Does Fixed Dose Combination Anti-tuberculosis Therapy Improve Treatment Outcomes?

A Systematic Review and Meta-Analysis

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Abbreviations

CI: Confidence interval

DOT: Directly Observed Therapy

DOTS: Directly Observed Therapy, Short Course

DST: Drug susceptibility testing

FDC: Fixed-dose combination

IUATLD: International Union Against Tuberculosis and Lung Disease

MTB: *Mycobacterium* TB

RR: Risk ratio

TB: Tuberculosis

WHO: World Health Organization

Abstract

Background: Fixed dose combination (FDC) anti-tuberculosis (TB) therapy is currently recommended to facilitate patient adherence, and prevent inadvertent or intentional mono-therapy. We have conducted a systematic review to evaluate the risk of treatment failure or relapse and acquired drug resistance, as primary outcomes, and the proportion of bacterial conversion after two months of treatment, adverse events, adherence, and treatment satisfaction, as secondary outcomes, associated with treatment of active TB using FDC or separate-drug formulations.

Methods: We searched four electronic databases for randomized controlled trials and cohort studies published in any language since 1980. Results from trials that directly compared FDC to separate-drug formulations were pooled. Results from other studies were reported separately.

Results: We identified 2450 potentially eligible articles from which 15 trials that directly compared FDC and separate-drug formulations as well as four additional relevant studies were included. In the 15 randomized 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 the combined outcome of treatment failure or disease relapse with FDC (pooled risk ratio, 1.28 [95% CI: 0.99, 1.65]). 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.

Conclusion: The results of this systematic review do not support the current recommendation for the use of FDC formulations for treatment of active TB.

Résumé

Contexte : La combinaison à dose fixe est la forme de thérapie contre la tuberculose recommandée pour favoriser l'adhésion du patient et prévenir la mono thérapie intentionnelle ou accidentelle. Nous avons procédé à un examen systématique visant à évaluer le risque d'échec ou de rechute, de résistance aux médicaments, à titre de résultats primaires; et la proportion de conversion bactérienne après deux mois de traitement, d'effets secondaires, d'adhésion et de satisfaction reliés au traitement de la TB active, à titre de résultats secondaires, en comparant la combinaison à dose fixe et la multithérapie.

Méthodes : Nous avons consulté quatre bases de données pour des essais contrôlés randomisés et des études de cohortes publiés en toute langue depuis 1980. Les résultats d'essais comparant directement la combinaison à dose fixe et la multithérapie furent regroupés. Les résultats d'autres études furent rapportés séparément.

Résultats : Nous avons identifié 2450 articles potentiellement éligibles. Quinze essais comparant directement la combinaison à dose fixe à la multithérapie, ainsi que quatre autres études pertinentes sont inclus. Les 15 essais randomisés n'ont soulevé aucune différence en rapport à la pharmaco-résistance, à la conversion bactérienne après deux mois de traitement, ou aux effets secondaires entre la combinaison à dose fixe et la multithérapie. On note toutefois une tendance de risque plus élevé avec la combinaison à dose fixe lorsqu'on combine les résultats 'échec du traitement et rechute' (ratio de risque combiné, 1.28 (95% CI :0.99, 1.65). Selon les résultats individuels d'études, seul un des deux essais randomisés

évaluant la satisfaction du traitement et aucun des cinq études évaluant l'observance ont favorisé la combinaison à dose fixe.

Conclusion : Les résultats de cet examen systématique d'appuient pas la recommandation actuelle qui favorise l'utilisation de combinaisons à dose fixe pour le traitement de la TB active.

CHAPTER I Introduction

I.1 Overview

Tuberculosis (TB) is the most important contagious disease in adult globally accounting for 8.8 million new cases and approximately 1.5 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] In 2010, the WHO reported that 28% of isolates from new TB patients in one region of north-western Russia were multidrug resistant strains, defined as resistant to rifampicin and isoniazid, which are the two most effective anti-TB drugs.[3]

Effective therapy for patients with active TB requires multiple medications for at least six months duration. Non-adherence to treatment and improper use of mono-therapeutic regimens are major risk factors for treatment failure, disease relapse, and emergence of drug resistant TB.[4-6] To facilitate patient adherence, by reducing the number of tablets, and prevent mono-therapeutic treatment, fixed-dose combination (FDC) anti-TB formulations, each with two or more anti-TB drugs, have been manufactured since the 1980s[7,8]and recommended by the WHO since 1994.[9]

After wide use of the FDC anti-TB formulations, concerns were raised about the bio-availability of its component drugs.[10] The effectiveness of FDC drugs for preventing unfavorable treatment outcomes have been assessed in many

studies; however, these formulation treatments have resulted in favorable,[11] unfavorable,[12] or unchanged[13] outcomes.

I.2 Standard tuberculosis treatment

Effective treatment for patients with active TB requires a combination regimen of multiple medications, usually rifampicin, isoniazid, pyrazinamide, and ethambutol, for a total treatment duration of at least 6 months.[14] Based on in-vitro laboratory studies, experts have established hypothetical roles of each component drug of the anti-TB regimens that are considered essential to eradicate the bacteria and achieve successful treatment.

Mycobacterium TB (MTB), the organism causing TB, has the ability to survive dormant in areas of human body with poor blood supply and high acidity such as calcified granuloma and caseous foci.[15,16] These areas are protected from most antimicrobial agents either because of difficult penetration or low PH medium, which inhibits antimicrobial activities. Although these non-replicating mycobacteria are not responsible for the clinical symptoms and disease progression, failure to eliminate them may lead to relapse of disease. In-vitro laboratory studies demonstrated that rifampicin has good sterilizing activity against MTB[17] and that pyrazinamide works effectively in anaerobic media with high acidity, which have similar condition of body areas with poor blood supply that harbor dormant mycobacteria.[18,19]

In persons with disease, early reduction of the burden of replicating bacteria protects against disease progression and infection transmission. Based on in-vitro studies, isoniazid has early bactericidal activities against MTB.[20,21]

Standard treatment regimens for newly-diagnosed drug-susceptible TB include: a) rifampicin and isoniazid for six months in addition to pyrazinamide during the first two months, or b) rifampicin and isoniazid for nine months.[22] Because of wide prevalence of isoniazid-resistant strains of MTB, the addition of ethambutol to these treatment regimens during the first two months, or until the drug susceptibility status is known, has been recommended.[14,23]

I.3 Evolution of drug-resistant tuberculosis

Single-drug treatment of active TB is an important risk factor for the development of drug-resistant TB. In patients with disease, who have a high bacterial load, some actively replicating bacilli undergo spontaneous chromosomal mutations and become resistant to one or more anti-TB drugs.[24] Among those patients, the estimated proportion of naturally resistant (due to spontaneous chromosomal mutations) mycobacteria to one drug is 1 in 10^6-10^8 and to two drugs is 1 in 10^{14}, indicating that the presence of organisms which are spontaneously resistant to more than one drug is extremely rare.[24] Therefore, treatment of active TB with a single drug eliminates the vast majority of organisms, which is associated with resolution of disease symptoms. However, the few remaining resistant bacilli will eventually replicate and cause disease recurrence with predominantly drug-resistant strains of MTB. This has been observed clinically in an early trial of streptomycin mono-therapy for patients

with active TB.[25] After six months of treatment, 80% of treated subjects had disease recurrence with a streptomycin-resistant form of TB. Two other trials compared streptomycin mono-therapy to bed-rest among patients with active TB.[26,27] Despite early favorable outcome among streptomycin treated subjects, the five-year mortality was comparable due to emergence of streptomycin-resistance among the intervention group.

I.4 Tuberculosis treatment in clinical practice

Despite the importance of constructing standard practice guidelines for TB treatment, TB control objectives will not be accomplished without implementation of these guidelines by health care providers. Prescription of fewer drugs than recommended, shorter treatment duration, wrong medications, and inadequate doses were widely encountered in clinical practice, especially in private health facilities.[28] These prescription errors were not limited to high TB incidence counties, but were observed also in developed countries that have low TB incidence. Based on a survey conducted in United States, for instance, physician errors were identified among 15% of patients treated for active TB. The proportion of errors was higher (38%) among patients treated by private physicians.[29] In high TB incidence regions, the size of this problem is much larger. Studies in India, the country which accounts for approximately one-fifth of global TB incident cases,[30] suggest that TB medications are widely prescribed by non-qualified doctors who are not familiar with TB regimens.[28] Among 106 general practitioners who received self-administered questionnaire about TB regimen, only 6 wrote a prescription of correct treatment regimen.[31] In a study of

private health care practice in Bombay, 80 different TB regimens were prescribed by 100 doctors; 50% of them used unacceptable regimens and only 12% used standard regimens.[28,32] Errors in TB treatment practice were commonly observed in other regions as well, such as Russia and sub-Saharan Africa.[33,34] In addition to prescription of incorrect TB treatment regimens, other doctor behaviors such as frequent change of TB regimens and the use of TB medications for treatment of non-tuberculous respiratory illnesses may contribute to the global spread of resistant forms of TB. A study of 35 patients with multi-drug resistant TB reported errors during previous TB treatment in 28 patients, with an average of 3.9 errors per patient.[35]

I.5 Patient adherence

One of the main reasons for using FDC formulation is to simplify TB treatment and improve patient adherence. Adherence and compliance are two terms used synonymously to indicate the extent to which patients act to maintain their personal health as recommended by the health care providers. However, adherence is more accepted term since it implies active collaboration with health care providers, while compliance indicates passive complies with doctor's orders.[36] The WHO define adherence as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.[37]"

Different methods are used for measurement of patient adherence, including direct observation of administered medications, drug blood level, biologic markers, questionnaire, diary, pill count (remaining pills with the

patient), prescription refill records, and electronic medication monitor. Although none of these methods is perfect, electronic medication monitor is considered the most reliable tool for measurement of patient adherence.[36]

The WHO estimated that adherence to long-term treatments is about 50% in the developed countries and much lower in the developing countries.[37] This low adherence rate compromises treatment effectiveness and has resulted in major health care consequences, especially with chronic infectious diseases, such as TB and HIV, where poor adherence contributes to emergence of drug-resistant form of disease.[5,38] Therefore, health professionals should play a responsible role, for which the WHO has published evidence-based practice guidelines, to facilitate patient adherence.[37]

