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Fixed Dose Combination Anti-tuberculosis Therapy: A Systematic Review and Meta-Analysis

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Study message:
The current evidence does not indicate that fixed-dose combinations of first-line tuberculosis drugs improve treatment outcomes

Abstract

Fixed-dose combination (FDC) formulations are currently recommended for treatment of active tuberculosis. We have conducted a systematic review to evaluate the risk of treatment failure or disease relapse, acquired drug resistance, bacterial conversion after two months of treatment, adverse events, adherence, and treatment satisfaction associated with treatment of active tuberculosis using FDC or separate drug formulations.

We searched four electronic databases for randomized controlled trials and cohort studies. Results from trials that directly compared FDC to separate drug formulations were pooled. Results from other studies were reported separately.

We identified 2450 citations from which 15 controlled trials and four additional relevant studies were included. In the 15 trials there were no differences in acquired drug resistance, bacterial conversion after two months of treatment, or adverse drug reactions with FDC or separate drug formulations. There was a trend toward higher risk of failure or relapse with FDC (pooled RR, 1.28 [95% CI: 0.99, 1.7]). Based on individual study results, only one of two trials that assessed treatment satisfaction, and none of five that assessed patient adherence favored FDC's.

Although FDC formulations simplify tuberculosis therapy, the current evidence does not indicate that these formulations improve treatment outcomes among patients with active tuberculosis.

Background

Tuberculosis (TB) is a global health problem accounting for 8.7 million new cases and approximately 1.4 million deaths annually [1]. Moreover, strains of *Mycobacterium tuberculosis* which are resistant to standard anti-TB therapy are emerging in almost all areas reporting to the World Health Organization (WHO) [2]. Non-adherence to treatment regimen and inappropriate prescription of TB therapy are believed to be major contributing factors to this public health problem [3,4]. Due to the large number of tablets used in the treatment regimens of TB, fixed-dose combination (FDC) tablets, each combining two or more anti-TB drugs, have been manufactured since the 1980s [5] to simplify TB therapy and facilitate physician and patient compliance with treatment recommendations [6]. These FDC tablets also prevent inadvertent mono-therapy, which may occur because of physician error in prescription, inadequate regimens, or patient error in selectively taking only one drug. In addition, dealing with one combined formulation that contains all essential drugs simplifies drug procurement, storage, and distribution, and may consequently reduce drug supply management errors and cost.

In 1994, the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommended the use of FDC anti-TB therapy [7]. Following the announcement of this recommendation, and its more widespread implementation, concerns were raised about adequate bio-availability of the component drugs, particularly rifampicin (RIF) due to its enhanced decomposition in the presence of isoniazid (INH) [8-11]. As a result, the WHO and the IUATLD established guidelines for assuring the bioavailability of FDC anti-TB drug components [12]. Currently, the WHO

Model List includes two-drug formulations ([INH + RIF] and [INH + ethambutol]), three-drug formulations ([INH + RIF + ethambutol] and [INH + RIF + pyrazinamide]), and a four-drug formulation (INH + RIF + ethambutol + pyrazinamide) [13].

Despite the anticipated advantages of FDC anti-TB drugs, questions about their effectiveness have not been answered. Many observational studies and clinical trials have been conducted to assess the effectiveness of FDC drugs in reducing treatment failure, disease relapse, and emergence of drug resistance. Among these studies, the use of FDC drugs has resulted in favorable [14], unfavorable [15], or unchanged treatment outcomes [16,17].

Due to the anticipated advantages, and despite the current conflicting evidence, the FDC formulations are recommended for treatment of active TB by the WHO [18], the International Standard for TB Care (Standard 8) [19], and the American Thoracic Society [20].

Study Questions

Primary: In patients who are treated for bacteriologically confirmed TB, is anti-TB therapy using FDC drug formulations, associated with lower rates of bacteriologically confirmed treatment failure, disease relapse, or emergence of drug resistance when compared to separate-drug formulations? Secondary: In patients receiving TB treatment, are adverse drug reactions, patient adherence and treatment satisfaction superior with FDC than separate-drug formulations?

Methods

Search strategy and study selection:

A search strategy was designed to retrieve articles investigating FDC anti-TB therapy published in any language between January 1980 and July 2011. The databases used for the literature search were Medline (Ovid platform); Medline In-Process or other Non-Indexed Citations (Ovid platform); EMBASE (Ovid platform); Cochrane Library (published by Wiley), which includes Cochrane Reviews, DARE, and Central Register of Controlled Clinical Trials; and LILACS (BIREME - PAHO – WHO Latin-American and Caribbean Center on Health Sciences Information) databases. The following four sets of search terms were combined with 'AND': 1- terms about TB, mycobacterium, and anti-TB; 2- terms to restrict for treatment regimens that contain both isoniazid and rifampicin; 3- terms to restrict for the use of combination formulations; and 4- restriction to human studies published since 1980.For more details about the terms used in each database refer to the supplementary materials.

