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**RESEARCH ARTICLE** 

The Effectiveness and Safety of Fluoroquinolone-Containing Regimen as a First-Line Treatment for Drug-Sensitive Pulmonary Tuberculosis: A Systematic Review and Meta-Analysis

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## Abstract

## Background

Fluoroquinolone is recommended as a pivotal antituberculous agent for treating multi-drugresistant pulmonary tuberculosis. However, its effectiveness as first-line treatment remains controversial. The present study was conducted to validate the fluoroquinolone-containing regimen for drug-sensitive pulmonary tuberculosis.

## Methods

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials until June 5, 2015. Randomized controlled trials (RCTs) that compared antituberculous regimens containing fluoroquinolone with the standard regimen were included.

## Results

Eleven RCTs that included 6,334 patients were selected. Fluoroquinolone-containing regimens had a higher rate of sputum culture conversion at 2 months of treatment (M-H fixed odds ratio [OR], 1.36; 95% confidence interval [CI], 1.20–1.54). However, the outcomes were less favorable (M-H fixed OR, 0.69; 95% CI, 0.59–0.82) and the associated total adverse events were more frequent (M-H fixed OR, 1.84; 95% CI, 1.46–2.31) in the fluoroquinolone-containing regimen group, without a significant heterogeneity according to treatment duration. Treatment with the fluoroquinolone-containing regimen for 4 months showed a higher relapse rate.

#### Conclusions

Despite a higher culture conversion rate at 2 months of treatment, the fluoroquinolone-containing regimen had limitations, including less favorable outcomes and more adverse events, as the first-line therapy for drug-sensitive pulmonary tuberculosis.

#### Introduction

Pulmonary tuberculosis (TB) is a contagious disease in which the human lung is primarily infected by a pathogen, *Mycobacterium tuberculosis*. According to the World Health Organization (WHO) report from 2014, 9 million occurrences and 1.5 million deaths of TB were found worldwide in 2013 [1]. Since the Stop TB Partnership was established in 1998, the prevalence of TB and mortality from TB slowly declined. It is estimated that about 37 million patients were saved through appropriate treatment such as the standard regimen of isoniazid (H), rifampin (R), ethambutol (E), and pyrazinamide (Z) (HREZ) with a successful treatment rate as high as from 86–95% [1,2].

Adherence to the treatment for drug-sensitive pulmonary TB is one of the most important factors for maximizing the efficacy of TB treatment and minimizing the occurrence of multiple drug resistance [3]. Patients' poor adherence to anti-TB therapy contributes to treatment failure, relapse, or death by pulmonary TB [4,5]. Therefore, numerous efforts have been made to improve the tolerance of patients to anti-TB medication by decreasing the treatment duration [6,7]. However, we still use HREZ for 6 months as a treatment of choice.

Fluoroquinolone is one of the anti-TB agents with a highly effective early bactericidal activity [8,9]. Studies have reported on the effectiveness and importance of fluoroquinolone for the successful treatment of multi-drug resistant pulmonary TB [10,11]. Fluoroquinolone also has been reported to have significant effectiveness on drug-sensitive pulmonary TB as first-line treatment. Previous randomized controlled trials (RCTs) have shown that ofloxacin-containing regimens can replace the HREZ regimen and reduce treatment duration [12,13]. Other fluoroquinolones such as gatifloxacin and moxifloxacin had good treatment effectiveness with an excellent sputum mycobacterial culture conversion rate at 2 months [14,15].

However, no significant differences in the sputum culture conversion rate at 2 months were found between the fluoroquinolone-containing regimen and standard regimen in a previous systematic review and meta-analysis [16,17]. Those studies did not include recent RCTs in which the fluoroquinolone-containing regimens with gatifloxacin or moxifloxacin and treatment duration of 4 months [18–20]. In addition, a meta-analysis to evaluate adverse events of various fluoroquinolones has not been sufficiently conducted.

Thus, we conducted a systematic review and meta-analysis that included recent trials [<u>18</u>–<u>22</u>] to evaluate the effectiveness and safety of the fluoroquinolone-containing regimen in the treatment of drug-sensitive pulmonary TB.

#### **Materials and Methods**

For the present systematic review and meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [23].

## Search Strategy and Selection Criteria

We searched the MEDLINE, EMBASE, and Cochrane Library databases (search date: June 5, 2015). The search terms were "tuberculosis," "quinolone," and "randomized protocol design." Quinolones included ofloxacin, levofloxacin, moxifloxacin, and gatifloxacin. Details of the search strategy are shown in the <u>S1 File</u>.

The inclusion criteria were as follows: 1) RCTs; 2) studies that included patients older than 18 years with newly diagnosed pulmonary TB that was microbiologically confirmed without evidence of resistance to rifampicin or fluoroquinolone; 3) studies that compared fluoroquinolone-containing regimens with standard therapy; and 4) published clinical trials and abstracts in the English language. Standard therapy was defined as HREZ for a 2-month intensive treatment period and HR for a 4-month maintenance treatment period or HRE for a 2-month intensive treatment period.

## Data Extraction and Assessment of the Risk of Bias

Two authors independently checked and selected studies based on titles and abstracts, in accordance to the inclusion criteria. They were blinded to the results of each report and excluded studies that did not meet the inclusion criteria, were duplicated, or were inaccessible. Any disagreement regarding the inclusion or exclusion of studies was resolved by referring to the original articles and discussing them as a group.

The risk of bias of each study was assessed in eight dimensions by applying the Cochrane risk of bias tool (S2 File) as follows: 1) selection bias by adequacy of random sequence generation and allocation concealment; 2) performance bias by appropriate blinding of participants and researchers; 3) attrition bias by knowing if missing data were absent, the reason of exclusion after randomization was not relevant to the study result, and the number and reason of missing data were similar between regimens; 4) reporting bias by reviewing the study protocol and checking the funnel plot; and 5) other biases. As the risk of bias was varied between the efficacy outcomes and safety outcomes in the same study, we applied different weights to each outcome regarding performance and attrition biases. The researchers discussed any disagreement together and reached a consensus.

The collected baseline data from the extracted studies were as follows: author, published year, number of study subjects, inclusion and exclusion criteria, and characteristics of the enrolled population. We determine the characteristics of the enrolled patients, such as sex, smoking status, country, ethnicity, human immunodeficiency virus (HIV) infection status, and existence of pulmonary cavity. We also determined the kinds of medicines used and the treatment duration in each study.

The primary outcome was the sputum culture conversion rate at 2 months of treatment between the fluoroquinolone-containing and standard regimens. Secondary outcomes were treatment failure, relapse, total favorable outcomes, adverse events, serious adverse events, mortality, and adherence. Sputum culture conversion at 2 months of treatment was defined as a negative sputum mycobacterial culture at the end of intensive treatment during the initial 2 months. Treatment failure was defined as at least two consistent positive sputum culture results after 2 months of anti-TB treatment. We determined relapse as a positive conversion of sputum mycobacterial culture after a favorable response at the end of treatment without evidence of reinfection. Total favorable outcome was defined as a negative sputum mycobacterial culture at the end of the whole anti-TB treatment without any outcomes classified as unfavorable. Unfavorable outcomes were events including treatment failure, relapse, death, and any schedule change in treatment due to medical problems, except pregnancy or the initiation of antiretroviral treatment. An adverse event was defined as any newly developed side effect after receiving anti-TB medication. The adverse events were analyzed separately. Gastrointestinal adverse events consisted of nausea, vomiting, abdominal pain, and diarrhea. Drug reactions included drug fever and skin rash. Serious adverse events were considered life-threatening conditions (grade IV), an anti-TB treatment regimen change, hospitalization, or death. Peri-treatment mortality included all-cause deaths during treatment and follow-up. Adherence was defined as compliance to >80% of the planned treatment of the prescribed regimen.