Factors that affect treatment satisfaction, such as the complexity of treatment regimen and adverse drug reactions, contribute to poor patient adherence. In a systematic review of 76 studies that used electronic medication monitor to measure patient adherence, the extent of adherence was inversely associated with the number of treatment doses (79% with one dose, 69% with two doses, 65% with three doses, and 51% with four doses).[39] However, it has been shown in a Cochrane review that all interventions that are effective for improving patient adherence are complex and require multifactorial approaches, including patient behavior, education about treatment benefits and risks, medication cost, and treatment satisfaction.[40]

To promote adherence among TB patients, the WHO established in 1991 a comprehensive management strategy called Directly Observed Therapy, Short Course (DOTS), which consists of the following five elements:

1- Political commitment of the national governments with clear strategic plans that address financial and technical requirements of TB health care.
2- Quality-assured laboratory methods of TB case detection.
3- Use of standardized short anti-TB regimens under direct treatment supervision.
4- Regular supply of quality-assured anti-TB medications.
5- Standardized recording and reporting system for individual patient data collection.[41]

This strategy has shown to be effective for improving adherence and treatment outcome.[42] In an interview-based study conducted in India, however, 68% of TB patients considered this modality of directly observed treatment unacceptable.[43]

I.6 Outcomes of tuberculosis treatment

Different treatment outcomes have been measured to indicate the effectiveness of FDC anti-TB therapy. Among unfavorable treatment outcomes, the commonly measured outcomes are treatment failure, disease relapse, and death. Treatment failure is defined by the WHO as "a patient who is sputum smear-positive at 5 months or later during treatment," disease relapse is defined as "smear- or culture-positive patient who was previously treated and declared cured or treatment completed," and death is defined as "a patient who dies for any

reason during the course of treatment.[23]" Other treatment outcomes include acquired drug resistant TB, defined as change of disease susceptibility status to any first-line anti-TB drug from drug-susceptible to drug-resistant during or after TB treatment; cure, defined as "sputum smear-negative in the last month of treatment and on at least one previous occasion during treatment"; treatment completion, defined as patients who complete the treatment but do not fulfill the definition of failure or cure; and default is defined as treatment interruption for two months or more.[23]

Failure and relapse are objectively measured outcomes which indicate unsuccessful eradication of MTB during TB treatment. After failure or relapse, the disease may become resistant to previously effective drugs used during the treatment. The acquisition of this drug resistant form of TB has major public health and economic impacts, since it substantially increases the risk of failure, relapse, death, and additional drug-resistance.[44,45] Furthermore, the treatment cost of one patient with multi-drug-resistant TB is equivalent to the treatment cost of 700 patients with drug-susceptible disease.[46] Hence, measuring the rate of acquired drug-resistant TB is important; however, it is not commonly performed because it requires drug susceptibility testing (DST), which is not routinely done, at the start and during TB therapy.

I.7 Fixed-dose combination (FDC) anti-tuberculosis therapy

I.7.1 FDC drug formulation and marketing

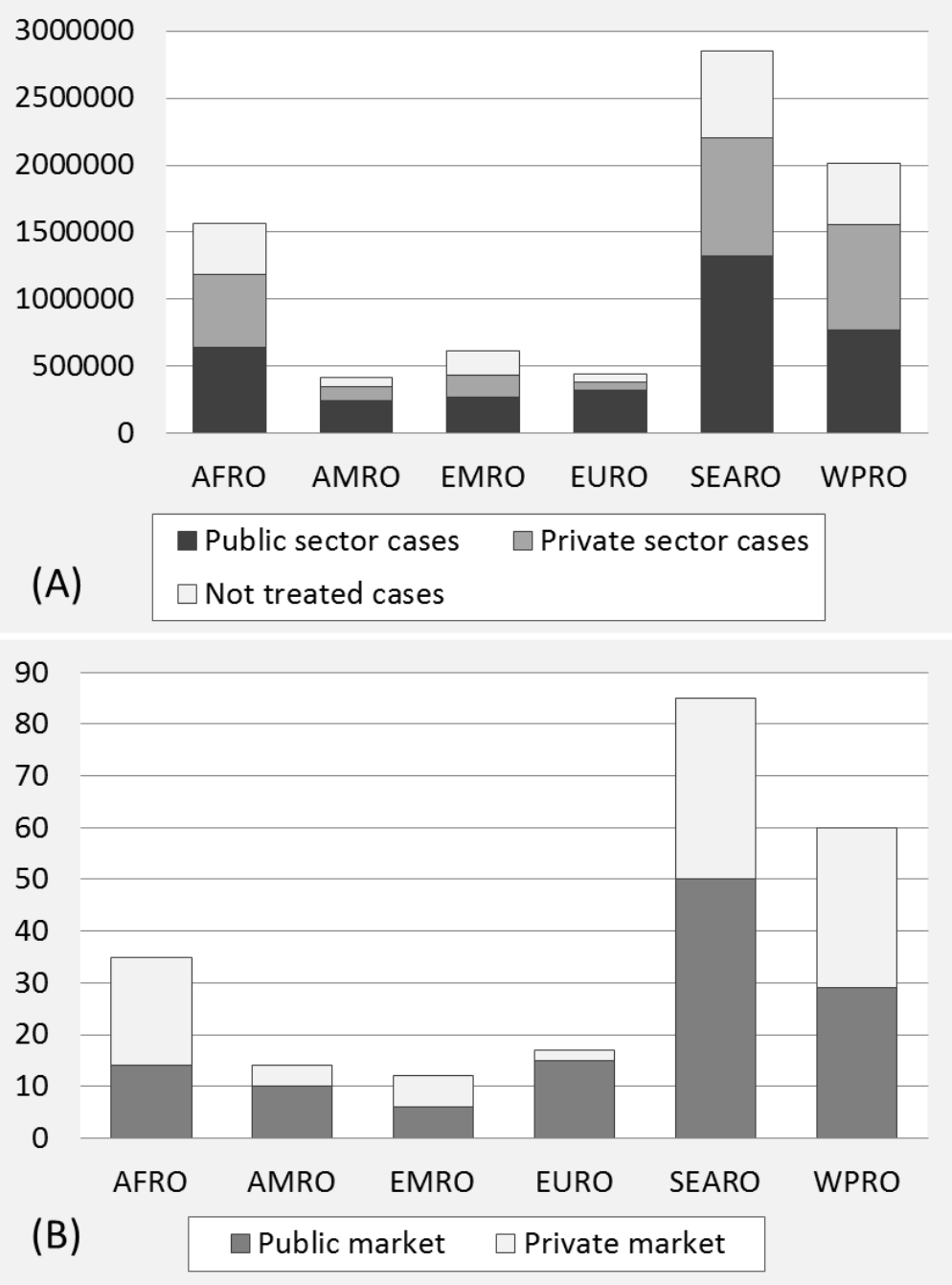
FDC anti-TB formulations are combination tablets containing two or more anti-TB drugs that have been manufactured to avoid mono-therapy, and simplify TB regimens by reducing the number of daily consumed tablets. Two-drug FDC formulations have been used for TB treatment since the 1980s; whereas three- and four-drug FDC formulations were introduced to the market more recently.[8]

In 1994, the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommended the use of FDC anti-TB therapy.[9] However, the four-drug formulation was not included in the WHO Model List of Essential Drugs until 1999.[47] Currently, the WHO Model List includes two-drug formulations ([isoniazid + rifampicin] and [isoniazid + ethambutol]), three-drug formulations ([isoniazid + rifampicin + ethambutol] and [isoniazid + rifampicin + pyrazinamide]), and a four-drug formulation (isoniazid + rifampicin + ethambutol + pyrazinamide).[48]

Announcements of the recommendations about FDC drugs promoted widespread use of these formulations for TB treatment. A global WHO survey of 85 countries in 1996 showed that 23.8% of all notified TB cases in the public health care sectors were treated with FDC formulations. Most of these FDC's were two-drug (isoniazid/rifampicin) formulation; only 4.7% of all notified TB cases used three-drug (isoniazid/rifampicin/pyrazinamide) formulation. As seen in

Figure 1, FDC anti-TB therapy was widely implemented in all different WHO regions and was used in both private and public health care sectors.[8]

Figure 1. (A) Estimated number of TB cases in different WHO regions. (B) Estimated size of the global marketing of rifampicin containing FDC (in tons).



Source of information: Norval et al. 1999.[8]
Abbreviations: AFRO, Regional Office for Africa; AMRO, Regional Office for the Americas; EMRO, Regional Office for the Eastern Mediterranean; EURO, Regional Office for Europe; SEARO, Regional Office for South East Asia; WPRO, Regional Office for the Western Pacific.

I.7.2 The rationale of recommending FDC anti-tuberculosis therapy

When conventional separate-drug formulation is used for active TB treatment, the number of taken tablets is usually 9-16 per day during the initial two months and 3-9 per day during the remaining four months of therapy. This large number of tablets can be reduced to 3-4 tablets per day throughout the TB therapy when FDC drug formulation is used.[49] This more convenient number of tablets may improve treatment satisfaction, and therefore improve patient adherence. As discussed above, poor adherence to TB treatment complicates TB control and can result in major public health consequences; therefore, the WHO enforces all possible efforts to facilitate patient adherence, including not only DOTS strategy but also FDC formulation therapy.[37] In addition to improving patient adherence, dealing with one combined formulation that contains all essential drugs simplifies drug procurement, storage, and distribution, and consequently reduces drug supply management errors and cost. FDC tablets will also simplify doctor's prescription and prevent inadvertent mono-therapy of TB and misuse of rifampicin for conditions other than TB. These anticipated advantages may ultimately reduce the incidence of treatment failure, disease relapse, and emergence of drug-resistant TB.