Studies that fulfilled all of the following criteria were eligible for full text review: 1- randomized clinical trial (RCT) or cohort study (the latter should include at least 50 subjects); 2- bacteriologically confirmed diagnosis of active TB, based on culture or smear analyses, among included subjects; 3- treatment with an FDC anti-TB formulation that contained at least RIF and INH; 4- treatment with an effective anti-TB regimen (i.e. daily or at least 3 times weekly administration of RIF and INH for 9 months, or for 6 months when pyrazinamide was added during the initial 2 months); 5- measurement of at least one of our primary treatment outcomes (i.e. bacteriologically confirmed treatment failure or relapse, or acquired drug resistance with diagnosis based

on baseline and follow-up drug sensitivity testing); and 6- follow up period of at least 5 months during the treatment.

Selection of eligible studies was performed in a stepwise fashion—titles, then abstracts, then full texts—by two reviewers (AA and BS) working independently. At each stage, all studies selected by either reviewer (i.e. concordant eligible or discordant) were included for full-text review. Inclusion of studies, after full-text review, was based on concordance of the two reviewers; disagreement was resolved by a third reviewer (DM).

Data extraction:

The extracted data included information about the context of the study (study design, location, and time period), characteristics of included subjects (age, sex, past TB treatment, HIV status, and comorbidities), disease status (disease site and drug sensitivity), and treatment outcomes (completion of treatment, compliance to treatment, adverse drug reaction, treatment failure, death during treatment, disease relapse, acquired drug resistance, and patient satisfaction). In addition, a quality assessment scale was adapted from the Cochrane Collaboration tool to assess the following five quality indicators: 1- sequential or randomized allocation of subjects to study groups; 2- concealment of the allocation, in case of RCT; 3- adequate assessment of incomplete outcome data; 4- reporting of pre-specified or all expected outcomes (to obviate the possibility of selective outcome reporting); and 5- adequate consideration of potential sources of bias. To ensure accurate and consistent data collection, both reviewers independently performed data extraction from a sample of nine articles. Important

missing data were obtained by correspondence with the studies' authors through email contact.

Outcome measures:

The pre-specified primary outcome measures were 'treatment failure or disease relapse', as one outcome, and acquired drug resistance as another. The pre-specified secondary outcomes were bacterial conversion after two months of treatment, adverse drug reaction, patient adherence, and treatment satisfaction. Pre-specified sub-group analysis stratified by baseline drug sensitivity testing, study quality, publication year, treatment supervision modality, type of treatment regimen, and FDC formulation/producer. Our decision to stratify the studies by their potential conflict of interest was made after collecting the data (post hoc analysis).

Data analysis:

Differences in the outcomes between the comparative groups were expressed as risk ratios (RR) and 95% confidence intervals (CI), using per-protocol analysis. The effect measures of comparative RCTs were pooled using the DerSimonian-Laird random effect model. The use of a random effects, rather than a fixed effect model was pre-specified to account for variations between studies related to the type and severity of prevalent disease, standard of care, and research quality. To obtain valid, unbiased comparative estimates, our analysis focused on the comparative RCTs, which represented the majority of the included studies. Summary of the effect measures from the other studies were not pooled and were reported separately. Between-study heterogeneity was assessed using *chi*-square (Cochran Q), indicating statistical

significance as $p < 0.1$, and *I*-square tests. The latter are interpreted as showing unimportant heterogeneity if values are less than 40%, moderate heterogeneity if values are between 40% and 60%, and substantial heterogeneity if values exceed 60%. In case of moderate or substantial heterogeneity of results, or inconsistent methods of ascertainment across studies, the outcome estimates were not pooled and were reported separately. Subgroup and meta-regression analyses were performed to detect factors that influenced the primary outcome results. Reporting bias, which includes publication bias, was assessed using funnel plot and Egger's test, which is based on linear regression analysis to test the association between the intervention effect (using logarithmic scale) and its standard error [21]. All analyses were conducted using STATA (version 12) software.

Results:

Of 2450 citations identified by our search strategy, 25 met inclusion criteria for this review. These 25 articles reported results of 19 different studies; refer to Figure 1 for details. Among these 19 studies, 15 randomized, controlled trials (RCT) directly compared FDC to separate drug formulations and included a total of 5,630 subjects (Table 1). The other four studies represent one comparative cohort [39], two non-comparative (i.e. no direct comparison between FDC and separate drug formulations) RCTs [40-42], and one non-comparative cohort [43] that included total numbers of 474, 310, and 1888 subjects, respectively; refer to supplementary materials for study descriptions.

Primary outcome results of the comparative RCTs:

In the 15 RCTs, there was a trend toward higher risk of treatment failure or disease relapse with FDC compared to separate drug formulations (pooled RR, 1.28 [95%CI: 0.99, 1.7]), with no significant heterogeneity between different studies' results (Figure 2). The incidence of failure or relapse was relatively low in both treatment arms (Table 2), and the pooled risk difference was 1% (95% CI: - 0.2, 2%) higher with FDC's.

As seen in Table 2, the risk of acquired drug resistance, based on pooled results from four RCTs, was very low in both treatment arms and the relative risk estimate was inconclusive.

In the sub-group analyses, baseline drug sensitivity status appeared to modify the risk of 'treatment failure or disease relapse'. Comparing FDC to separate drug formulations, the risk was significantly higher with FDC's within the stratum of subjects with baseline drug-susceptible TB (pooled RR, 1.48 [95% CI: 1.04, 2]) and lower, though not significantly, with FDC's within the drug-resistant stratum. In addition, FDC formulation was inferior to separate-drug formulation among subjects receiving self-administered therapy and in studies with no potential conflict of interest (Figure 3).