## Statistical analysis

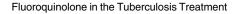
Meta-analysis was used to estimate the odds ratio (OR) with the 95% confidence interval (CI) for the outcome data by using the Mantel-Haenszel (M-H) methods and the fixed effect model. The Q-statistic method with the chi-square test was performed to identify and measure heterogeneity among the pooled data. Heterogeneity among the studies was assumed when the p value was <0.1. The  $I^2$  statistics was calculated for quantification of inconsistency among studies to compensate for the limitation of the chi-square test. If the  $I^2$  was >30%, we considered verifying the meta-analysis result by using the random-effects model. We described the  $I^2$ value first and then the p value by using the chi-square test. We conducted subgroup analyses on the following: 1) trials of fluoroquinolone-containing regimens for 6 months compared with 4 months, 2) trials of adding fluoroquinolone to the standard regimen compared with trials that replaced ethambutol with fluoroquinolone and trials that replaced isoniazid with fluoroquinolone, and 3) trials with HREZ as the standard regimen. A sensitivity analysis was performed to assess the effect of a later-generation fluoroquinolone in each meta-analysis (i.e., moxifloxacin, gatifloxacin, and levofloxacin). Publication bias was assessed by using a funnel plot. All the analyses were performed with Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014).

## Results

We found 739 studies in MEDLINE, 42 in EMBASE, and 110 in the Cochrane Library by searching for the key terms in titles and abstracts. We found 77 duplicated studies. We excluded 781 studies that were not suitable according to the study objective. After reviewing the full text of 34 studies, we finally selected 11 that met the inclusion criteria (Fig 1). After data extraction, the risk of bias was assessed according to 10 areas of bias items (S1 Fig) with PRISMA checklist (S3 File).

## Baseline characteristics of patients in the included studies

The 11 RCTs included 6,334 patients enrolled from 1992 to 2014. We found the following three types of interventions: fluoroquinolone added to standard therapy in 2 studies [22,24], fluoroquinolone replaced ethambutol in 7 [12,14,15,19–21,25], and fluoroquinolone replaced isoniazid in 3 [18,20,26]. Each study had anti-TB treatment durations of 4, 6, or 9 months. We found several types of fluoroquinolones used as an intervention as follows: moxifloxacin in 8 studies, gatifloxacin in 3, ofloxacin in 2, and levofloxacin in 1 (Table 1). Control therapy was used as the standard HREZ regimen for 6 months, except in 1 study that used an HRE regimen for 9 months. All the control standard regimens were administered for a longer duration. Most of the patients were men, ranging from 62% to 77% of the study subjects, and non-white patients. Eight studies included HIV and non-HIV patients, 1 included only HIV patients, 1 excluded HIV patients, and 1 did not evaluate the patients' HIV status. HIV-seropositive status was confirmed in 1,024 patients, and pulmonary cavitary lesions were found in 3,655 patients.



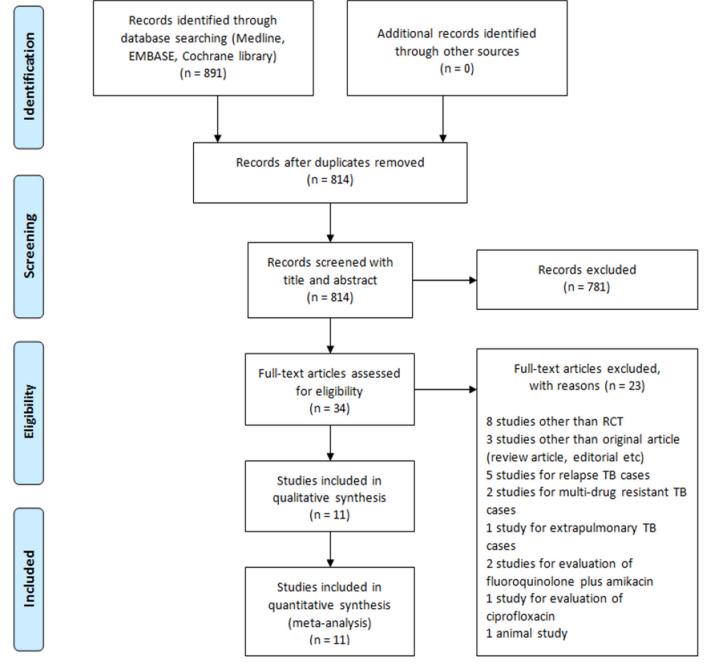


Fig 1. PRISMA flow chart for the meta-analysis.

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# Effectiveness of replacing the standard regimen with the fluoroquinolone-containing regimen

Sputum mycobacterial culture conversion at 2 months of treatment. Eleven RCTs were included to compare the sputum culture conversion rate between the fluoroquinolone-containing and standard regimens (Fig 2). The meta-analysis showed the superiority of the fluoroquinolone-containing regimen over the standard regimen in terms of sputum culture conversion rate at 2 months of treatment (M-H fixed odds ratio [OR], 1.36; 95% CI, 1.20–1.54). Although



Study	Published year	Type of fluoroquinolone used in the intervention	Standard regimen	Male sex	Smoking status	Region	HIV status	Cavity
Kohno et al.[ <u>12]</u>	Cohno et al.[ <u>12]</u> 1992 Ofloxacin		HRE	69%	No remark	Japan	No remark	80%
El-Sadr et al.[24]	1998	Levofloxacin	HREZ	77%	No remark	United States	100%	10%
Burman et al.[25]	2006	Moxifloxacin	HREZ	67%	No remark	Africa, North America	22%	74%
Rustomjee et al. [ <u>14]</u>	2008	Gatifloxacin, Moxifloxacin, Ofloxacin	HREZ	67%	No remark	Africa	59%	94%
Dorman et al.[26]	2009	Moxifloxacin	HREZ	72%	Never smoked: 60%	North America, Brazil, Africa, Spain	11%	76%
Conde et al.[15]	2009	Moxifloxacin	HREZ	62%	Never smoked: 55%	Brazil	3%	68%
Jawahar et al.[21]	2013	Moxifloxacin, Gatifloxacin	HREZ	74%	No remark	India	No remark	No remark
Velayutham et al. [22]	2014	Moxifloxacin	HREZ	75%	No remark	India	All excluded	36%
Merle et al.[ <u>19]</u>	2014	Gatifloxacin	HREZ	73%	No remark	Africa	18%	61%
Jindani et al.[18]	2014	Moxifloxacin	HREZ	64%	Never smoked: 49%	Africa	27%	65%
Gillespie et al.[20]	2014	Moxifloxacin	HREZ	70%	Never smoked: 46%	Africa, India, China, Mexico	7%	71%

#### Table 1. Baseline characteristics of each included study.

HREZ = isoniazid, rifampin, ethambutol, and pyrazinamide; HRE = isoniazid, rifampin, ethambutol.

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substantial heterogeneity was found ( $I^2 = 70\%$ , p = 0.0003), at least the superiority of the fluoroquinolone-containing regimen over the standard regimen was consistently observed in the subgroup analyses. The random-effects model yielded similar results (data not shown). We could not find evidence of publication bias in the funnel plot (S2 Fig).

**Relapse.** Six RCTs were analyzed to determine the differences of relapse between the fluoroquinolone-containing and standard regimens. Significantly more relapses occurred with the fluoroquinolone-containing regimen (M-H fixed OR, 2.68; 95% CI, 2.06–3.50; Fig 3). However, in the subgroup analyses, relapse after 6 months of treatment with the fluoroquinolone-containing regimen did not significantly differ to that with the standard regimen. Although moderate heterogeneity was observed ( $I^2 = 45\%$ , p = 0.12), the subgroup analyses showed consistent results.

**Treatment failure.** Four RCTs were included in the meta-analysis of treatment failure. The fluoroquinolone-containing regimen did not reduce the treatment failure rate (M-H fixed OR, 0.68; 95% CI, 0.39–1.21; <u>S3 Fig</u>). No heterogeneity was found ( $I^2 = 0\%$ , p = 0.92), and the results were similar in the subgroup analyses.

## Safety of replacing the standard regimen with the fluoroquinolonecontaining regimen

**Total favorable outcomes.** Six RCTs were available for the meta-analysis of total favorable outcomes. The incidence of total favorable outcomes was significantly lower in the fluoroquinolone-containing regimens (M-H fixed OR, 0.69; 95% CI, 0.58–0.82; Fig 4). No heterogeneity was found ( $I^2 = 0\%$ , p = 0.75), and the results were similar in the subgroup analyses.