I.7.3 Concerns about FDC anti-tuberculosis therapy

Despite the anticipated advantages from using FDC anti-TB therapy, there have been concerns about the bioavailability of its component drugs. Screening of drug samples collected from TB programs and pharmacies in different countries (Colombia, Estonia, India, Latvia, Russia and Vietnam) identified poor drug

quality in 21% of rifampicin samples in the FDC formulations and 13% of rifampicin samples in the separate-drug formulations.[50] Of ten different FDC formulations that have been used in the global market, the bioavailability of rifampicin in seven formulations was found to be impaired.[51] However, the results of different comparative cross-over bioequivalence trials are conflicting; some trials demonstrated inferior bioavailability of rifampicin in the FDC as compared to separate formulations,[52-54] others showed bioequivalent results.[55-57] Isoniazid and pyrazinamide components of FDC, on the other hand, did not exhibit such variability, due to their high solubility and permeability, and were bioequivalent to their separate-drug forms.[58]

Causes that contribute to the impaired rifampicin bioavailability in the FDC formulations are not clearly understood. A comparison across eight bioequivalence trials showed more variability in the blood level of rifampicin when administered as FDC compared to separate-drug formulations.[58] This was attributed to extrinsic factors related to complexity in manufacturing the FDC formulations. Some investigators, however, provided evidence suggesting that the impaired bioavailability is due to in-situ decomposition of rifampicin in the acidic condition of the stomach, which is enhanced by isoniazid.[53,54,59] Various other reasons have been also hypothesized, including changes in the crystalline form of rifampicin,[60] impaired drug absorption,[59] and rifampicin decomposition in the combined formulations during storage.[61]

The standard dose of rifampicin is believed to be at the lower therapeutic range.[62] Hence, small reduction in its bioavailability can result in inadequate TB

treatment. Thus, the WHO and IUATLD issued a joint statement recommending that the use of combination formulations should be restricted to FDC tablets of good quality and proven rifampicin bioavailability.[9] This was followed by establishing guidelines for assuring the bioavailability of FDC component drugs.[63]

Another concern is the potential misconception that FDC formulation treatment substitutes DOTS strategy, which has been shown to be effective,[42] to facilitate adherence. Finally, withdrawal of one TB agent in case of serious adverse drug-reaction related to that agent is not possible when using FDC formulation therapy. In such situation, the patient should be referred to a TB treatment center, where separate-drug formulations are available.[64]

I.7.4 Effectiveness of FDC formulation therapy for improving adherence and preventing unfavorable treatment outcomes

A systematic review of studies that compared adherence to FDC versus separate-drug formulations, which were used for treatment of different diseases, was conducted in 2007.[65] Three randomized controlled trials, out of which two were in TB and one was in HIV, and six cohorts, out of which four were in hypertension and two were in diabetes, were included for meta-analysis. None of the three trials (TB and HIV treatment trials) showed significant improvement in adherence with FDC formulation therapy. However, the pooled estimate of the cohort studies and the overall estimate (including both clinical trials and cohorts) were in favor of FDC therapy. Although the authors concluded that FDC improves adherence, based on the overall combined results, this improvement was limited to cohort studies of hypertension treatment.

There have been ecologic observations of low incidence of acquired drug-resistant TB in high TB prevalent countries that have been using FDC anti-TB therapy, such as Brazil and South Africa.[49,66,67] These ecologic observations were further investigated in cohort studies and clinical trials to assess the effectiveness of FDC drugs in reducing treatment failure, disease relapse, and emergence of drug resistance. In some studies that compared FDC to separate-drug formulations, the use of FDC drugs resulted in favorable outcomes, such as reduced incidence of acquired-drug resistance, but resulted in unfavorable outcomes in other studies, such as increased incidence of disease relapse,[12] or unchanged treatment outcomes (failure, relapse or TB-related death) in other studies.[13] These conflicting results prompted a systematic review of the current evidence about the effectiveness of FDC formulations.

I.7.5 Cost-effectiveness of FDC anti-tuberculosis therapy

Moore and his group performed a cost-effectiveness analysis, using decision-analysis model, to compare three TB treatment strategies—self-administered separate-drug formulation therapy; self-administered FDC therapy; and directly observed therapy (DOT), using a separate-drug formulation regimen.[68] The authors estimated that the drug cost of six-month treatment per person is $608 with separate-drug formulation ($9 for isoniazid, $191 for rifampicin, $231 for ethambutol, and $177 for pyrazinamide), $632 with FDC ($252 for Rifater®, $149 for Rifamate®, and $231 for ethambutol), and $351 with DOT. Completion of therapy was estimated to be 60% with separate-drug formulations, 75% with FDC and 90% with DOT. Outcomes among patients who

did and did not complete TB therapy were estimated based on published literature. As shown in Table 1, the total cost per person treated was lower with the FDC and DOT treatment strategies than the conventional separate-drug treatment strategy.

Although the authors have provided comprehensive details about the estimation of cost, they did not provide evidence to support their assumption about the difference in completion rates. To our knowledge, this difference in treatment completion has not been found in clinical trials.

Table 1. Cost and effectiveness of tuberculosis treatment

	Separate-drug	**FDC**	**DOT**
Relapse [a]	133	96	31
Acquired drug resistant TB [a]	5	2	1
Death [a]	13	8	3
Cost per person treated	$15,003	$13,959	$13,925
Cost per relapse averted	$17,305	$15,446	14,378
Cost per life saved	$15,200	$14,068	13,966

Source of information: Moore et al. 1996.[68]
Abbreviations: FDC, fixed dose combination; DOT, directly observed therapy; TB, tuberculosis. **Notes:** [a] Outcome rates were estimated as number of events per 1000 treated persons.

I.8 Current statement recommendations about the use of FDC formulations for tuberculosis treatment

Due to anticipated advantages, and despite the current conflicting evidence, the FDC formulations are currently recommended for treatment of active TB. The following statements are the most recent statement recommendations from different international organizations:

WHO 2010 statement:[14] "*While evidence on fixed-dose combinations (FDCs) of anti-TB drugs was not systematically reviewed for this fourth edition, WHO continues to recommend their use, as does Standard 8 of the ISTC.*"

International standard for TB care (Standard 8) 2006 statement:[69] "*Fixed dose combinations of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide), and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended, especially when medication ingestion is not observed."*

American Thoracic Society 2003 statement:[22] *"Fixed-dose combination preparations minimize inadvertent monotherapy and may decrease the frequency of acquired drug resistance and medication errors. These preparations should generally be used when therapy cannot be administered under DOT."*

CHAPTER II Study rationale and objectives

II.1 Study rationale

The rationale of recommending FDC formulations by international organizations for TB treatment is to facilitate patient adherence and ultimately improve treatment outcomes. The only justification for this recommendation is that these formulations simplify the treatment and prevent mono-therapy, both of which were considered self-evident.[64] However, there is conflicting evidence that these formulations will improve adherence and outcome of TB therapy. In addition, there is evidence of impaired bioavailability of the rifampicin component of some FDC formulations.[51] This may result in reduced efficacy of rifampicin—creating inadequate or, in some cases, mono-therapeutic treatment regimens.

Questions about the effectiveness of FDC anti-TB formulations are not answered, and the results of published studies are conflicting. In the 2010 report on TB treatment guidelines, the WHO recommended the use of FDC's despite declaring that the evidence was not systematically reviewed.[14] Although some narrative reviews about FDC formulation treatment for patients with active TB have been published;[70,71] to our knowledge, no systematic review of this topic has yet been conducted.

II.2 Primary objective

Our primary objective is to systematically review the currently published evidence to answer the following 'PICO' style question: In patients who are

treated for bacteriologically-confirmed tuberculosis (P), is anti-TB therapy using FDC drug formulations (I), associated with lower rates of bacteriologically-confirmed treatment failure, disease relapse, or emergence of drug resistance (O) when compared to separate-drug formulations (C)?

II.3 Secondary objective

In patients who are treated for bacteriologically-confirmed tuberculosis, are two-month culture conversion rate, adverse drug reactions, patient adherence and patient treatment satisfaction superior with FDC than separate-drug formulations?

CHAPTER III Methods

III.1 Search strategy

A search strategy was designed to retrieve all original studies investigating the effectiveness of FDC anti-TB formulation therapy that were published in any language since 1980, the year since which FDC anti-TB formulations have been available in the market.[8] The following electronic databases were used for the literature search:

1- Medline (Ovid platform);
2- Medline In-Process or other Non-Indexed Citations (Ovid platform);
3- EMBASE (Ovid platform);
4- Cochrane Library (published by Wiley), which includes Cochrane Reviews, DARE, and Central Register of Controlled Clinical Trials; and
5- LILACS (BIREME – PAHO – WHO Latin-American and Caribbean Center on Health Sciences Information).

The following four sets of search terms were combined with 'AND':

1- terms about tuberculosis, mycobacterium, and anti-tuberculosis;
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.

Refer to Table 2 for more details about the terms used in each database.

Table 2. Database search strategies

	Medline (Ovid) [a]	Embase (Ovid) [b]	Cochrane Library [c]	Medline In-Process (Ovid) [d]	LILACS [e]
1 *terms combined with **or***	EXP TUBERCULOSIS/DT EXP ANTITUBERCULAR AGENTS MYCOBACTERIUM TUBERCULOSIS/DE tuberculosis ***and*** drug ***adj*** (therapy ***or*** effect*) antitubercul* tuberculostatic (anti ***adj*** tubercul*)	EXP TUBERCULOSIS/DT EXP TUBERCULOSTATIC AGENT MYCOBACTERIUM TUBERCULOSIS/DT tuberculosis ***and*** drug ***adj*** (therapy ***or*** effect*) antitubercul* tuberculostatic (anti ***adj*** tubercul*)	EXP TUBERCULOSIS/DT EXP ANTITUBERCULAR AGENTS MYCOBACTERIUM TUBERCULOSIS/DE tuberculosis ***and*** drug ***next*** (therapy or effect*) antitubercul* tuberculostatic (anti ***next*** tubercul*)	tuberculosis ***and*** drug ***adj*** (therapy ***or*** effect*) antitubercul* tuberculostatic (anti ***adj*** tubercul*)	tubercul$ antitubercul$
2	isoniazid ***and*** (rifampin ***or*** rifampicin)	isoniazid ***and*** (rifampin ***or*** rifampicin)	isoniazid ***and*** (rifampin ***or*** rifampicin)	isoniazid ***and*** (rifampin ***or*** rifampicin)	isoniazid ***and*** (rifampin ***or*** rifampicin)
3 *terms combined with **or***	DRUG COMBINATIONS fdc 4fdc 3fdc (fixed ***or*** multiple ***or*** combin*) ***adj3*** (drug* ***or*** dose* ***or*** dosage* ***or*** formula* ***or*** preparat* ***or*** regimen*)	DRUG COMBINATION fdc 4fdc 3fd (fixed ***or*** multiple ***or*** combin*) ***adj3*** (drug* ***or*** dose* ***or*** dosage* ***or*** formula* ***or*** preparat* ***or*** regimen*)	DRUG COMBINATIONS fdc 4fdc 3fdc (fixed ***or*** multiple ***or*** combin*) ***near/3*** (drug* ***or*** dose* ***or*** dosage* ***or*** formula* ***or*** preparat* ***or*** regimen*)	fdc 4fdc 3fdc (fixed ***or*** multiple ***or*** combin*) ***adj3*** (drug* ***or*** dose* ***or*** dosage* ***or*** formula* ***or*** preparat* ***or*** regimen*)	fdc combin$
4	1980-current ***and*** human	1980-current ***and*** human	1980-2011		
final combinations	1 ***and*** 2 ***and*** 3 ***and*** 4 1716 hits (July 27, 2011)	1 ***and*** 2 ***and*** 3 ***and*** 4 1271 hits (July 28, 2011)	1 ***and*** 2 ***and*** 3 ***and*** 4 258 hits (July 27, 2011)	1 ***and*** 2 ***and*** 3 11 hits (July 28, 2011)	1 ***and*** 2 ***and*** 3 38 hits (July 27, 2011)

Notes: Subject keyword terms were used in all databases; formal subject headings (MeSH, EMTREE) were also used where available, as were subheadings and features such as word adjacency and "explode" (to include associated narrower terms in hierarchical subject headings thesauri). Terms were combined using Boolean "and" and "or."
[a] MeSH terms in upper case, other terms are keywords (.mp); [b] EMTREE terms in upper case, other terms are keywords (.mp); [c] MeSH terms in upper case, other terms are "textword"; [d] all terms are keywords (.mp); [e] all terms searched as "word".