Univariate meta-regression analyses did not indicate a significant influence of publication year or study quality on the outcome results (Figure 4). After including these two covariates with drug susceptibility, treatment supervision, and potential conflict of interest variables in a multivariate meta-regression model, drug susceptibility was the only variable that significantly modified the outcome results (comparing the point estimate within drug-resistant to the point estimate within drug-susceptible strata, the RR = 0.32 [95% CI: 0.11, 0.94]; p-value = 0.04).

Funnel plot analysis demonstrated a symmetric distribution of ‘treatment failure or relapse’ effect estimates across studies and the regression line indicated that small studies, which have less precise estimates (larger standard errors), tended to shift the treatment effect in favor of FDC treatment (Figure 5). However, the small-study effect was not significant (estimated bias coefficient, -0.36 [95% CI: -1.2, 0.49]; p = 0.39).

Secondary outcome results of comparative RCTs:

As seen in Table 2, FDC treatment was almost similar to separate formulation treatment for eliminating mycobacterial isolation after two months of treatment and had similar association with adverse drug reaction. The estimated results of patient adherence and treatment satisfaction outcomes were not pooled because of inconsistent ascertainment methods and significant heterogeneity of results (I^2, 67% and 98% respectively) across the included RCTs. Only one of two RCTs that assessed treatment satisfaction, and none of five that assessed patient adherence favored FDC’s.

Outcome results of the cohort and non-comparative studies:

Among included studies, the comparative cohort [39] presented the highest proportion of ‘treatment failure or disease relapse’ outcome, ranging from 5% to 11% among drug-susceptible and from 21% to 35% among drug-resistant TB patients. The crude RR comparing FDC to separate formulation treatments was 0.46 (95% CI: 0.2, 0.98) among drug-susceptible and 0.6 (95% CI: 0.2, 1.5) among drug-resistant TB patients. Results from the non-comparative studies [40-43] indicated low proportion of ‘treatment failure or disease relapse’, ranging from 0.5% to 2%, and acquired drug resistance, ranging from 0 to 0.3%, among TB treated patients; for details refer to the supplementary materials.

Discussion:

Based on pooled results of RCTs, the FDC therapy was associated with a trend toward increased risk of ‘treatment failure or disease relapse’, statistically insignificant difference in the emergence of drug resistance and adverse drug reactions, and clinically unimportant difference in culture conversion after two months of treatment. Although one study identified better treatment satisfaction, none of the included studies identified better patient adherence among TB patients treated with FDC compared to separate drug formulations.

While the pooled result of the RCTs suggests that FDC treatment does not reduce the risk of failure or relapse (RR estimate with a lower 95% CI range of 0.99 [close to the null value of 1.0]), it suggests potential increase in this risk (RR estimate with an upper 95% CI range of 1.7). This could be explained by reduced bioavailability of FDC component drugs [8-12], when compared to separate drug formulations. Because these outcomes were infrequent, the absolute increased risk of failure or relapse with FDC treatment was only 1%, with an upper 95% CI of 2%. Using non-inferiority design, two of the included RCTs [16,17] demonstrated a clinically insignificant risk of unfavorable outcomes with FDC’s compared to separate drug formulations. However, this study design does not address the question of whether or not FDC’s improve treatment outcomes.

Despite the potential for providing the highest level of evidence in therapeutic intervention research, RCTs have been criticized because of limited generalizability of their results. RCTs are often conducted under optimal medical care and may

underestimate the potential benefit of using FDC formulation to enhance adherence in settings where mal-practice or unmonitored therapies are common. In spite of this limitation, however, important differences in adherence have been found in many randomized trials [44]. To better estimate treatment effectiveness, pragmatic clinical trials may be more appropriate as these trials are conducted in a way that more closely resembles usual clinical practice [45,46].

We designed our research protocol to include observational studies, despite their inherent susceptibility to confounding, since they better reflect real medical practice. However, only one comparative cohort study [39], which presented crude estimates that were not adjusted for potential confounding, met the inclusion criteria. Failure to adjust for potential confounding in this observational study may have reduced the validity of results since the use of FDC formulations, may correlate with adherence to other standard treatment recommendations that influence disease outcomes. Because of this limitation and because the results of this comparative cohort were significantly different from the RCTs results, we did not pool both results.

One of the limitations of this meta-analysis is the small number of studies that investigated the risk of acquired drug resistance, resulting in less precise estimates. Another limitation is the inconsistent ascertainment methods of patient adherence and treatment satisfaction in different studies; because of these heterogeneous methods, we did not pool these study results. In addition, we could not assess mortality as an outcome because it was defined differently in the studies (all-cause versus TB specific mortality), measured over different follow-up periods—ranging from one to five years—and, in some studies was not reported or was not reported by treatment group.