Adverse events. We used 6 RCTs in the meta-analysis of total adverse events and found considerable heterogeneity among the studies. The result showed that the fluoroquinolone-

Study or Subgroup	roquinolone r Events	Total	tandard re Events		Weight	Odds Ratio M-H. Fixed, 95% Cl	Odds Ratio M-H, Fixed, 95% Cl
. Subgroup analysis acco				Total	worum		
Treatment for 4 months	-	cathent u					
		4 004	100		10.00	4 40 14 47 4 74	_
Gillespie 2014 Jawahar 2013	571 208	1221 245	229 128	600 164	43.6% 6.2%	1.42 (1.17, 1.74) 1.58 (0.95, 2.63)	-
Merle 2014	634	752	639	750	26.8%	0.93 [0.70, 1.24]	
Subtotal (95% CI)	004	2218		1514	76.6%	1.26 [1.08, 1.48]	•
Total events	1413		996				•
Heterogeneity: Chi <sup>2</sup> = 6.56, c	df = 2 (P = 0.0	4); I² = 70%					
Test for overall effect Z = 2.9	98 (P = 0.003)	)					
Treatment for 6 months							
		400		400	7.04	4 04 (0 60 4 70)	
Burman 2006 Conde 2009	99 59	139 74	98 45	138 72	7.6% 2.5%	1.01 [0.60, 1.70]	
Dorman 2009	99	164	45 90	164	2.5% 9.5%	2.36 [1.13, 4.95] 1.25 [0.81, 1.94]	
Rustomjee 2008	104	149	32	50	3.9%	1.30 [0.66, 2.55]	
Subtotal (95% CI)		526		424	23.4%	1.30 [0.98, 1.71]	
Total events	361		265				•
Heterogeneity: Chi <sup>2</sup> = 3.42, d	df = 3 (P = 0.3	3); <b>I</b> ² = 12%					
Test for overall effect Z = 1.8							
Subgroup analysis acc			roquinoio	ne-conta	ining re	gimen	
Fluoroquinolone added		d regimen					
El-Sadr 1998	49	53	72	79	0.9%	1.19 [0.33, 4.29]	
Velayutham 2014	563	590	122	151	1.8%	4.96 [2.83, 8.67]	
Subtotal (95% CI)	04.0	643		230	2.6%	3.72 [2.20, 6.28]	<b>—</b>
Total events	612 41-1/0-00	A- 12 - 754	194				
Heterogeneity: Chi <sup>2</sup> = 4.05, (	•						
Test for overall effect: $Z = 4.9$	90 (F × 0.000						
Fluoroquinolone replaci	ing H						
Dorman 2009	99	164	90	164	7.1%	1.25 [0.81, 1.94]	<b></b> +
Gillespie 2014	277	604	229	600	24.6%	1.37 [1.09, 1.73]	
Jindani 2014	394	436	187	219	4.7%	1.61 [0.98, 2.62]	
Subtotal (95% CI)		1204		983	36.4%	1.38 [1.14, 1.67]	◆
Total events	770		506				
Heterogeneity: Chi <sup>2</sup> = 0.55, o							
Test for overall effect: Z = 3.3	35 (P = 0.000	8)					
Fluoroquinolone replaci	ing F						
	-		~~				
Burman 2006 Dondo 2000	99 50	139	98	138	5.6%	1.01 [0.60, 1.70]	
Conde 2009 Dillocatio 2014	59	74 61 7	45	72	1.8%	2.36 [1.13, 4.95]	
Jillespie 2014 Jawahar 2013	294 208	617 245	229 128	600 164	24.0% 4.6%	1.47 [1.17, 1.85] 1.58 [0.95, 2.63]	
Kohno 1992	48	245 62	49	62	4.0% Z.Z%	0.91 [0.39, 2.14]	
Merle 2014	634	752	639	750	19.9%	0.93 [0.70, 1.24]	<b>-</b>
Rustomjee 2008			32	50	2.9%	1.30 [0.66, 2.55]	
	104	149				1.26 [1.09, 1.46]	◆
	104	149 2038	•-		61.0%		
Subtotal (95% CI)	104 1446	2038		1836	61.0%	1.20 [1.03, 1.40]	
Subtotal (95% CI) Fotal events	1446	2038	1220		61.0%	1.20 [1.03, 1.40]	
Subtotal (95% CI) Fotal events Heterogeneity: Chi² = 10.97,	1446 , df = 6 (P = 0.1	2038 09); I² = 45%			61.0%	1.20 [1.03, 1.40]	
Subtotal (95% CI) Fotal events Heterogeneity: Chi¤ = 10.97, Fest for overall effect Z = 3.0	1446 , df = 6 (P = 0. 06 (P = 0.002)	2038 09); I² = 45%	1220	1836	61.0%	1.20 [1.09, 1.40]	
Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>a</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acco	1446 , df = 6 (P = 0. 06 (P = 0.002) ording to ty	2038 09); I² = 45%	1220	1836	61.0%	1.20 [1.03, 1.40]	
Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>a</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acco	1446 , df = 6 (P = 0. 06 (P = 0.002) ording to ty	2038 09); I² = 45%	1220	1836	61.0%	1.20 (1.03, 1.40)	
Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acco 2HREZ/4HR as standard	1446 , df = 6 (P = 0. 06 (P = 0.002) ording to ty	2038 09); I² = 45%	1220	1836	61.0%	1.01 (0.60, 1.70)	
Subtotai (95% CI) Totai events Heterogeneity: Chi <sup>#</sup> = 10.97, Test for overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Burman 2006	1446 , df = 6 (P = 0. 06 (P = 0.002) ording to ty d regimen	2038 09); I <sup>2</sup> = 45% y <b>pe of stan</b>	1220 dard regi	1836 men			
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Subtotal (95% CI) Total events Heterogeneity: Chi™ = 10.97, Test for overall effect Z = 3.0 <b>Subgroup analysis acc</b> <b>2HREZ/4HR as standard</b> Surman 2006 Sornda 2009 Jorman 2009 Jorman 2009 Ballespie 2014	1446 , df = 6 (P = 0.) 06 (P = 0.002) ording to ty d regimen 99 59 99 49 49 571	2038 09); I² = 45% ype of stan 139 74 164 53 1221	1220 dard regi 98 45 90 72 229	1836 men 138 72 164 79 600	6.7% 2.2% 8.4% 1.0% 38.6%	1.01 [0.60, 1.70] 2.30 [1.13, 4.95] 1.25 [0.81, 1.94] 1.19 [0.33, 4.29] 1.42 [1.17, 1.74]	
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Subtotal (95% CI) Total events Heterogeneity: Chi™ = 10.97, Test for overall effect Z = 3.0 Subgroup analysis acco 2HREZ/4HR as standard Burman 2006 Sorda 2009 Dorman 2009 E-Sairt 1998 Billespie 2014 Jawahar 2013 Jindani 2014	1446 df = 6 (P = 0.1 06 (P = 0.002) ording to ty d regimen 99 59 99 49 571 208 394 634	2038 09); I <sup>≠</sup> = 45% ype of stan 139 74 164 53 1221 245 436 752	1220 dard regi 98 45 90 72 229 128 187 639	1836 men 138 72 164 79 600 164 219 750	6.7% 2.2% 1.0% 38.6% 5.5% 5.7% 23.7%	1.01 [0.60, 1.70] 2.36 [1.13, 4.95] 1.25 [0.81, 1.94] 1.19 [0.33, 4.29] 1.42 [1.17, 1.74] 1.58 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24]	
Subtotal (95% CI) Total events deterogeneity, Chi <sup>#</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acco 2HREZ/4HR as standard Jurman 2006 Dornde 2009 Dorman 2009 E-Sadr 1998 Billespie 2014 Javahar 2013 Lindani 2014 Ateria 2014 Austomjee 2008	1446 df = 6 (P = 0.102) ording to ty d regimen 99 59 99 49 571 208 394 634 104	2038 09); I <sup>2</sup> = 45% <b>ype of stan</b> 139 74 164 53 1221 245 436 752 149	1220 dard regi 98 45 90 72 229 128 187 639 32	1836 men 138 72 164 79 800 164 219 750 50	6.7% 2.2% 8.4% 38.6% 5.5% 5.7% 23.7% 3.4%	1.01 [0.60, 1.70] 2.30 [1.13, 4.95] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.58 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55]	
Subtotal (95% CI) Total events Heterogeneity, Chi <sup>®</sup> = 10.97, Fest for overall effect Z = 3.0 <b>Subgroup analysis acc</b> <b>2HREZ/4HR as standard</b> Burman 2006 Sonde 2009 Dorman 2009 El-Sadr 1998 Billespie 2014 Jawahar 2013 Indani 2014 Aferla 2014 Rustomjee 2008 Pelayutham 2014	1446 df = 6 (P = 0.) 06 (P = 0.002) ording to ty d regimen 99 59 99 49 571 208 394 634	2038 09);  * = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590	1220 dard regi 98 45 90 72 229 128 187 639	1836 men 138 72 164 79 600 164 219 750 50 50	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.5% 23.7% 3.4% 2.1%	1.01 [0.60, 1.70] 2.30 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.42 [1.17, 1.74] 1.63 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67]	