III.2 Study selection

Studies that fulfilled all of the following criteria were eligible for inclusion in this review:

1- Controlled trials or comparative cohorts, which directly compared FDC to separate-drug formulations. We also included studies (trials or cohorts) that used FDC anti-TB regimens in all treatment arms (did not have our defined control [separate-drug formulation]), which we considered as non-comparative or uncontrolled in this review. We did not limit our systematic review to controlled trials, which usually provide higher level of evidence than observational studies, because we were initially concerned we would not find an adequate number of published papers. In a large cohort study, conducted in a high TB incidence area,[72] the incidence of failure and relapse were 4.3% and 6.5% respectively; 65% of failure cases and 8% of relapse cases (meaning 2.8% and 0.5% of the total population respectively) acquired drug-resistant forms of TB. To detect differences in these rare outcomes between treatment groups, we anticipated needing large sample sizes, and were concerned this may not be achieved if there were only a few published controlled trials. In addition, observational studies may provide information that is more generalizable to the usual health care practice than controlled trials.

2- At least 50 included subjects in cohort studies, cohorts with smaller number of subjects were considered case-series and were not eligible.

3- Bacteriologically-confirmed diagnosis of active TB, based on culture or smear analyses, among included subjects.
4- Treatment with an FDC anti-TB formulation that contained at least rifampicin and isoniazid.
5- Treatment with an effective anti-TB regimen (i.e. daily or at least 3 times weekly administration of rifampicin and isoniazid for 9 months, or for 6 months if pyrazinamide was added during the initial 2 months).
6- Measurement of at least one of our primary treatment outcomes (i.e. bacteriologically-confirmed failure or relapse, or acquired drug resistance with diagnosis based on pre-treatment and follow-up drug susceptibility testing).
7- Follow up period for at least five months during the treatment.

All retrieved citations were installed in an EndNote reference library. After deleting duplicate citations, the selection of eligible studies was performed in a stepwise fashion—titles, then abstracts, then full texts. These steps were carried out by two reviewers (Amr Albanna and Benjamin Smith) 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 (Dick Menzies).

Research Ethics Board review was not required for this systematic review of previously published data.

III.3 Data extraction and study quality assessment

A data abstraction form was designed (Appendix) to collect the following relevant information:

1- Study characteristics (study design, location, potential conflict of interest, and study duration and time period).

2- Factors related to subject characteristics (age, sex, past TB treatment, HIV status, and comorbidities) and disease status (disease site and drug sensitivity) that may influence treatment outcomes. Based on published studies about factors that influence treatment outcomes, pre-treatment drug-susceptibility status and HIV co-infection are the most influential factors.[44,45,73,74] Other commonly encountered factors include history of previous TB, diabetes and other comorbid diseases, alcohol and drug abuses, older age, and male sex.[74,75]

3- Treatment outcomes (completion of treatment, adherence to treatment, adverse drug reaction, treatment failure, death during treatment, disease relapse, acquired drug resistance, and treatment satisfaction).

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 randomized controlled trial;

3- adequate reporting 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.

Each of these quality indicators scores one if appropriately performed and reported. The total quality score for each study ranges from zero to five. Blinding was not included in this quality scale because it is not possible to blind the subjects or evaluators from the number of tablets which must be different between the treatment arms.

To ensure accurate and consistent data collection, the two reviewers (Amr Albanna and Benjamin Smith) independently performed data extraction, using the data abstraction form (Appendix), and quality assessment in a sample of nine articles. The data from the two reviewers were entered into Excel spreadsheets and compared. Important missing data were obtained by correspondence with the studies' authors through email contact. Translation of foreign language articles required multiple meetings and discussions with native speakers of these languages to ensure accurate data extraction.

III.4 Outcome measures

The primary outcome measures were treatment failure or disease relapse, combined as one outcome, and acquired drug resistance as another. Treatment failure was defined as a positive acid fast bacilli (AFB) smear, or positive culture for MTB after five months or more of treatment; and disease relapse was defined as positive AFB smear, or positive culture for MTB in patients who were

successfully treated (i.e. cured or completed treatment) from TB. Acquired drug-resistant TB was defined as change of disease susceptibility to one or more first-line anti-TB drugs from drug-susceptible to drug-resistant. These outcomes were chosen as primary outcomes because they are objectively measured and specifically related to the adequacy of TB treatment, features which are particularly important for meta-analysis to reduce between-study heterogeneity of outcome ascertainment and results. The secondary outcomes were bacterial conversion (i.e. change of the laboratory smear or culture results from positive to negative) after two months of treatment, adverse drug reaction (overall), patient adherence, and treatment satisfaction. Although the two-month smear/culture conversion has been commonly used as a surrogate marker of treatment efficacy,[76] we considered it as a secondary outcome in this study because it has low sensitivity for predicting failure or relapse, based on a recent meta-analysis of 15 studies.[77] Since adherence and satisfaction were secondary outcomes, we used a descriptive approach and did not construct a pre-specified inclusion or restriction criteria.

III.5 Data analysis

Using per-protocol analysis, the differences in the outcomes between the comparative groups were expressed as risk ratios (RR) and 95% confidence intervals (CI). We did not use intention-to-treat analysis because many included articles did not provide enough information about randomized subjects who were missed during the follow-up period, which was greatly variable between trials.

Between-study heterogeneity was assessed using *chi*-square (Cochran Q) test, indicating statistical significance as $p < 0.1$, and *I*-square test, in which heterogeneity was considered not important with values less than 40%, moderate with values between 40% and 60%, and substantial with values over 60%. In case of significant heterogeneity of results or inconsistent methods of ascertainment across studies, the outcome estimates were not pooled and were reported separately.

The effect measures were pooled using the DerSimonian-Laird random effect model. The use of random rather than fixed effect model was pre-specified, regardless of the result of our heterogeneity analysis, to account for variations between studies related to the type and severity of prevalent disease, standard of care, and research quality. In case of rare events (less than 1%), where DerSimonian-Laird random effect model may provide biased estimate,[78,79] a sensitivity analysis was performed using an alternative pooling method (Peto model), in which odds ratio was used as approximation of RR.

We followed recommendations from the 'Cochrane Handbook for Systematic Reviews of Interventions' for dealing with trials with zero events.[78] Trials with zero events in one of the treatment arms were included for meta-analysis and their point estimates were calculated by adding 0.5 to each cell of the 2X2 table. However, trials with zero events in both treatment arms were excluded from the meta-analysis, since the direction and magnitude of the relative effect are not clear. This is the default meta-analysis method when using 'metan' code in STATA software. Considering other opinions regarding this issue,[80] we also

performed the meta-analysis including trials with zero events in both arms after adding 0.5 to each cell of the 2X2 table, using ‘meta’ code in STATA.

Subgroup analysis was performed to detect factors that influenced the primary outcome results. These factors included pre-treatment DST, treatment supervision modality, type of treatment regimen, and FDC formulation producer/manufacturer. In addition, we stratified the studies by their potential for conflict of interest, defined as funding or drug supply by an FDC manufacturer company.

Univariate meta-regression analysis was performed to assess the influence of study quality and publication year on the pooled estimate. In addition, all potentially influencing variables were included in a multivariable meta-regression model.

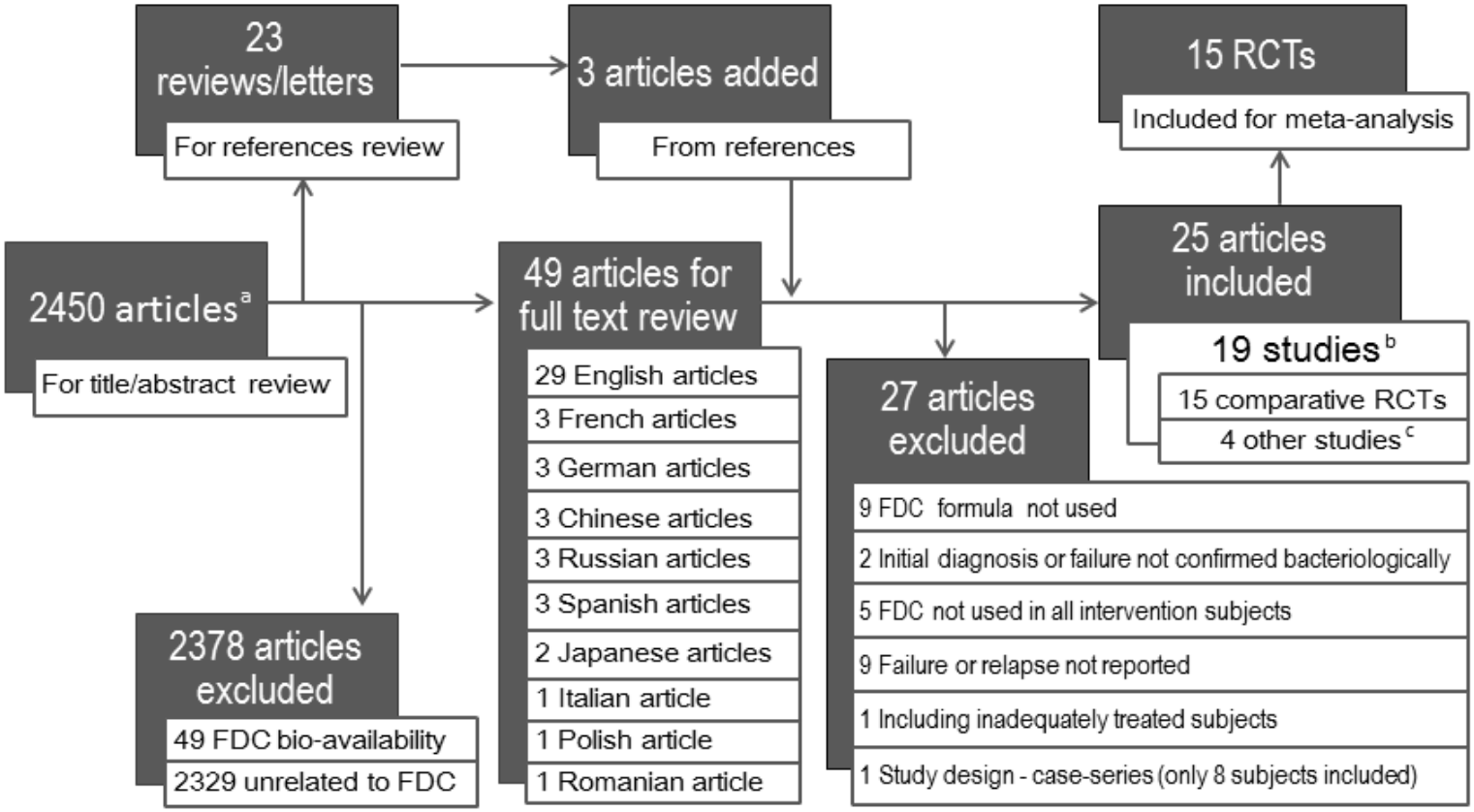
Reporting bias, which includes publication bias, was assessed using funnel plot and Egger’s test, which is based on linear regression analysis to test the association between the intervention effect (using logarithmic scale) and its standard error.[78] All analyses were conducted using STATA (version 12) software.