Despite these limitations, this systematic review has a number of strengths. Our systematic review was conducted without language restriction to accurately represent the existing evidence. Lack of significant heterogeneity of the estimates of 'treatment failure or disease relapse' in the different trials permitted pooling and increased precision of our results. Another strength is the ability to stratify subjects based on their baseline drug susceptibility, which was a significant covariate factor influencing the risk of 'treatment failure or disease relapse'. Comparing FDC to separate drug formulation treatments, this risk tended to be higher within the stratum of subjects with baseline drug-susceptible TB and lower (in favor of FDC) within the stratum of subject with baseline drug-resistant TB. This finding was unexpected because FDC formulations, which contain first-line anti-TB drugs, are inappropriate for patients with disease that is resistant to one or more of its component drugs. However, the result of the drug-resistant stratum included small numbers of patients with very heterogeneous forms of resistance to anti-TB drugs.

In summary, we used a strict search strategy, to limit subjective selection of published studies; combined study results only when appropriate, using random effect meta-analysis which account for between-study variations; and followed the PRISMA Statement to report our data. Despite the advantage of FDC formulation in simplifying drug supply management (procurement, storage, and distribution), doctor's prescription, and patient consumption of anti-TB medications, this systematic review provides evidence that FDC formulations are not superior to separate drug formulations for preventing treatment failure or disease relapse . Furthermore, there is no evidence that FDC formulations will improve patient compliance, and inconsistent evidence that FDC

regimens improve treatment satisfaction. These findings may not be generalizable to settings with unstandardized or uncontrolled medical practice.

This systematic review of current evidence does not support the use of FDC formulations for the purpose of improving treatment outcomes among patients with active tuberculosis. To provide high-quality evidence for health policies and clinical decisions, further research on clinical effectiveness of FDC anti-TB formulations should utilize pragmatic trial designs to simulate real-world clinical practice while minimizing confounding.

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Conflicts of interest:

The authors declare that they have no conflicts of interest.

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Legends to Figures:

Figure 1. Study selection

Abbreviation: FDC, fixed dose combination. Notes: [a] After excluding duplicate articles; [b] some studies were published in more than one articles; [c] one comparative cohort and three non-comparative studies.

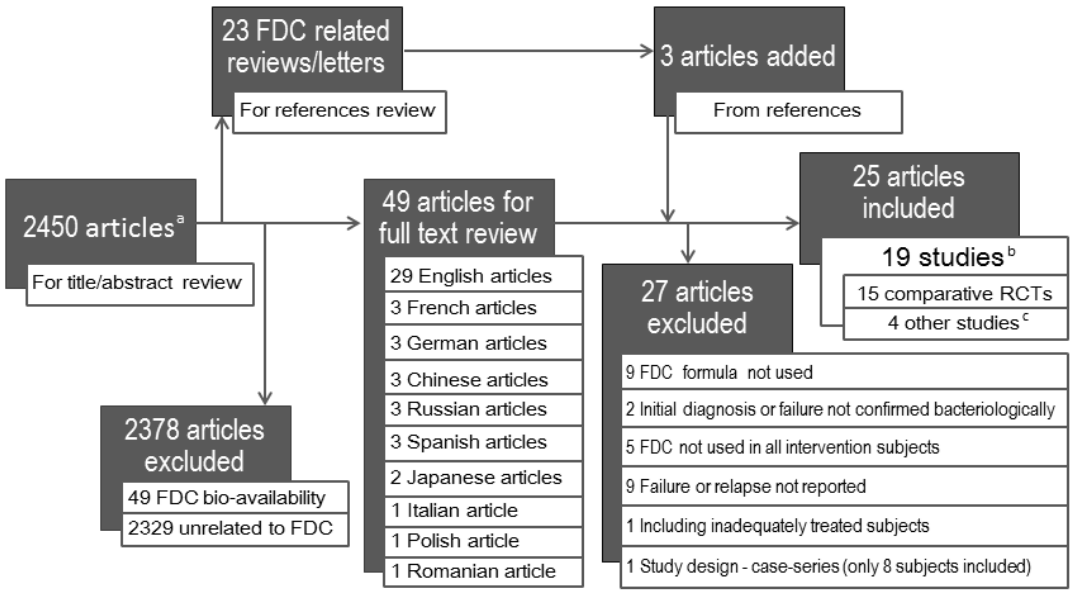


Figure 2. Forest plot of risk ratios of failure or relapse (main outcome) among fixed dose combination versus separate drug formulation groups, stratified by baseline drug susceptibility testing.

Abbreviations: FDC, fixed dose combination. **Notes:** [a] Excluded because of zero

events in both arms, hence risk ratio (RR) not estimated. When including these studies and adding 0.5 to each cell of the 2X2 table, the pooled RR of the RCTs within drug sensitive stratum became 1.45 (95% CI: 1.03, 2.04) , and the overall RR became 1.26 (95%CI: 0.98, 1.63).