Subtotal (95% CI) Total events Heterogeneity: Chi™ = 10.97, Test for overall effect Z = 3.0 <b>Subgroup analysis acc</b> <b>2HREZ/AHR as standard</b> Burman 2006 Dorman 2009 E-Sadr 1998 Billespie 2014 Bawahar 2013 Billespie 2014 Arene 2014 Arene 2014 Arene 2014 Valobatal (55% CI)	1446 df = 6 (P = 0.002) ording to the generation of the generation	2038 09); I <sup>2</sup> = 45% <b>ype of stan</b> 139 74 164 53 1221 245 436 752 149	1220 dard regi 98 45 90 72 229 128 187 639 32 122	1836 men 138 72 164 79 800 164 219 750 50	6.7% 2.2% 8.4% 38.6% 5.5% 5.7% 23.7% 3.4%	1.01 [0.60, 1.70] 2.30 [1.13, 4.95] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.58 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55]	
Subtotal (95% CI) Total events -deterogeneity, Chi <sup>a</sup> = 10.97, Testfor overall effect Z = 3.0 . Subgroup analysis accu 2HREZ/4HR as standard Jurman 2006 Dornde 2009 Dorman 2009 Ei-Sadr 1998 Dillespie 2014 Javavahar 2013 Jindani 2014 Methe 2018 Velsothale 2008 Velsytham 2014 Subtotal (95% CI) Total events	1446 df = 6 (P = 0.002) ording to ty g g g g g g g g g g g g g g g g g g g	2038 09); I <sup>≠</sup> = 45% ype of stan 139 74 163 1221 245 436 752 149 590 3823	1220 dard regi 98 45 90 72 229 128 187 639 32 122 1642	1836 men 138 72 164 79 600 164 219 750 50 50	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.5% 23.7% 3.4% 2.1%	1.01 [0.60, 1.70] 2.30 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.42 [1.17, 1.74] 1.63 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67]	
Subtotal (95% CI) Total events -deterogeneity, Chi <sup>=</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Burman 2006 Sornda 2009 Dorman 2009 El-Sadr 1998 Sillespie 2014 Jawahar 2013 Lindani 2014 Merla 2014 Rustomjee 2008 /elayutham 2014 Subtotal (95% CI) Fotal events -detrogeneity: Chi <sup>=</sup> = 31.90,	1446 df = 6 (P = 0.002) ording to ty d regimen 99 99 49 571 208 394 634 104 563 2780 df = 9 (P = 0.1	2038 09);  * = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002);  * = 72	1220 dard regi 98 45 90 72 229 128 187 639 32 122 1642	1836 men 138 72 164 79 600 164 219 750 50 50	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.5% 23.7% 3.4% 2.1%	1.01 [0.60, 1.70] 2.30 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.42 [1.17, 1.74] 1.63 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67]	
Subtotal (95% CI) Total events -deterogeneity, Chi <sup>=</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Burman 2006 Sornda 2009 Dorman 2009 El-Sadr 1998 Sillespie 2014 Jawahar 2013 Lindani 2014 Merla 2014 Rustomjee 2008 /elayutham 2014 Subtotal (95% CI) Fotal events -detrogeneity: Chi <sup>=</sup> = 31.90,	1446 df = 6 (P = 0.002) ording to ty d regimen 99 99 49 571 208 394 634 104 563 2780 df = 9 (P = 0.1	2038 09);  * = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002);  * = 72	1220 dard regi 98 45 90 72 229 128 187 639 32 122 1642	1836 men 138 72 164 79 600 164 219 750 50 50	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.5% 23.7% 3.4% 2.1%	1.01 [0.60, 1.70] 2.30 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.42 [1.17, 1.74] 1.63 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67]	
Subtotal (95% CI) Total events -deterogeneity, Chi <sup>a</sup> = 10.97, Testfor overall effect Z = 3.0 . Subgroup analysis accu 2HREZ/4HR as standard Jurman 2006 Dornde 2009 Dorman 2009 Ei-Sadr 1998 Dillespie 2014 Javavahar 2013 Jindani 2014 Methe 2018 Velsothale 2008 Velsytham 2014 Subtotal (95% CI) Total events	1446 df = 6 (P = 0.002) ording to ty d regimen 99 99 49 571 208 394 634 104 563 2780 df = 9 (P = 0.1) 00 (P < 0.0000	2038 09);  * = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002);  * = 72	1220 dard regi 98 45 90 72 229 128 187 639 32 122 1642	1836 men 138 72 164 79 600 164 219 750 50 50	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.5% 23.7% 3.4% 2.1%	1.01 [0.60, 1.70] 2.30 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.42 [1.17, 1.74] 1.63 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67]	
Subtotal (95% CI) Total events -teterogeneity, Chi <sup>®</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Burman 2006 Dornda 2009 Dorman 2009 El-Sadr 1998 Billespie 2014 Jawahar 2014 Jawahar 2014 Austomiee 2008 /elayutham 2014 Subtotal (95% CI) Total events Heterogeneity; Chi <sup>®</sup> = 31.90, Test for overall effect Z = 4.9	1446 df = 6 (P = 0.002) ording to ty d regimen 99 99 49 571 208 394 634 104 563 2780 df = 9 (P = 0.1) 00 (P < 0.0000	2038 09);  * = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002);  * = 72	1220 dard regi 98 45 90 72 229 128 187 639 32 122 1642	1836 men 138 72 164 79 600 164 219 750 50 50	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.5% 23.7% 3.4% 2.1%	1.01 [0.60, 1.70] 2.30 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.42 [1.17, 1.74] 1.63 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67]	
Subtotal (95% CI) Total events Heterogeneity, Chi <sup>™</sup> = 10.97, Test for overall effect Z = 3.0 <b>Subgroup analysis acc</b> <b>2HREZ/4HR as standard</b> Burman 2006 Sonda 2009 Dorman 2009 E-Sadr 1998 Billespie 2014 Havahar 2013 Billespie 2014 Merle 2014 Merle 2014 Austomjee 2008 (elayutham 2014 Subtotal (95% CI) Total events Heterogeneity, Chi <sup>™</sup> = 31.90, Test for overall effect Z = 4.9 <b>9HRE as standard regin</b> Cohno 1992	1446 df = 6 (P = 0.002) ording to ty d regimen 99 59 99 49 571 208 208 208 208 208 208 208 208 208 208	2038 09);  * = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002);  * = 72 11)	1220 dard regi 98 45 90 72 229 128 187 639 32 122 122 1642 %	1836 men 138 72 164 79 800 164 219 750 50 151 2387	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.7% 23.7% 24.7% 97.4%	1.01 [0.60, 1.70] 2.30 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.58 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67] 1.37 [1.21, 1.55]	
Subtotal (95% CI) Total events -deterogeneity, Chi <sup>®</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Burman 2006 Dorman 2009 El-Sadr 1998 Sillespie 2014 Jawahar 2013 Bindani 2014 Merla 2014 Rustomjee 2008 (elayutham 2014 Subtotal (95% CI) Fotal events Hetrogeneity: Chi <sup>®</sup> = 31.90, Fest for overall effect Z = 4.9 9HRE as standard regin	1446 df = 6 (P = 0.002) ording to ty d regimen 99 59 99 49 571 208 208 208 208 208 208 208 208 208 208	2038 2038;  ² = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002); P = 72 11) 62	1220 dard regi 98 45 90 72 229 128 187 639 32 122 122 1642 %	1836 men 138 72 164 79 600 164 219 750 50 151 2387	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.7% 23.7% 3.4% 2.1% 97.4%	1.01 [0.60, 1.70] 2.36 [1.13, 4.95] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.58 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67] 1.37 [1.21, 1.55]	