CHAPTER IV Results

IV.1 Study selection

A total of 2450 different citations were identified by our search strategy; and an additional 3 articles were identified from searching references of published literatures. Of these, 49 were selected for full text review; of which, a total of 25 articles met our inclusion criteria. These 25 articles reported results of 19 different studies; refer to Figure 2 for detail.

Figure 2. Study selection.



Abbreviation: FDC, fixed dose combination. Notes: [a] After excluding 844 duplicate articles; [b] some studies were published in more than one articles; [c] one comparative cohort and three non-comparative studies.

Among the 19 included studies, 15 were randomized controlled trials that directly compared FDC to separate-drug formulations, and four were other studies (Table 3). Because the comparative randomized trials represented the majority of the included studies, and to obtain valid, unbiased comparative estimates of treatment outcomes, our analysis focused on these 15 controlled trials. In addition, the comparative estimates from different study designs were different; therefore, pooling them was not appropriate. A summary of the effect measures from the other studies is reported separately (see section IV.5).

Table 3. Type of included studies.

	No. of studies	Total No. of included subjects
Controlled trials [a]	15	5, 630
Comparative cohort [a]	1	474
Non-comparative trials [b]	2	310
Non-comparative cohort [b]	1	1888

Notes: [a] Directly compared fixed-dose combination to separate-drug formulation treatments; [b] studies used FDC anti-TB regimens in all treatment arms.

IV.2 Reliability of data collection and data entry

Data from a sample of 9 articles were extracted and entered into an Excel spreadsheet by each of the two reviewers. As seen in Table 4, a total of 225 pairs of data elements were compared. Of these pairs, 94% were concordant. Upon review, the 14 discordant data points were all related to unclear documentation in the original articles.

Table 4. Reviewers agreement

		Concordant pairs	Discordant pairs	Concordant /total (%)
Study design		9	0	9/9 (100)
Treatment regimen	Used drugs	9	0	45/45 (100)
	Frequency	9	0	
	Duration	9	0	
	FDC formulation	9	0	
	DOT	9	0	
Drug sensitivity testing		9	0	9/9 (100)
Subject characteristics	Age	9	0	51/54 (94)
	Sex	9	0	
	Past TB	8	1	
	Comorbidities	7	2	
	HIV	9	0	
	Disease severity	9	0	
Study follow up (F/U)	No. of included subjects	8	1	24/27 (89)
	Duration	9	0	
	% completed F/U	7	2	
Outcomes	Failures	8	1	33/36 (92)
	Relapses	8	1	
	Acquired drug resistance	9	0	
	Secondary outcomes	8	1	
Quality assessment	Allocation sequence	9	0	40/45 (89)
	Allocation concealment	9	0	
	Follow-up completion	8	1	
	Outcome measure	6	3	
	Assessment of bias	8	1	
Total		211	14	211/225 (94)

Abbreviations: FDC, fixed dose combination; DOT, directly observed therapy; TB, tuberculosis.

IV.3 Descriptive characteristics and quality assessment of included studies

As shown in Table 5, most included studies were conducted in high TB incidence countries. Subjects were predominantly males in their thirties, and most of them had not received TB treatment previously. Different treatment regimens and types of FDC formulations were used, and follow-up durations ranged from 6 months to 5 years.

Table 6 shows our assessment of the studies' quality. Due to poor documentation, we could not assess the appropriateness of randomization in many trials.

Table 5. Summary of studies included in the review

Author	Publication year	Study place	Age (Mean)	Male (%)	Treat. Regimen	FDC formulation	F/U (months)	DOT	Past TB (%)	Potential conflict of interest [a]
Comparative trials (direct comparison between FDC and separate-drug formulation treatments)										
RCTAI[81]	1989	India	29 [b]	70	HRZ	Rifater/Rifinah	12	No	0	Yes [c]
Cowie et al[82]	1990	South Africa	38	100	HRZ±S	Rifater	24	Yes	0	Yes [d]
HKCS/BMRC[83,84]	1991	China	35 [b]	66	HRZ±S	Rifater	60	Yes	NR	Yes [e]
Glatthaar et al[85]	1991	South Africa	NR	NS	HRZE	Rifater	24	Yes	0	Yes [f]
Macnab et al[86]	1994	South Africa	NR	NR	HRZE	Rifater	6	Yes	0	Unclear
Chaulet et al[87-89]	1995	Algeria	28 [b]	75	HRZ [g]	NR	30	No [h]	0	No
Zhang et al[90]	1996	China	41 [b]	65	HRZ	Rifater/Rifinah	24	Yes	0	Yes [i]
Zhu et al[91]	1998	China	37 [b]	70	HRZ	Rifater/Rifinah	6	NR	0	Unclear
Teo[92,93]	1999	Singapore	39 [b]	66	HRZ±S	Rifater	60	Yes	0	No
Su et al[94]	2002	Taiwan	NR	89	HRZ	Rifater/Rifinah	12	No	0	Unclear
Munteanu et al[95]	2004	Romania	37 [b]	63	HRZE	NR	24	Yes [j]	0	Unclear
Xu et al[96]	2004	China	49	76	HRZE	NR	6	NR	NR	Unclear
Suryanto et al[12,97]	2008	Indonesia	37	57	HRZE	Svizera	36	No	NR	No
Bartacek et al[98]	2009	5 countries [k]	37	69	HRZE	Rimstar/Rimactazid	12	NR	19 [l]	Unclear
SCTG[13]	2011	9 countries [m]	34	67	HRZE [g]	Svizera	30	Yes	0	No
Non-comparative trials										
Brändli et al[99,100]	1993	Switzerland	48	71	HR±Z [n]	Rifater/Rimactazid	48	NR	0	Unclear
Punnotok et al[101]	1995	Thailand	35	68	HRZ	Rifater/Rifinah	36	No	0	Unclear
Comparative cohort										
Sokolova et al[102]	2002	Russia	NR	NR	HRZE	Myrin P	≥ 6	NR	0	Unclear
Non-comparative cohort										
Churchyard et al[103]	2000	South Africa	41	NR	HRZ	NR	48	Yes	26	No

Abbreviations: FDC, fixed-dose combination; F/U, follow up; DOT, direct observed therapy; TB, tuberculosis; RCTAI, Research Committee of the Tuberculosis Association of India; H, isoniazid; R, rifampicin; Z, pyrazinamide; S, streptomycin; E, ethambutol; HKCS, Hong Kong Chest Service; BMRC, British Medical Research Council; NR, not reported; SCTG, Study C Trial Group. **Notes:** [a] defined as funding or drug supply by an FDC manufacturer company, [b] the mean was estimated from a stratified age distribution; [c] M/S Merrel Dow and Tata Pharma India supplied Rifater, Rifinah, Pyrazinamide tablets and Rifampicin capsules; [d] Mer-National supplied the Rifater tablets; [e] Gruppo Lepetit of Milan supplied Rifater and Bracco Industria Chimica of Milan supplied pyrazinamide; [f] financially supported by Mer-National; [g] during continuation phase, FDC was given to both groups; [h] treatments were under direct supervision only during the first 3 weeks of therapy; [i] financially supported by Hoechst Marion Roussel, Singapore; [j] DOT was given only during the initial phase of treatment; [k] Egypt, India, Pakistan, Philippine, and Thailand; [l] comparable between the groups [m] Algeria, Colombia, Guinea, Vietnam, Nepal, Peru, Mozambique, Tanzania, and Bolivia; [n] either 9 months HR regimen or 6 months HRZ regimen.

Table 6. Quality assessment of included studies

Author	Allocation sequence [a]	Allocation concealment	Follow-up completion [b]	Non-selective outcomes [c]	Free of bias [d]
Comparative trials (direct comparison between FDC and separate-drug formulation treatments)					
RCTAI[80]	Yes	Unclear	Yes	Yes	Yes
Cowie et al[82]	No [e]	Yes	Yes	Yes	No [f]
HKCS/BMRC[83,84]	Unclear	Unclear	Yes	Yes	Yes
Glatthaar et al[84]	Unclear	Unclear	Yes	Yes	Unclear
Macnab et al[86]	No [e]	Unclear	No [g]	Yes	Unclear
Chaulet et al[87-89]	Unclear	Unclear	Yes	Yes	Yes
Zhang et al[90]	Yes	Unclear	Yes	Yes	Yes
Zhu et al[91]	Unclear	Unclear	Yes	Yes	Yes
Teo[92,93]	Unclear	Unclear	Yes	Yes	Yes
Su et al[94]	Unclear	Unclear	No [g]	Yes	Unclear
Munteanu et al[95]	Unclear	Unclear	Yes	Yes	Yes
Xu et al[96]	No [e]	Unclear	Yes	Yes	Unclear
Suryanto et al[12,97]	Yes	No [h]	Yes	Yes	Unclear
Bartacek et al[98]	Yes	Yes	Yes	Yes	Yes
SCTG[13]	Yes	Yes	Yes	Yes	Yes
Non-comparative trials					
Brändli et al[99,100]	Unclear	NA	Yes	Unclear	Yes
Punnotok et al[101]	Yes	NA	Yes	Yes	Yes
Comparative cohort					
Sokolova et al[102]	Unclear	NA	Unclear	Unclear	Unclear
Non-comparative cohort					
Churchyard et al[103]	Yes	NA	Unclear	Yes	Unclear

Abbreviations: FDC, fixed-dose combination; RCTAI, Research Committee of the Tuberculosis Association of India; HKCS, Hong Kong Chest Service; BMRC, British Medical Research Council; SCTG, Study C Trial Group; NA, not applicable. **Notes:** [a] Proper sequence of allocation in case of RCT, and consequence of subject recruitment in case of cohort study; [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] equivalent subject characteristics and management between comparison groups, and the sample population has no specific risks that could influence their treatment outcomes; [e] allocation based on even vs. odd generated numbers; [f] streptomycin was added to the treatment of only one of the two groups; [g] less than 75% of subjects completed the follow up; [h] the subjects were alternatively allocated to each study group.