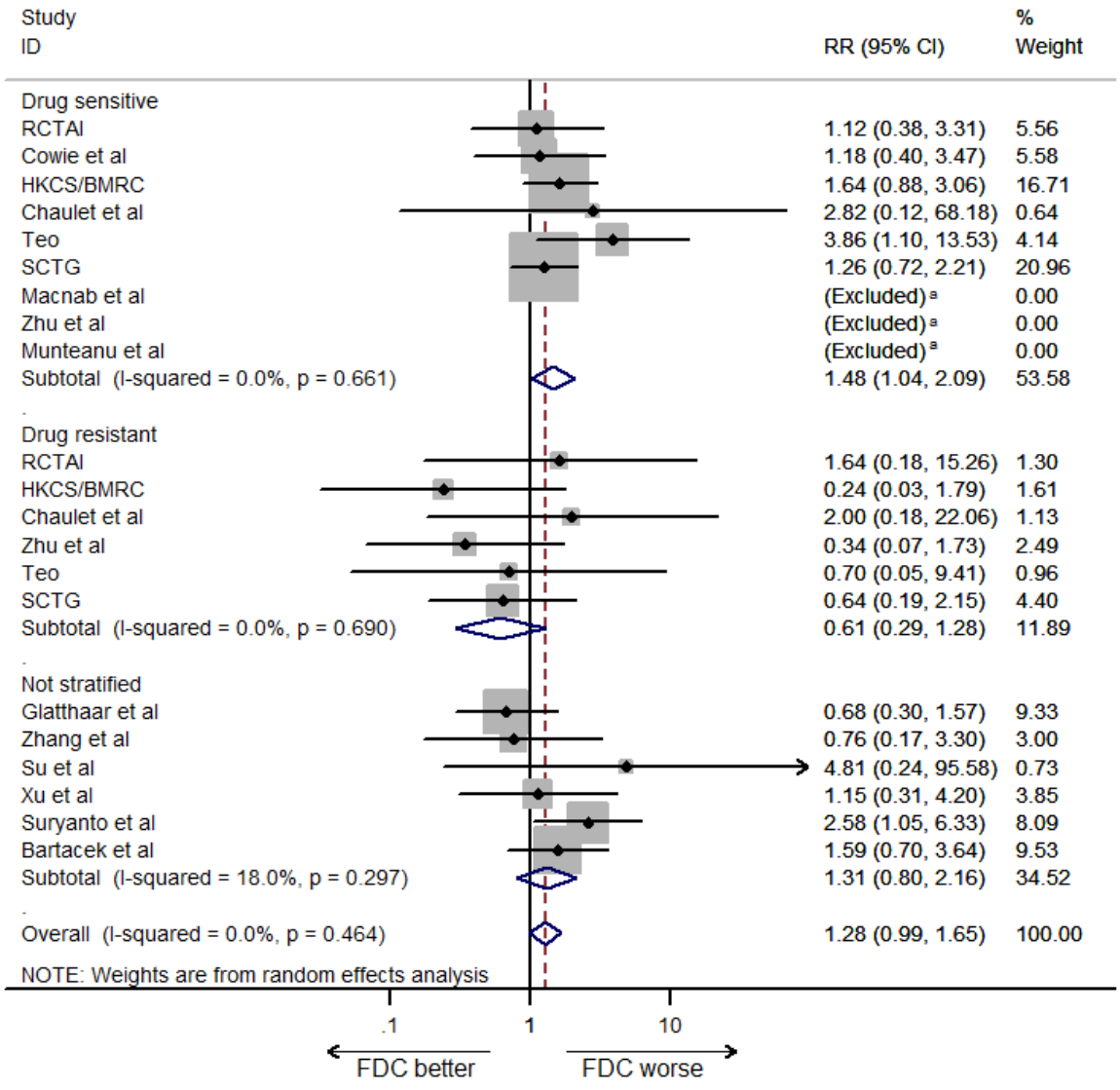


Figure 3. Subgroup analysis of the risk ratio of 'treatment failure or disease relapse' among patients treated with FDC or separate drug formulations.

Abbreviations: H, isoniazid; R, rifampicin; Z, pyrazinamide; S, streptomycin; E, ethambutol; 'FDC, fixed dose combination; NS, not specified. **Notes:** [a] Including funds and/or drug supplies.

