что эффективность и безопасность хинолонов, как правило, использовались в качестве препарата второй линии выбора для лечения туберкулёза лёгких по сравнению с контрольной группой.

Ключевые слова

эффективность, лечение первой линии, хинолоны, безопасность, туберкулёз