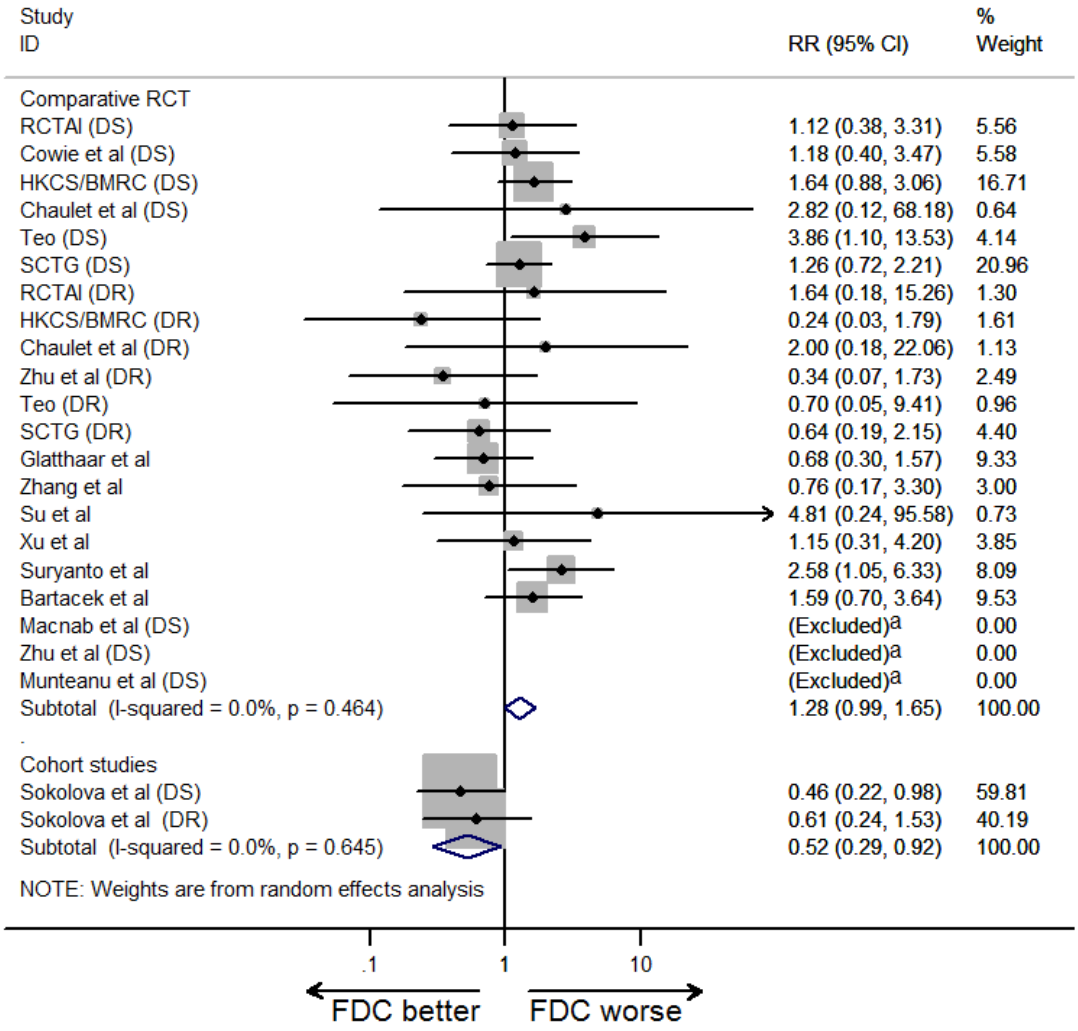
IV.4 Outcome results of the comparative randomized trials

IV.4.1 Treatment failure or disease relapse combined outcome

IV.4.1.1 Pooled estimates

In the 15 controlled trials, there was a trend toward higher risk of failure/relapse combined outcome with FDC compared to separate drug formulations (pooled RR, 1.28 [95%CI: 0.99, 1.65]), and there was no significant heterogeneity between different studies' results (I^2, 0%; p = 0.46), (Figure 3). The incidence of failure or relapse was relatively low in both treatment arms (Table 7), and the pooled risk difference was 1% (95% CI: - 0.2, 2%) higher with FDC's.

Figure 3. Forest plot showing the risk ratios (RR) of failure or relapse among FDC versus separate-drug formulation groups, stratified by study design.



Abbreviations: RCT, randomized controlled trials; FDC, fixed-dose combination; DS, drug-susceptible; DR, drug-resistant. **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 became 1.26 (95% CI: 0.98, 1.63).

Table 7. Pooled outcome results of controlled trials.

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							
Pooled result	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							
Pooled result	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							
Pooled result	12	2354	94 (91, 96)	2443	91 (89, 92)	1.03 (1.01, 1.04)	13/0.32
Adverse drug reaction							
Pooled result	10	2416	16 (9, 23)	2195	20 (11, 28)	0.88 (0.75, 1.03)	23.7/0.23
Patient adherence [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)	
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)	
Bartacek et al [g]	1	411	81 (77, 85)	422	57 (52, 61)	1.43 (1.30, 1.58)	

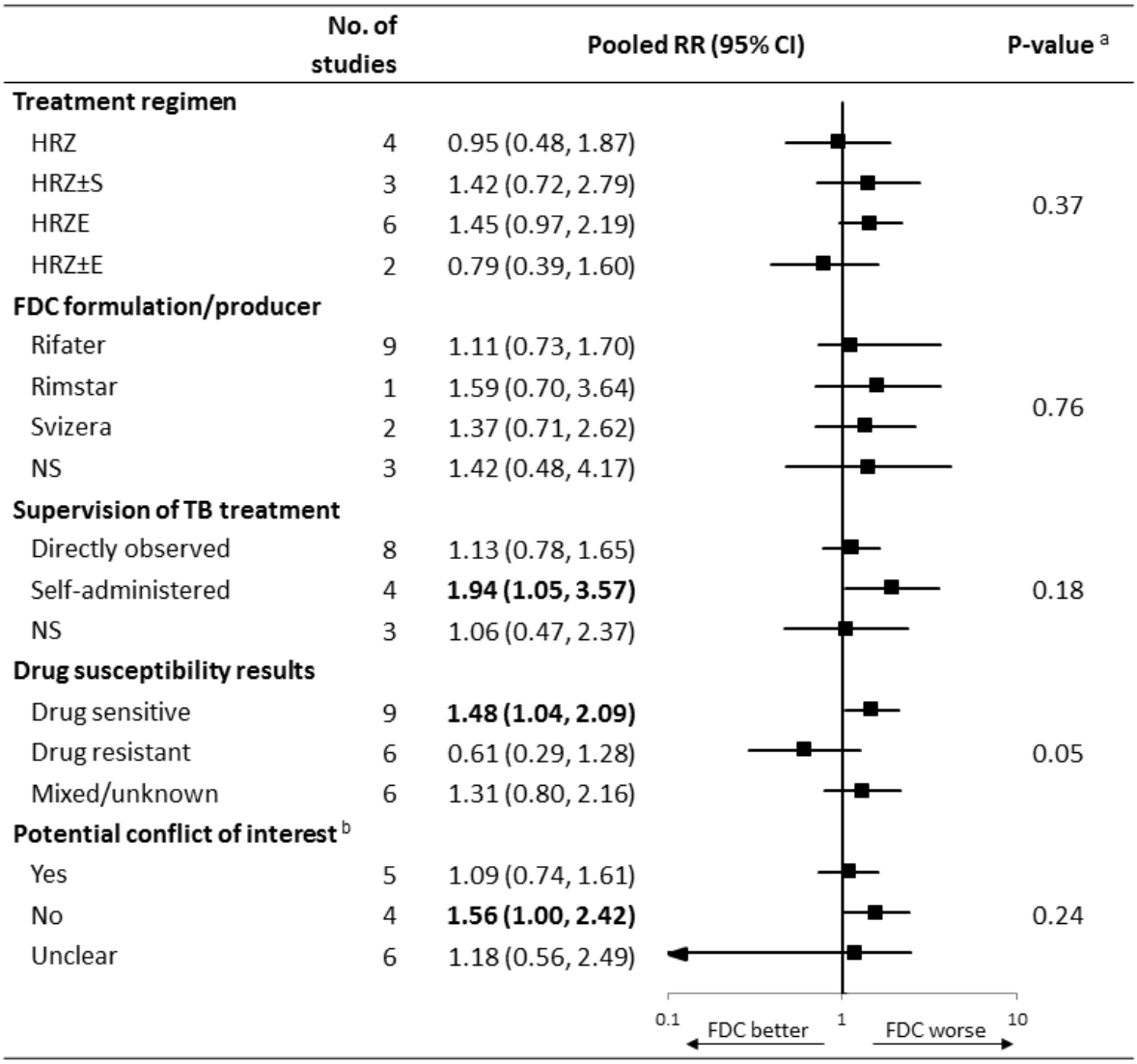
Abbreviations: FDC, fixed-dose combination; CI, confidence interval; RR, risk ratio; TB, tuberculosis. **Notes:** [a] study results were not pooled because of inconsistent methods for measurement of the outcome; [b] assessment of adherence was based on monthly home visits and count of the number of remaining 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.