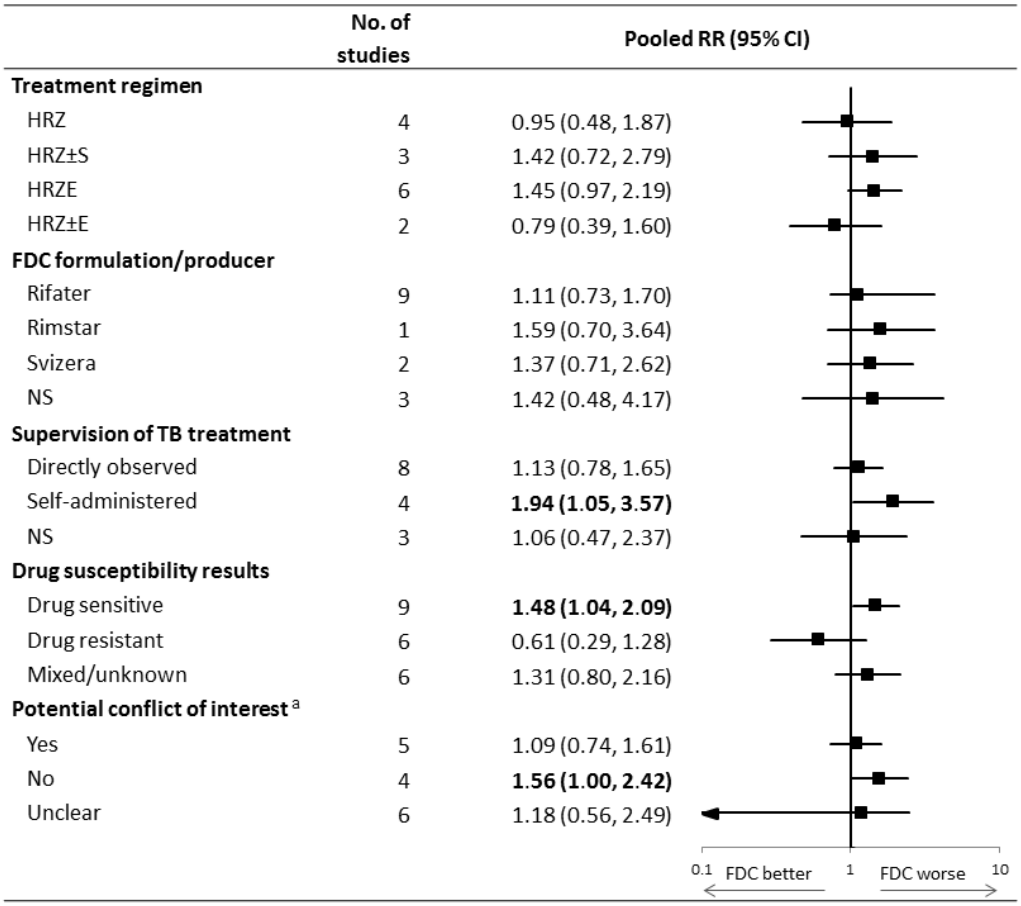
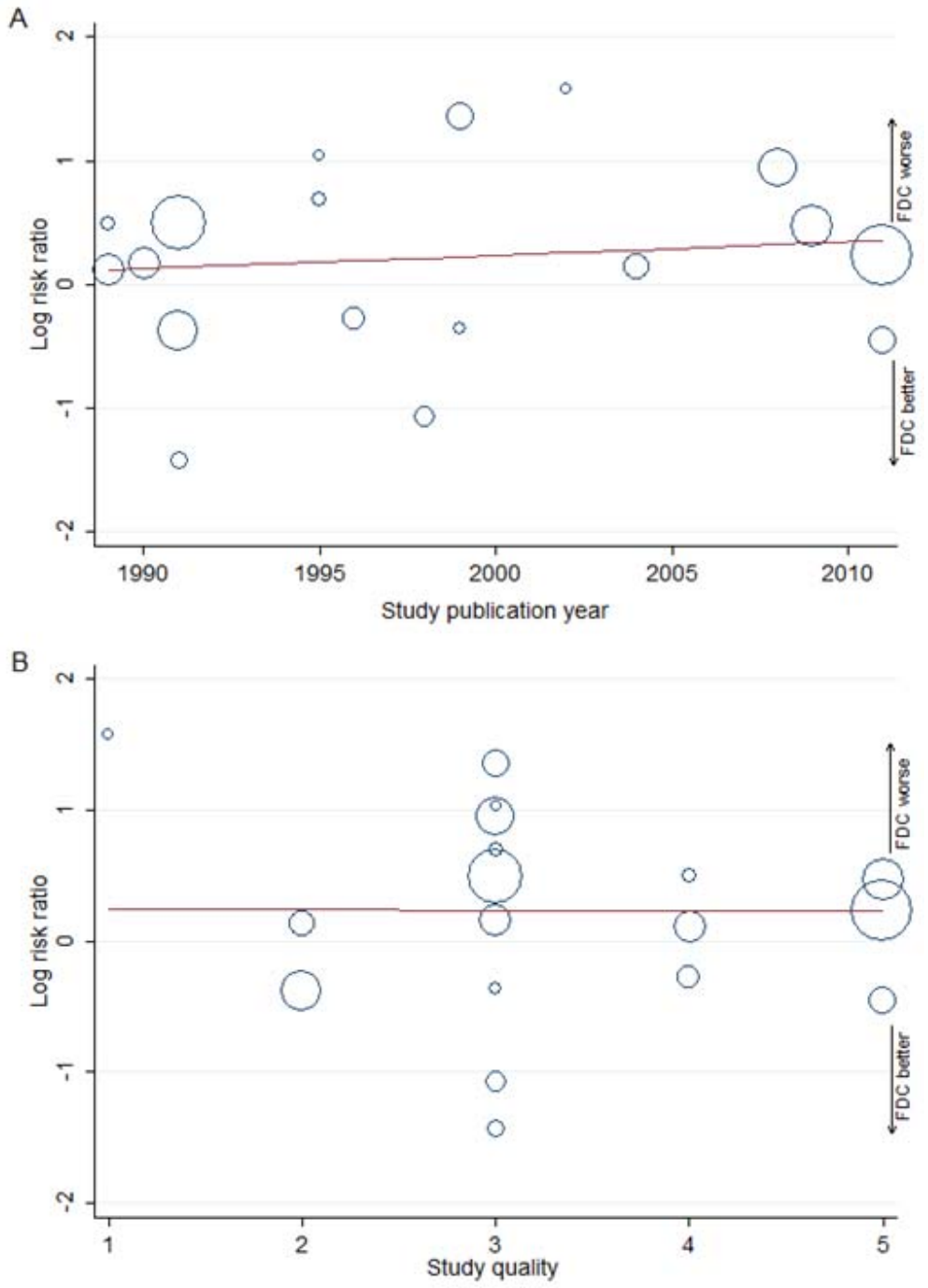


Figure 4. Univariate meta-regression for estimating the effect of continuous covariates on the risk ratios of failure or relapse (main outcome) among fixed dose combination versus separate drug formulation groups. A) Study publication year. B) Study quality scale.