Subtotal (95% CI) Total events -teterogeneity, Chi <sup>®</sup> = 10.97, Festfor overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Jurman 2006 Dornde 2009 Dorman 2009 E-Sadr 1998 Billespie 2014 Jawahar 2013 Bindani 2014 Austomjee 2008 (elayutham 2014 Subtotal (95% CI) Fest for overall effect Z = 4.9 9HRE as standard regin Kohno 1992 Subtotal (95% CI)	1446 df = 6 (P = 0.002) ording to ty d regimen 99 59 99 49 571 208 394 634 104 633 106 653 2780 df = 9 (P = 0.1 20 (P < 0.0000 men 48 48	2038 2038;  ² = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002); P = 72 11) 62	1220 dard regi 98 45 90 72 229 128 187 639 32 122 122 1642 %	1836 men 138 72 164 79 600 164 219 750 50 151 2387	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.7% 23.7% 3.4% 2.1% 97.4%	1.01 [0.60, 1.70] 2.36 [1.13, 4.95] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.58 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67] 1.37 [1.21, 1.55]	
Subtotal (95% CI) Total events -deterogeneity, Chi <sup>=</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Burman 2006 Dorman 2009 El-Sadr 1998 Sillespie 2014 Jawahar 2013 Bindani 2014 Merla 2014 Rustomjee 2008 (elayutham 2014 Subtotal (95% CI) Fotal events Subtotal (95% CI) Total events	1446 df = 6 (P = 0.002) ording to ty d regimen 99 53 49 49 571 208 384 634 104 563 2780 df = 9 (P = 0.0000 men 48 48 48	2038 2038;  ² = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002); P = 72 11) 62	1220 dard regi 98 45 90 72 229 128 187 639 32 122 122 1642 %	1836 men 138 72 164 79 600 164 219 750 50 151 2387	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.7% 23.7% 3.4% 2.1% 97.4%	1.01 [0.60, 1.70] 2.36 [1.13, 4.95] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.58 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67] 1.37 [1.21, 1.55]	
Subtotal (95% CI) Total events -deterogeneity, Chi <sup>=</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Burman 2006 Conde 2009 Dorman 2009 El-Sadr 1998 Billespie 2014 Jawahar 2013 Indani 2014 Merla 2014 Merla 2014 Rustomjee 2008 /elayutham 2014 Subtotal (95% CI) Fotal events -detrogeneity: Not applicabl Total eyents Heterogeneity: Not applicabl Total eyents Heterogeneity: Not applicabl Total eyents	1446 df = 6 (P = 0.002) ording to ty d regimen 99 53 49 49 571 208 384 634 104 563 2780 df = 9 (P = 0.0000 men 48 48 48	2038 2038;  ² = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002); P = 72 11) 62	1220 dard regi 98 45 90 72 229 128 187 639 32 122 122 1642 %	1836 men 138 72 164 79 600 164 219 750 50 151 2387	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.7% 23.7% 3.4% 2.1% 97.4%	1.01 [0.60, 1.70] 2.36 [1.13, 4.95] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.58 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67] 1.37 [1.21, 1.55]	
Subtotal (95% CI) Total events Heterogeneity, Chi <sup>™</sup> = 10.97, Fest for overall effect Z = 3.0 Subgroup analysis acco 2HREZ/4HR as standard Burman 2006 Dorman 2009 Dorman 2009 Dorman 2009 Dorman 2009 Dorman 2019 Dorman 2019 Dirada (2014 Avayhar 2013 Inidani 2014 Merls 2014 Rustomjee 2008 (elayutham 2014 Subtotal (95% CI) Total events Heterogeneity: Not applicabl Total	1446 df = 6 (P = 0.002) ording to ty d regimen 99 53 49 49 571 208 384 634 104 563 2780 df = 9 (P = 0.0000 men 48 48 48	2038 09);  ² = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002); P = 72 11) 62 62	1220 dard regi 98 45 90 72 229 128 187 639 32 122 122 1642 %	1836 men 138 72 164 79 600 164 219 750 50 151 2387 62 62	6.7% 2.2% 8.4% 1.0% 38.6% 5.7% 23.7% 3.4% 21% 97.4%	1.01 [0.60, 1.70] 2.36 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67] 1.37 [1.21, 1.55] 0.91 [0.39, 2.14] 0.91 [0.39, 2.14]	
Subtotal (95% CI) Total events -deterogeneity, ChI <sup>™</sup> = 10.97, Festfor overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Jurman 2006 Dornde 2009 Dorman 2009 E-Sadr 1998 Billespie 2014 Jawahar 2013 Bindani 2014 Austomjee 2008 Aelaytham 2014 Subtotal (95% CI) Fotal events Heterogeneity: Not applicabl Total overall effect Z = 0.2 . Total Total (95% CI)	1446 df = 6 (P = 0.002) ording to ty g regimen 99 59 99 49 571 208 394 571 208 394 563 208 394 634 104 563 2780 df = 9 (P = 0.1 30 (P < 0.0000 nen 48 48 le 22 (P = 0.83)	2038 2038;  ² = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002); P = 72 11) 62	1220 dard regi 98 45 90 72 229 128 187 639 32 122 122 1642 %	1836 men 138 72 164 79 600 164 219 750 50 151 2387 62 62	6.7% 2.2% 8.4% 1.0% 38.6% 5.5% 5.7% 23.7% 3.4% 2.1% 97.4%	1.01 [0.60, 1.70] 2.36 [1.13, 4.95] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.58 [0.95, 2.63] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67] 1.37 [1.21, 1.55]	
Subtotal (95% CI) Total events -deterogeneity, Chi <sup>=</sup> = 10.97, Fest for overall effect Z = 3.0 . Subgroup analysis acc 2HREZ/4HR as standard Burman 2006 Dorman 2009 El-Sadr 1998 Billespie 2014 Jawahar 2013 Bindani 2014 derls 2014 Qustomjee 2008 /elayutham 2014 Subtotal (95% CI) Total events -detrogeneity: Not applicabl Foet for overall effect Z = 0.2 . Total Total (95% CI) Total events	1446 df = 6 (P = 0.002) ording to ty d regimen 99 59 99 49 571 208 394 634 104 1563 2780 df = 9 (P = 0.1 30 (P < 0.0000 men 48 48 48 48 48 48 48 48 48	2038 09);  * = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002);  * = 72 10 62 62 3885	1220 dard regi 98 45 90 72 229 128 187 639 32 122 1642 49 49 49 49	1836 men 138 72 164 79 600 164 219 750 50 151 2387 62 62	6.7% 2.2% 8.4% 1.0% 38.6% 5.7% 23.7% 3.4% 21% 97.4%	1.01 [0.60, 1.70] 2.36 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67] 1.37 [1.21, 1.55] 0.91 [0.39, 2.14] 0.91 [0.39, 2.14]	
Subtotal (95% CI) Total events Heterogeneity, Chi <sup>®</sup> = 10.97, Test for overall effect Z = 3.0 . Subgroup analysis acco 2HREZ/4HR as standard Jurman 2006 Sconde 2009 Dorman 2009 H-Sadr 1998 Solllespie 2014 Awayhar 2013 Sillespie 2014 Awayhar 2014 Austomiee 2008 Velayutham 2014 Subtotal (95% CI) Total events Heterogeneity, Not applicabl Test for overall effect Z = 0.2 . Total Total (95% CI)	1446 df = 6 (P = 0.002) ording to ty d regimen 99 59 99 99 99 93 49 571 208 634 104 563 2780 df = 9 (P = 0.1 30 (P < 0.0000) nen 48 48 48 18 22 (P = 0.83) 2828 df = 10 (P = 1)	2038 09);  * = 45% ype of stan 139 74 164 53 1221 245 436 752 149 590 3823 0002);  * = 72 17) 62 62 62 3885 0.0003);  * = 45%	1220 dard regi 98 45 90 72 229 128 187 639 32 122 1642 49 49 49 49	1836 men 138 72 164 79 600 164 219 750 50 151 2387 62 62	6.7% 2.2% 8.4% 1.0% 38.6% 5.7% 23.7% 3.4% 21% 97.4%	1.01 [0.60, 1.70] 2.36 [1.13, 4.96] 1.25 [0.81, 1.94] 1.42 [1.17, 1.74] 1.61 [0.98, 2.62] 0.93 [0.70, 1.24] 1.30 [0.66, 2.55] 4.96 [2.83, 8.67] 1.37 [1.21, 1.55] 0.91 [0.39, 2.14] 0.91 [0.39, 2.14]	