IV.4.1.2 Subgroup and meta-regression analyses

In the sub-group analyses, pre-treatment drug susceptibility status appeared to modify the risk of failure/relapse outcome. Comparing FDC to separate-drug formulations, the risk was significantly higher within the stratum of subjects with drug-susceptible TB (pooled RR, 1.48 [95% CI: 1.04, 2]) and lower, though not significantly, within the drug-resistant stratum (RR, 0.61 [95% CI: 0.3, 1.3]). In addition, the risk of failure/relapse was significantly higher with FDC formulation among subjects received self-administered therapy (RR, 1.94 [95% CI: 1.05, 3.57]) and in studies with no potential conflict of interest (1.56 [95% CI: 1.0, 2.4]), (Figure 4).

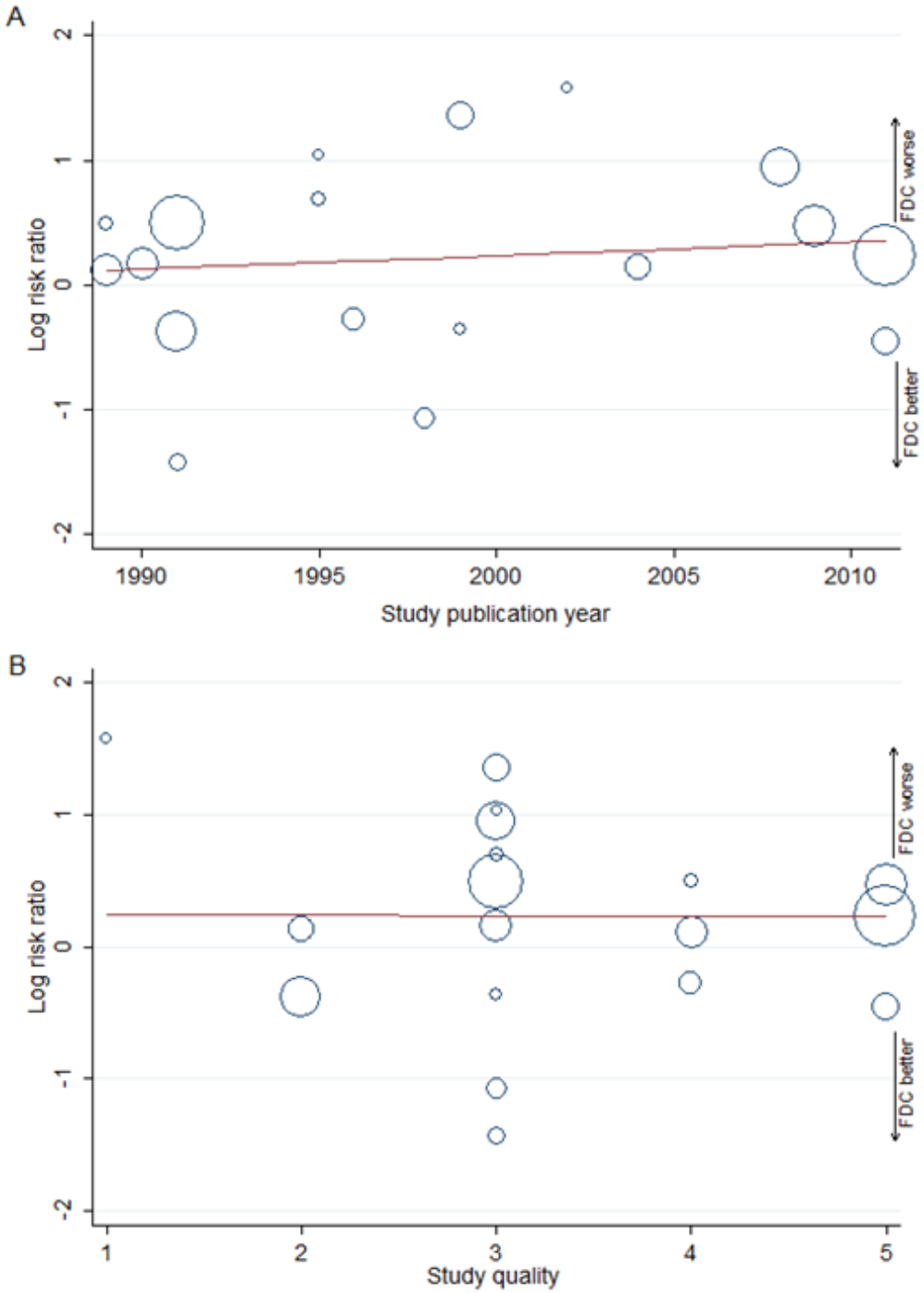
Univariate meta-regression analyses did not indicate a significant influence of publication year or study quality on the outcome results (Figure 5). After including these two covariates with drug susceptibility, treatment supervision, and potential conflict of interest variables in a multivariate meta-regression model, drug susceptibility was the only variable that significantly modified the outcome results. Comparing the point estimate within the drug-resistant stratum to the point estimate within the drug-susceptible stratum, the RR was 0.32 (95% CI: 0.11, 0.94). This value provides an estimation of the effect of the covariate ‘drug susceptibility status’ on the pooled estimate after adjusting for other covariates in the model (RR of 1.0 would indicate no effect). The RR of 0.32 indicates that the drug-resistant cases, as compared to drug-susceptible cases, shifted the pooled estimate toward a lower risk of failure/relapse with use of FDC’s.

Figure 4. 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] P-value of difference was measured using univariate meta-regression analysis; [b] including funds and/or drug supplies.

Figure 5. Univariate meta-regression for estimating the effect of continuous covariates on the risk ratio of failure or relapse (main outcome) among fixed-dose combination versus separate-drug formulation groups. A) Study publication year. B) Study quality scale.

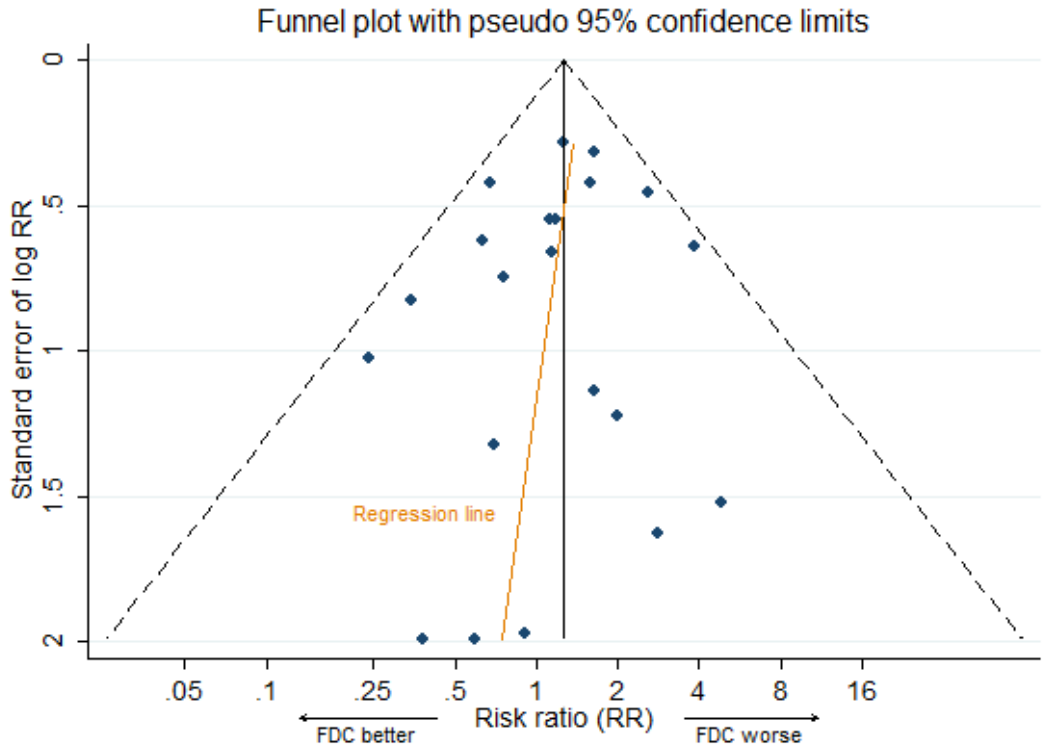


Abbreviations: FDC, fixed-dose combination. **Notes:** The circles' areas are inversely proportional to the variance. The study quality scale in figure (B) ranges from 0-5 as the quality changes from low to high.

IV.4.1.3 Assessment of reporting bias

Funnel plot analysis demonstrated a symmetric distribution of 'treatment failure or relapse' effect estimates across studies, and Egger's regression analysis indicated that small studies, which have less precise estimates (larger standard errors), tended to shift the treatment effect in favor of FDC treatment (Figure 6). However, the small-study effect was not significant (estimated bias coefficient, - 0.36 [95% CI: -1.2, 0.49]; p = 0.39).

Figure 6. 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).

IV.4.2 Acquired drug resistance outcome

As seen in Table 7, the incidence of acquired drug resistance, based on pooled results from four controlled trials, was very low in both treatment arms (0.26% [95% CI: 0, 0.7%] in the FDC group and 0.08% [95% CI: 0, 0.35%] in the separate-drug formulation group), and the relative risk estimate was inconclusive with wide confidence interval (1.6 [95% CI: 0.5, 5.4]).

Stratified analysis based on pre-treatment drug susceptibility status provided inconclusive estimates within both drug-susceptible (RR = 4.8 [95% CI: 0.8, 30]) and drug-resistant (RR = 0.68 [95% CI: 0.13, 3.48) strata.

Using Peto model, which may provide unbiased estimate in case of rare events,[78,79] the overall odds of acquired drug resistance were inconclusive (OR, 2.01 [95% CI: 0.5, 8.0]); however, the stratum specific odds of this outcome were significantly higher within the drug-susceptible stratum (OR = 6.8 [95% CI: 1.08, 43) and inconclusive within the drug-resistant stratum (OR = 0.42 [95% CI: 0.05, 3.4]).

IV.4.3 Secondary outcomes

As compared to separate formulation treatment, FDC treatment had almost similar culture conversion rate after two months of treatment (RR, 1.03 [95% CI: 1.01, 1.04]), and had similar association with adverse drug reaction (RR, 0.88 [95% CI: 0.75, 1.03]). The estimated results of patient adherence and treatment satisfaction outcomes were not pooled because of inconsistent ascertainment methods across the included trials; see Table 7 for details. Only one of two trials

that assessed treatment satisfaction, and none of five that assessed patient adherence favored FDC's.