Abbreviations: FDC, fixed dose combination. **Notes:** The circles' areas are inversely proportional to the variance. The study quality scale in figure (B) ranges from 0-5 as the quality changes from low to high.

Figure 5. Funnel plot for the 'treatment failure or disease relapse' outcome

Abbreviations: FDC, fixed dose combination. **Notes:** Egger's regression line represents the effect of smaller studies (higher standard error) as compared to the larger studies (lower standard error).

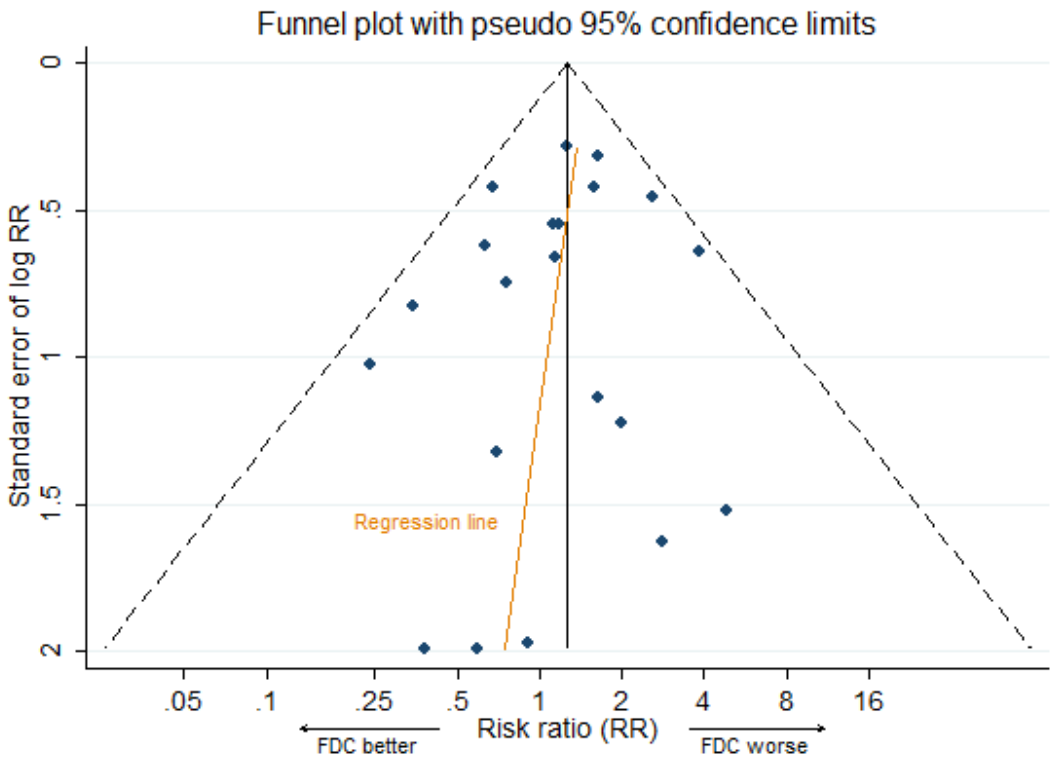


Table 1. Summary of the comparative RCTs.