Fig 2. Sputum culture conversion rates at 2 months of treatment. H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide.

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Study or Subgroup	Events	Total I	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
. Subgroup analysis acc				. otul	Trongit		
Treatment for 4 month	s						
Gillespie 2014	110	1119	13	555	19.4%	4.55 [2.53, 8.15]	
Jawahar 2013	30	230	10	155	12.9%	2.17 [1.03, 4.59]	
Jindani 2014	26	193	5	188	5.4%	5.70 [2.14, 15.18]	
Merle 2014	101	694	47	662	51.0%	2.23 [1.55, 3.21]	
Subtotal (95% CI)		2236		1560	88.8%	2.94 [2.24, 3.85]	•
Total events	267		75				
Heterogeneity: Chi <sup>2</sup> = 6.74, Test for overall effect: Z = 7.							
Treatment for 6 month	s						
Conde 2009	3	85	4	85	4.8%	0.74 [0.16, 3.41]	
Jindani 2014	5	212	5	188	6.4%	0.88 [0.25, 3.10]	
Subtotal (95% CI)		297	Ŭ,	273	11.2%	0.82 [0.31, 2.17]	
Total events	8		9				
Heterogeneity: Chi <sup>2</sup> = 0.03, Test for overall effect: Z = 0.							
. Subgroup analysis acc			roquinolo	one-con	taining	regimen	
Fluoroquinolone added	to standa	ard regimen					
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applicat Test for overall effect: Not ap							
Fluoroquinolone replac	ing H						
Gillespie 2014	64	551	13	555	13.4%	5.48 [2.98, 10.07]	
Jindani 2014	31	405	5	188	7.4%	3.03 [1.16, 7.93]	
Subtotal (95% CI)		956		743	20.8%	4.61 [2.75, 7.72]	•
Total events	95		18		2010/0	101 [210,112]	-
Heterogeneity: Chi <sup>2</sup> = 1.04,		31): I <sup>2</sup> = 4%					
Test for overall effect: Z = 5.	81 (P < 0.00						
Fluoroquinolone replac	-						
Conde 2009	3	85	4	85	4.5%	0.74 [0.16, 3.41]	
Gillespie 2014	46	568	13	555	14.2%	3.67 [1.96, 6.88]	
Jawahar 2013	30	230	10	155	12.2%	2.17 [1.03, 4.59]	
Kohno 1992	0	70	0	68		Not estimable	
Merle 2014	101	694	47	662	48.3%	2.23 [1.55, 3.21]	
Subtotal (95% CI)	4.00	1647	74	1525	79.2%	2.39 [1.81, 3.18]	•
Total events Heterogeneity: Chi² = 4.27, Test for overall effect: Z = 6.			74				
. Subgroup analysis acc			dard reg	imen			
2HREZ/4HR as standard	d regimen						
Conde 2009	3	85	4	85	5.0%	0.74 [0.16, 3.41]	
Gillespie 2014	110	1119	13	555	20.3%	4.55 [2.53, 8.15]	
Jawahar 2013	30	230	10	155	13.4%	2.17 [1.03, 4.59]	
Jindani 2014	31	405	5	188	8.2%	3.03 [1.16, 7.93]	
Merle 2014	101	694	47	662	53.2%	2.23 [1.55, 3.21]	
Subtotal (95% CI)		2533			100.0%	2.68 [2.06, 3.50]	•
Total events	275		79				
Heterogeneity: Chi <sup>2</sup> = 7.21, 1 Test for overall effect: Z = 7.							
9HRE as standard regin	nen						
Kohno 1992	0	70	0	68		Not estimable	
Subtotal (95% CI)	~	70	×	68		Not estimable	
Total events	0		0				
Heterogeneity: Not applicab Test for overall effect: Not a	le		÷				
. Total							
		2602		4742	100.0%	2 60 12 66 2 603	
Total (95% CI) Total events	275	2603	70	1/13	100.0%	2.68 [2.06, 3.50]	-
rotarevents	275		79				
Hotorogonoity Ohiz - 7.04	df = A D = 0	121-12-450					
Heterogeneity: Chi <sup>2</sup> = 7.21, Test for overall effect: Z = 7.							0.01 0.1 1 10



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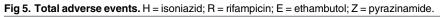
containing regimen was associated with more adverse events (M-H fixed OR, 1.84; 95% CI, 1.46–2.31; Fig 5). Substantial heterogeneity was found in the evaluation of total adverse events ( $I^2 = 75\%$ , p = 0.001). In the subgroup analysis, regimens that replaced isoniazid with fluoro-quinolone did not cause more adverse events than HREZ.