Author	Public. year	Study place	Age (Mean)	Male (%)	Treat. regimen	FDC formulation	DOT	Allocation sequence[a]	Allocation concealment	Follow-up completion[b]	Non-selective outcomes[c]	Free of bias[d]
RCTAI [22]	1989	India	29 [e]	70	HRZ	Rifater/Rifinah	No	Yes	Unclear	Yes	Yes	Yes
Cowie et al [23]	1990	South Africa	38	100	HRZ±S	Rifater	Yes	No [f]	Yes	Yes	Yes	No [g]
HKCS/BMRC [24,25]	1991	China	35 [e]	66	HRZ±S	Rifater	Yes	Unclear	Unclear	Yes	Yes	Yes
Glatthaar et al [26]	1991	South Africa	NS	NS	HRZE	Rifater	Yes	Unclear	Unclear	Yes	Yes	Unclear
Macnab et al [27]	1994	South Africa	NS	NS	HRZE	Rifater	Yes	No [f]	Unclear	No [h]	Yes	Unclear
Chaulet et al [28-30]	1995	Algeria	28 [e]	75	HRZ [i]	NS	No [j]	Unclear	Unclear	Yes	Yes	Yes
Zhang et al [31]	1996	China	41 [e]	65	HRZ	Rifater/Rifinah	Yes	Yes	Unclear	Yes	Yes	Yes
Zhu et al [32]	1998	China	37 [e]	70	HRZ	Rifater/Rifinah	NS	Unclear	Unclear	Yes	Yes	Yes
Teo [33,34]	1999	Singapore	39 [e]	66	HRZ±S	Rifater	Yes	Unclear	Unclear	Yes	Yes	Yes
Su et al [35]	2002	Taiwan	NS	89	HRZ	Rifater/Rifinah	No	Unclear	Unclear	No[h]	Yes	Unclear
Munteanu et al [36]	2004	Romania	37 [e]	63	HRZE	NS	Yes[k]	Unclear	Unclear	Yes	Yes	Yes
Xu et al [37]	2004	China	49	76	HRZE	NS	NS	No[f]	Unclear	Yes	Yes	Unclear
Suryanto et al [15,38]	2008	Indonesia	37	57	HRZE	Svizera	No	Yes	No [l]	Yes	Yes	Unclear
Bartacek et al [17]	2009	5 countries[m]	37	69	HRZE	Rimstar/Rimactazid	NS	Yes	Yes	Yes	Yes	Yes
SCTG [16]	2011	9 countries[n]	34	67	HRZE [i]	Svizera	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: FDC, fixed dose combination; DOT, direct observed therapy; RCTAI, Research Committee of the Tuberculosis Association of India; RCT, randomized controlled trial; H, isoniazid; R, rifampicin; Z, pyrazinamide; S, streptomycin; E, ethambutol; HKCS, Hong Kong Chest Service; BMRC, British Medical Research Council; NS, not specified; SCTG, Study C Trial Group; NA, not applicable.

Notes: [a]Proper sequence of allocation; [b]Complete follow up for at least 75% of subjects, and assessment of the reasons for incomplete follow up; [c]free of selective outcome (i.e. reporting all expected or pre-specified outcomes); [d]equivalentsubject characteristics and management between comparison groups, and the sample population has no specific risks that could influence their treatment outcomes; [e]the mean was estimated from a stratified age distribution; [f]allocation based on even vs. odd generated numbers; [g] streptomycin was added to the treatment of only one of the two groups; [h]less than 75% of subjects completed the follow up;[i]during continuation phase, FDC was given to both groups; [j]treatments were under direct supervision only during the first 3 weeks of therapy; [k]DOT was given only during the initial phase of treatment;[l]the subjects were alternatively allocated to each study group; [m]Egypt, India, Pakistan, Philippine, and Thailand; [n]Algeria, Colombia, Guinea, Vietnam, Nepal, Peru, Mozambique, Tanzania, and Bolivia.

Table 2. Pooled outcome results of comparative RCTs.

Outcomes	No. of studies	FDC		Separate drug formulation		RR (95%CI)	Heterog. I^2/ P-value
		No. of subjects	% (95% CI)	No. of subjects	% (95% CI)		
Treatment failure or disease relapse							
Comparative RCTs (pooled)	15	2750	4.2 (2.6, 5.8)	2880	3.1 (1.9, 4.2)	1.28 (0.99, 1.7)	0/0.46
Acquired drug resistance							
Comparative RCTs (pooled)	4	1113	0.26 (0, 0.7)	1405	0.08 (0, 0.35)	1.6 (0.5, 5.4)	0/0.4
TB culture conversion after 2 months of treatment							
Comparative RCTs (pooled)	12	2354	94 (91, 96)	2443	91 (89, 92)	1.03 (1.01, 1.04)	13/0.32
Adverse drug reaction							
Comparative RCTs (pooled)	10	2416	16 (9, 23)	2195	20 (11, 28)	0.88 (0.75, 1.03)	23.7/0.23
Patients' adherence to treatment [a]							
RCTAI [b]	1	95	77 (67, 85)	101	73 (64, 82)	1.05 (0.89, 1.23)	
Cowie et al [c]	1	69	58 (46, 70)	81	84 (74, 91)	0.69 (0.55, 0.86)	
Macnab et al [d]	1	121	65 (55, 73)	79	57 (45, 68)	1.13 (0.90, 1.43)	66.5/0.02
Teo	1	154	95 (90, 98)	153	97 (93, 99)	0.97 (0.93, 1.02)	
Su et al [e]	1	57	70 (57, 82)	48	67 (52, 80)	1.05 (0.81, 1.37)	
Treatment satisfaction [a]							
Teo [f]	1	154	92 (86, 95)	153	90 (84, 94)	1.02 (0.95, 1.09)	97.8/0.00
Bartacek et al [g]	1	411	81 (77, 85)	422	57 (52, 61)	1.43 (1.30, 1.58)	

Abbreviations: FDC, fixed dose combination; CI, confidence interval; RR, risk ratio; RCT, randomized controlled trial; TB, tuberculosis. Notes: [a]studies' results were not pooled because of significant heterogeneity between them and inconsistent methods for measurement of the outcome; [b]assessment of adherence was based on monthly home visits and count of the number of remaining capsules; [c]assessment of adherence was based on urine tests and reports from medical staff; [d] assessment of adherence was based on completion of at least 75% of the treatment doses; [e]assessment of adherence was based on the loss of follow-up and alteration of treatment regimen; [f]assessment of satisfaction was based on spontaneous complaints; [g] assessment of satisfaction was based on patient's acceptance of the tablet number and size and complaint from swallowing problem.