Fluroquinolone r	-		Total	Weight N	Odds Ratio	Odds Ratio M-H. Random, 95% Cl
			Total	Wording III	- In number of CI	
	acadinent	utration				
	100	101	100	15.00	0 45 10 07 0 761	
141		101				
141	155	161	100	13.370	0.45 [0.27, 0.70]	
		101				
	3)					
					0.60 [0.46, 0.79]	
548		548				
1923	2211	1335	1500	04.170	0.75 [0.55, 0.51]	•
	df = 3 (P = 0		ň			
		.21/,1 - 20				
is according to	type of flu	oroquinol	one-con	taining re	egimen	
dded to standa	rd regimer	ı				
	0		0		Not estimable	
0		0				
Not applicable						
eplacing H						
	551	469	555	26.5%	0.59 (0.44, 0.90)	
024		101				
743		629				
	df = 1 (P = 0	.65); I <sup>2</sup> = 0%				
Z = 3.78 (P = 0.00)	02)					
and a local de						
548		548				
1783	15/10	1736	1440	02.5%	0.7 1 [0.50, 0.60]	•
	df = 3 (P = 0)					
		.00),1 = 0.10				
is according to	type of sta	andard reg	imen			
ndard regimen						
855	1119	468	555	41.7%	0.60 [0.46, 0.79]	<b>-</b> _
237	246	158	163	2.4%	0.83 [0.27, 2.53]	
324	405	161	188	13.2%	0.67 [0.42, 1.08]	
548	694	548	662	40.2%	0.78 [0.59, 1.02]	
	2464		1568	97.6%	0.69 [0.58, 0.82]	-
1964		1335				
		.59); I* = 0%				
Z = 4.23 (P < 0.00)	UT)					
regimen						
-	70	62	68	2.4%	0.75 [0.25, 2.29]	
•••	70		68	2.4%		
62		62				
	)					
	2534		1636	100.0%	0.69 [0.58, 0.82]	•
2026		1397				
0.00; Chi <sup>2</sup> = 1.94,	df = 4 (P = 0	.75); I <sup>2</sup> = 0%				2 5 1 0.2
	Events       is according to       is according to       ionths       141       plicable       237       183       548       0.01; Chi*= 3.91,       Z = 2.74 (P = 0.00)       is according to       idded to standa       0       plicable       Not applicable       eplacing H       419       324       743       0.00; Chi*= 0.20,       Z = 3.78 (P = 0.00)       eplacing E       436       237       62       548       1283       0.00; Chi*= 1.45,       Z = 3.49 (P = 0.00)       is according to       ndard regimen       855       237       324       548       1283       0.00; Chi*= 1.45,       Z = 3.49 (P = 0.00)       is according to       ndard regimen       855       237       324       548	Events     Total       is according to treatment       is according to treatment       ionths       141       plicable       Z = 2.99 (P = 0.003)       ionths       855       1119       237       246       183       237       246       183       237       246       183       212       548       694       2271       1823       0.01; Chi*= 3.91, df = 3 (P = 0       Z = 2.74 (P = 0.006)       is according to type of flu       dded to standard regimen       0       100; Chi*= 0.20, df = 1 (P = 0       237       246       324       405       548       237       246       62       70       548       624       1283       0.00; Chi*= 1.45, df = 3 (P = 0       237       246	is according to treatment duration for the second of the	is according to treatment duration tooths 141 193 161 188 141 161 plicable Z = 2.99 (P = 0.003) tooths 655 1119 468 555 237 246 158 163 183 212 161 188 548 694 548 662 2271 1568 1823 1335 0.01; Chi <sup>*=</sup> 3.91, df = 3 (P = 0.27); i <sup>*</sup> = 23% Z = 2.74 (P = 0.006) is according to type of fluoroquinolone-cond dded to standard regimen 0 0 0 plicable Not applicable eplacing H 419 551 468 555 324 405 161 188 956 743 743 629 0.00; Chi <sup>*=</sup> 0.20, df = 1 (P = 0.65); i <sup>*</sup> = 0% Z = 3.78 (P = 0.0002) eplacing E 436 568 468 555 237 246 158 163 62 70 62 68 548 694 548 662 1578 1448 1283 1236 0.00; Chi <sup>*=</sup> 1.45, df = 3 (P = 0.69); i <sup>*</sup> = 0% Z = 3.49 (P = 0.0005) is according to type of standard regimen ndard regimen 855 1119 468 555 237 246 158 163 324 405 161 188 548 694 548 662 1578 1448 1283 1236 0.00; Chi <sup>*=</sup> 1.91, df = 3 (P = 0.69); i <sup>*</sup> = 0% Z = 4.23 (P < 0.0001) regimen 62 70 62 68 1964 1335 0.00; Chi <sup>*=</sup> 1.91, df = 3 (P = 0.59); i <sup>*</sup> = 0% Z = 4.23 (P < 0.0001) regimen 62 70 62 68 1964 1335 0.00; Chi <sup>*=</sup> 1.91, df = 3 (P = 0.59); i <sup>*</sup> = 0% Z = 4.23 (P < 0.0001) regimen 62 70 62 68 548 694 548 662 2464 1335 0.00; Chi <sup>*=</sup> 1.91, df = 3 (P = 0.59); i <sup>*</sup> = 0% Z = 4.23 (P < 0.0001) regimen 62 70 62 68 548 694 548 662 2464 1335 0.00; Chi <sup>*=</sup> 1.91, df = 3 (P = 0.59); i <sup>*</sup> = 0% Z = 4.23 (P < 0.0001) regimen 62 70 62 68 64 70 62 68 62 70 62 68 62 70 62 68 62 70 62 68 62 70 62 68 63 70 62 68 64 70 68 64 70 68 70 69 70 68 70 68 70 68	Events     Total     Events     Total     Weight     N       is according to treatment duration bonths     141     193     161     188     15.9%       141     193     161     188     15.9%     141       plicable     Z = 2.99 (P = 0.003)     0     0     0     0       attal     237     246     158     163     4.4%       183     212     161     188     13.9%       548     694     548     662     32.6%       22.71     1568     84.1%     1335       0.01; Chi*= 3.91, df = 3 (P = 0.27); i* = 23%     Z = 2.74 (P = 0.006)     is according to type of fluoroquinolone-containing redded to standard regimen       0     0     0     0     0       plicable     0     0     0     0       eplacing H     419     651     468     555     26.6%       324     405     161     188     10.9%     237     246     158     163     1.9%     62     70     62	Events     Total     Events     Total     Weight     M.H., Random, 95% CI       is according to treatment duration conths     141     193     161     188     15.9%     0.45 [0.27, 0.76]       141     161     188     15.9%     0.45 [0.27, 0.76]       plicable     2     2.99 (P = 0.003)     0.00 [0.46, 0.79]       237     246     158     163     4.4%     0.83 [0.27, 2.53]       183     2.12     101     188     13.9%     1.00 [0.60, 1.80]       237     246     158     163     4.4%     0.83 [0.27, 2.53]       183     2.12     101     188     13.9%     1.00 [0.60, 1.80]       247     1335     0.78 [0.59, 0.91]     123     1335       0.01; ChiP= 3.91, df = 3 (P = 0.27); i'' = 23%     Z = 274 (P = 0.006)     is according to type of fluoroquinolone-containing regimen       dded to standard regimen     0     0     Not estimable       0     0     0     Not estimable       183     165     26.5%     0.59 [0.44, 0.80]       184     <

Fig 4. Total favorable outcomes. H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide.

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tudy or Subgroup	uroquinolone re Events	-	andard re Events	-	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% Cl
Subgroup analysis a							
reatment for 4 mon	ths						
awahar 2013	122	251	31	165	18.9%	4.09 [2.57, 6.49]	
indani 2014	11	275	12	275	11.3%	0.91 [0.40, 2.11]	
ubtotal (95% CI)		526		440	30.3%	2.90 [1.96, 4.29]	◆
otal events	133		43				
leterogeneity: Chi² = 9.4 est for overall effect: Z =							
reatment for 6 mon	ths						
urman 2006	31	167	19	165	15.3%	1.75 [0.95, 3.25]	
orman 2009	39	214	32	205	26.3%	1.20 [0.72, 2.01]	
indani 2014	15	277	12	275	11.2%	1.25 [0.58, 2.73]	
lustomjee 2008	113	163	41	76	16.9%	1.93 [1.10, 3.38]	
ubtotal (95% CI)	100	821	101	721	69.7%	1.51 [1.12, 2.03]	$\bullet$
otal events leterogeneity: Chi² = 1.9 'est for overall effect: Z =			104				
Subgroup analysis a			roquinol	one-con	taining i	regimen	
luoroquinolone add	ed to standar	rd regimen					
ubtotal (95% CI)		0		0		Not estimable	
otal events	0		0				
leterogeneity: Not applic est for overall effect: No							
luoroquinolone repl	acing H						
orman 2009	39	214	32	205	28.5%	1.20 [0.72, 2.01]	
indani 2014	26	552	12	275	16.2%	1.08 [0.54, 2.18]	
ubtotal (95% CI)		766		480	44.7%	1.16 [0.77, 1.76]	<b>•</b>
otal events	65		44				
leterogeneity: Chi² = 0.0 est for overall effect: Z =							
luoroquinolone repl	acing E						
urman 2006	31	167	19	165	16.6%	1.75 [0.95, 3.25]	
awahar 2013	122	251	31	165	20.5%	4.09 [2.57, 6.49]	
lustomjee 2008	113	163	41	76	18.3%	1.93 [1.10, 3.38]	
ubtotal (95% CI)		581		406	55.3%	2.67 [1.97, 3.63]	•
otal events	266		91				
leterogeneity: Chi² = 6.3 est for overall effect: Z =							
Subgroup analysis a	according to t	ype of stan	dard reg	imen			
HREZ/4HR as stand							
urman 2006	31	167	19	165	14.1%	1.75 [0.95, 3.25]	
orman 2009 Leadr 1999	39 15	214 87	32 26	205 140	24.2%	1.20 [0.72, 2.01]	
I-Sadr 1998 awahar 2013	15	87 251	26 31	140	14.9% 17.4%	0.91 [0.45, 1.84] 4.09 [2.57, 6.49]	
indani 2014	26	552	12	275	13.8%	4.09 [2.57, 6.49]	
ustomjee 2008	113	163	41	76	15.5%	1.93 [1.10, 3.38]	
ubtotal (95% CI)		1434			100.0%	1.84 [1.46, 2.31]	
otal events	346		161				
eterogeneity: Chi² = 20. est for overall effect: Z =			%				
HRE as standard reg	gimen						
ubtotal (95% CI)		0		0		Not estimable	
otal events	0	-	0	-			
leterogeneity: Not applic est for overall effect: No	able						
Total							
otal (95% CI)		1434		1026	100.0%	1.84 [1.46, 2.31]	
otal (95% CI) otal events	346	1434	161	1020	100.0%	1.04 [1.40, 2.31]	•
		001); J2 = 759					<b>⊢ ⊢ ⊢ ⊢</b>
leterogeneity: Chi <sup>2</sup> = 20.			· •				0.01 0.1 1 10



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In the evaluation of hepatotoxicity, drug rash and fever, and serious adverse events, no significant differences were found between the two regimens (<u>S4–S6</u> Figs). However, gastrointestinal adverse events, dizziness, and joint pain were detected significantly more frequently in the patients that received fluoroquinolone-containing regimens (<u>S7–S9</u> Figs). Regimens that replaced ethambutol with fluoroquinolone, especially showed a higher OR for the occurrence of several adverse events than other fluoroquinolone-containing regimens.

**Mortality.** No significant difference in peri-treatment mortality was observed between the fluoroquinolone-containing and standard regimens (M-H fixed OR, 0.92; 95% CI, 0.66–1.29; S10 Fig). The observed duration for detecting death was different among the studies. Four studies assessed all deaths that occurred during and after treatment [15,18–20], 1 study evaluated deaths during treatment [26], and 2 studies included only deaths until 2 months of treatment [24,25]. The subgroup analysis showed a similar mortality rate in each group, and statistical heterogeneity was not found ( $I^2 = 0\%$ , p = 0.84).

Adherence. We found no significant difference in treatment adherence between the fluoroquinolone-containing and standard regimens (M-H fixed OR, 1.19; 95% CI, 0.97–1.45; <u>S11</u> Fig). Heterogeneity was found because 1 study used a stricter definition of adherence than the other studies and reported favorable results of treatment adherence to the gatifloxacin-containing regimen for 4 months ( $I^2 = 35\%$ , p = 0.09) [<u>19</u>].

Effectiveness and safety of later-generation fluoroquinolone-containing regimen. Sensitivity analysis was performed after excluding populations who used ofloxacin and their counterparts in 2 studies [12,14]. A sensitivity analysis revealed that neither the effectiveness nor the safety of a later-generation fluoroquinolone-containing regimen showed obviously different results (data not shown).

#### Discussion

The present study showed a significantly higher sputum mycobacterial culture conversion rate at 2 months of treatment with the fluoroquinolone-containing regimen than with the HREZ or HRE regimen. We did not find statistically significant differences in treatment failure and treatment adherence between the fluoroquinolone-containing and standard regimens. However, the fluoroquinolone-containing regimen group showed less favorable outcomes. In addition, more total adverse events were occurred in the fluoroquinolone-containing regimen group. Significantly more cases of gastrointestinal adverse events, dizziness, and joint pain were associated with the fluoroquinolone-containing regimen.

Previous systematic reviews have reported no significant difference in the rate of sputum mycobacterial culture conversion at 2 months of treatment between the fluoroquinolone-containing regimen and standard regimen, whereas relapse or treatment failure was not fully evaluated because of the lack of available studies [16,17]. In terms of safety, only nausea was more frequently associated with the fluoroquinolone-containing regimen [16]. The present study included 5 studies that were evaluated previously and 6 additional studies [12,18–22], and we performed subgroup meta-analyses according to the treatment duration, which has not been done before.

Our study found that fluoroquinolone has a strong anti-TB effectiveness, as evidenced by, for example, a high sputum mycobacterial culture conversion rate at 2 months of treatment, which is consistent with previous results of good early bactericidal effects [8,27]. Sputum mycobacterial culture conversion rate at 2 months of treatment has been regarded as an important surrogate marker of relapse and has been used as a primary outcome [28]. However, considering that more relapses are found in the fluoroquinolone-containing regimen group, a higher sputum mycobacterial culture conversion rate at 2 months of treatment alone cannot

guarantee successful TB treatment. A negative sputum mycobacterial culture conversion rate at 2 months of treatment and treatment duration should both be considered predictors of relapse. Previous reports have implied that only a very high sputum mycobacterial culture conversion rate at 2 months of treatment can decrease the relapse rate and treatment duration [28]. According to these studies, a 99% culture-negative conversion rate is necessary to reduce the treatment duration from 6 months to 4 months without relapse of >5%. In our study, the fluoroquinolone-containing regimen showed only a 72.8% sputum mycobacterial culture conversion rate at 2 months of treatment. Fluoroquinolone is not powerful enough to reduce the treatment duration. This finding is also supported by a result that the 6-month fluoroquinolone-containing regimen did not increase the relapse rate. In the present study, the 4-month fluoroquinolone-containing regimen had an 11.9% relapse rate, whereas treatment with fluoroquinolone for 6 months showed a 2.7% relapse rate. The 4- and 6-month fluoroquinolone-containing regimen groups showed less total favorable outcomes regarding treatment failure, relapse, death, and unexpected treatment changes, which suggest that the 6-month fluoroquinolone-containing regimen has limitations in replacing the standard regimen. Although fluoroquinolone-containing regimen with 6-month treatment duration can be considered as an alternative regimen, it is not easy to replace the current standard regimen. Our study showed that the fluoroquinolone-containing regimen is inferior to the standard regimen in terms of adverse events. In addition, previous studies have suggested reserving fluoroquinolone for the future treatment of drug-resistant TB [29,30], and fluoroquinolone is not as accessible and affordable in low-income countries [29].

The strength of this study was in the detection that the fluoroquinolone-containing regimen was superior in terms of the sputum culture conversion at 2 months of treatment and inferior in terms of relapse, which was not demonstrated in previous systematic reviews. In addition, we clarified previous issues regarding adverse events by determining the profiles of each adverse event. Adherence, one of the important factors to achieve successful treatment, was assessed and determined to have no significant difference between the fluoroquinolone-containing regimen and standard regimen.

Several limitations were found in the process of this review. First, significant heterogeneity was found in the meta-analysis for primary outcome. However, all subtotal ORs with a 95% CI were <1.0 in the subgroups, which means that at least fluoroquinolone is superior to the standard regimen according to the 2-month conversion rate. Second, studies that used levo-floxacin, which is widely used in the treatment of TB, were few. Third, HRE was included as a standard regimen in this study, which could have led to a lower 2-month conversion rate in the standard regimen group. However, the sensitivity analysis showed similar results. Fourth, there may be an issue with generalization. The frequency of HIV infection and condition of the pulmonary cavity were known risk factors affecting the clinical outcome and were considerably different among evaluated studies. Most studies were conducted in Africa, America, and India, and studies were rarely conducted in Asian countries and Russia despite a high prevalence of TB.

In conclusion, our systematic review of RCTs revealed that although the fluoroquinolonecontaining regimen, including ofloxacin, gatifloxacin, levofloxacin, and moxifloxacin, resulted in a higher culture conversion rate at 2 months of treatment, it led to less favorable outcomes and more total adverse events compared with the standard regimen for drug-sensitive pulmonary TB. The results that suggest that the fluoroquinolone-containing regimen has limitations as the first-line therapy for pulmonary TB could help clinicians make treatment choices in everyday clinical practice.

## **Supporting Information**

S1 Fig. Summary of the assessment of each risk of bias item (%) for each included study. (TIF)

**S2** Fig. Funnel plot of the sputum culture conversion at 2 months of treatment. (TIF)

**S3 Fig. Forest plot of the assessment of treatment failure.** H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide. (TIF)

**S4 Fig. Forest plot of the assessment of hepatotoxicity.** H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide.

(TIF)

**S5 Fig. Forest plot of the assessment of drug rash and fever.** H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide. (TIF)

**S6 Fig. Forest plot of the assessment of serious adverse events.** H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide. (TIF)

**S7 Fig. Forest plot of the assessment of gastrointestinal adverse events.** H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide. (TIF)

**S8 Fig. Forest plot of the assessment of dizziness.** H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide. (TIF)

**S9 Fig. Forest plot of the assessment of joint pain.** H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide. (TIF)

**S10 Fig. Forest plot of the assessment of peri-treatment mortality.** H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide. (TIF)

**S11 Fig. Forest plot of the assessment of adherence to treatment.** H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide. (TIF)

**S1 File. Details of the search strategy.** (TIF)

**S2** File. The details of how to analyze the quality of methodology of the sources. (DOC)

**S3 File.** Preferred reporting items for systematic review and meta-analysis checklist. (DOC)

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Hyun Woo Lee searched and reviewed the studies for meta-analysis, performed the statistical analyses, and wrote the present manuscript. Chang-Hoon Lee, the corresponding author, contributed to the conception or design of the work, helped draft the work, and revised it critically for important intellectual content. Jung Kyu Lee helped search for studies, extracted data, and assessed the risk of bias. Eunyoung Kim established the search methods for MEDLINE, EMBASE, and the Cochrane Library. Jae-Joon Yim provided advice for designing the study and made suggestions for the analysis and interpretation of data for the work.

## **Author Contributions**

Conceived and designed the experiments: HWL JJY CHL. Performed the experiments: HWL JKL. Analyzed the data: HWL JKL EK. Contributed reagents/materials/analysis tools: HWL EK CHL. Wrote the paper: HWL JKL EK JJY CHL. Funding: CHL.

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