IV.5 Outcome results of the cohort and non-comparative studies

Among included studies, the comparative cohort presented the highest proportion of failure/relapse combined outcome, ranging from 5% to 11% among drug-susceptible and from 21% to 35% among drug-resistant TB patients. The crude RR of failure/relapse 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 indicated low incidence of failure or disease, ranging from 0.5% to 2%, and acquired drug resistance, ranging from 0 to 0.3%, among TB treated patients (Table 8).

Table 8. Individual study results of the comparative cohort and non-comparative studies.

Outcomes	No. of studies	FDC		Separate-drug formulation		RR (95%CI)
		No. of subjects	% (95% CI)	No. of subjects	% (95% CI)	
Treatment failure or disease relapse						
Sokolova et al (cohort) —DS	1	258	5 (2.7, 8.5)	110	10.9 (5.9, 18.3)	0.46 (0.2, 0.98)
Sokolova et al (cohort) —DR	1	19	21 (6, 46)	87	35 (25, 45)	0.61 (0.24, 1.53)
Brändli et al (trial) [a]	1	213	0.5 (0.01, 2.6)	No comparative group [b]		
Punnotok et al (trial)	1	97	2 (0.3, 7.3)	No comparative group [b]		
Churchyard et al (cohort) [a]	1	1888	1.5 (1, 2)	No comparative group [b]		
Acquired drug resistance						
Brändli et al (trial) [a]	1	213	0 (0, 1.7)	No comparative group [b]		
Churchyard et al (cohort) [a]	1	1888	0.26 (0.1, 0.6)	No comparative group [b]		
TB culture conversion after 2 months of treatment						
Punnotok et al (trial)	1	97	99 (94, 100)	No comparative group [b]		
Adverse drug reaction						
Punnotok et al (trial)	1	98	32 (23, 42)	No comparative group [b]		
Patient adherence						
Churchyard et al (cohort) [c]	1	1601	99.5 (99, 100)	No comparative group [b]		

Abbreviations: FDC, fixed-dose combination; CI, confidence interval; RR, risk ratio; DS, drug-susceptible; DR, drug-resistant; TB, tuberculosis. **Notes:** [a] drug-resistant TB cases were excluded; [b] FDC anti-TB regimens were used in all treatment arms; [c] assessment of adherence was based on the duration of treatment interruption (less than 2 months).

CHAPTER V Discussion

V.1 Main findings

In this systematic review of published evidence, pooled results of controlled trials comparing FDC to separate-drug formulations showed that therapy with FDC's was associated with a trend toward increased risk of failure/relapse combined outcome and no difference in the emergence of drug resistance, adverse drug reactions, or culture conversion after two months of treatment. Although one study identified better treatment satisfaction, in none of the included studies was adherence better among patients treated with FDC compared to separate-drug formulations.

V.2 Validity and generalizability of included studies

Randomized controlled trials, which usually provide the best comparative unbiased estimates, represented the majority of the included studies in this review (15 studies). Therefore, our main analysis focused on these controlled trials, since we found only few studies with other designs and these would add little at the expense of reduced validity of our overall result. However, because we originally planned to include cohorts and non-comparative trials, these were still presented in this review to explore comprehensively what has been published in the literature.

The research quality across included trials was different and, in some trials, difficult to judge as key methodological aspects were poorly documented.

However, the study quality score in these trials did not significantly influence our overall estimate, based on meta-regression analysis.

Despite the potential for controlled trials to provide the highest level of evidence in drug efficacy research, they are usually conducted under optimal medical care. Generalization of controlled trial results is limited to environments with similar practice standards and may not reflect the potential benefit of using FDC formulation to treat TB in settings where mal-practice or unmonitored therapies are common. For this reason, observational studies, despite their inherent susceptibility to confounding, may better reflect real medical practice. However, the comparative cohort in this review presented crude estimates, which could be biased by confounding factors that were not adjusted for. This may explain the significant difference between the results of this cohort and the controlled trials. The non-comparative cohort, on the other hand, reported incidence of unfavorable outcomes that were comparable to the ones in the controlled trials, which may reflect similar level of patient care.

V.3 Limitations

Due to small number of studies that investigated the risk of acquired drug resistance, which was a rare outcome in these studies (5 events out of 1113 subjects in the FDC group versus 4 events out of 1405 subjects in the separate-drug formulation group), the pooled estimate was not sufficiently precise to provide a conclusive result. Although the result of sensitivity analysis, using Peto pooling method, suggested higher odds of acquired drug resistance with FDC

treatment among patients with pre-treatment drug-susceptible TB, this result should be interpreted with caution.

The ascertainment methods of patient adherence and treatment satisfaction were not based on validated measurement tools and were inconsistent across 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 less than one to five years—and, in some studies, not reported or not attributed to the treatment groups.

Our estimates were based on per-protocol analysis which does not account for loss of follow-up after randomization. Differential loss of follow-up that is related to the type of intervention may introduce biased estimate of the results. However, this is unlikely in our study since the adherence to follow-up visits was similar between the comparative groups.

Although there was no evidence of reporting bias, based on funnel plot and Egger's regression analysis, this does not completely exclude the possibility of reporting bias.

Finally, the multiple meta-regression model included five covariates which are many, relative to the number of included studies (15 studies); therefore, model overfitting is a potential concern.

V.4 Strengths

Our systematic review was conducted without language restriction to accurately represent the existing evidence. Additionally, the lack of significant heterogeneity between the controlled trial estimates of failure/relapse outcome permitted appropriate pooling and increased precision of our results.

Another strength was the ability to stratify subjects based on their pre-treatment drug susceptibility status, which was a significant covariate influencing the primary outcome. Comparing FDC to separate-drug formulation treatments, the risk of treatment failure or disease relapse tended to be higher within the stratum of subjects with pre-treatment drug-susceptible TB and lower (in favor of FDC) within the stratum of subject with pre-treatment 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 is difficult to interpret since it included a relatively small number of patients with heterogeneous patterns of drug resistance to anti-TB drugs.

V.5 Clinical implications

Our findings suggest that, compared to separate-drug formulation, the use of FDC formulations does not reduce the risk of treatment failure or disease relapse; if anything this risk may be actually higher with FDC, especially among patients with pre-treatment drug-susceptible disease. This potential increase in risk, however, may not be clinically important. We identified an absolute increased risk of failure or relapse among FDC treated patients of 1% with an

upper 95% CI of 2%. This is less than the risk difference value (4%) of unfavorable outcomes (defined as failure, relapse, or TB related death) that has been estimated to be clinically important.[13]

Existence of unresolved controversies about the bioequivalence of FDC component drugs,[59] reports of impaired rifampicin bioavailability in many marketed FDC formulations,[51] and lack of evidence that FDC therapy will improve the effectiveness of TB treatment, together raise concerns about the use of FDC formulations for TB therapy.

V.6 Summary and conclusion

In summary, this systematic review provides evidence that FDC formulations are not superior, and may actually be inferior, to separate drug formulations for preventing treatment failure or disease relapse among TB treated patients. This may not be generalizable to settings with unstandardized or uncontrolled medical practice. Furthermore, there is no evidence that FDC formulations will improve patient adherence, and inconsistent evidence that FDC regimens improve treatment satisfaction.

We conclude that the published evidence, summarized in this review, does not support recommendations for the use of FDC formulations for the treatment of active tuberculosis.

Appendix

FDC Data Abstraction FORM

1 - Screening for Eligibility

Reviewer:

Author: **Year 1st Pub'n:** **Papers (N):**

Ref ID (IDs): **Study ID:**

Language: □ English □ French □ Spanish □ Other _____

***Design**: □RCT □Cohort □Case Control □Other

*__Diagnosis__: □ Active TB (%) □ Latent TB (%)

Bacteriological confirmation: □Culture or Smear (%) □Neither (%)

***Treatment regimens:**

FDC contains at least INH+RIF □Yes □No

Treatment duration: □ ≥ 6 months □ < 6 months

***Number of included patients, if cohort study**:

□ ≥ 50 patients □ < 50 patients

SUMMARY: □ INCLUDED □ EXCLUDED FOR FURTHER REVIEW

Reasons:

2 – Assessment of Quality **(If included)**

How complete is reporting:

	N	
Started on treatment /entered study (Total)	_____	
Excluded for pregnancy, Not TB, NTM, other valid reasons	_____	
Treated and eligible for outcomes analysis	_____	
During Treatment		
Non-compliant/ Refused	_____	
Dropped out/ Lost	_____	
Transfer out/ Moved	_____	
Protocol violation/ Incomplete data	_____	
Others:	_____	
Sub-total - Not analyzed for Study problems	_____	%
Side effects (stopped treatment)	_____	
Died during treatment	_____	
Completed treatment (includes failures and cures)	_____	
After Treatment (If follow-up or relapse)		
Duration of follow-up after treatment (mean or median in months)	_____	
Completed treatment AND assumed cured	_____	
Lost to follow-up (AFTER end of Tx)	_____	
Completed follow-up (or relapsed TB or died)	_____	

Other quality indicators:

If RCT:

Randomization adequate? □ Yes □ No □ Not described

If Cohort:

Patient selection: □ All (consecutive) □ Random sample

□ Convenience sample □ Not described

3 – Study Description **(If included)**

Sponsor: □ Corporate (C) □ Public (P) □ Not stated

Number of included patients:

Study period:

Country:

Patient's characteristics:

Age: _____(mean) _____(median) □ Not given

% Male: _____ % □ Not given

HIV co-infection: (%) □ Not done □ Not stated

Past TB treatment: (%) □ Not stated

Comorbidity: (%) □ Not stated

Diagnosis:

Bacteriologic diagnosis: □Smear (%) □Culture (%) □Not clear (%)

Disease site: □Pulmonary TB (%) □Extra-pulmonary (%) □Unknown

Baseline DST: □Drug-susceptible (%) □Drug-resistant (%) □Unknown

Treatment regimens:

	1	2	3	4	5	6
Abbreviation (HRZE)						
Frequency (2 3 5 7)						
Initial						
Continuation						
Supervision (Y N NS)						
Initial						
Continuation						
FDC used (Y N)						
Initial						
Continuation						
RIF months (0 – 12)						
PZA months (0 – 12)						
STREP months (0 – 12)						
INH months (0 – 12)						
N drugs – initial						
N drugs – continuation						

Treatment regimen (summary): □ Similar in the groups □ Not similar

FDC formula name/bio-availability:

Treatment duration:

Follow up (F/U) duration:

% Loss of F/U:

4 – Outcomes

Primary Outcomes:

□Treatment failure
Bacteriologically confirmed: □ Yes (%) □ No (%)

□ Disease relapse
Bacteriologically confirmed: □ Yes (%) □ No (%)
Follow up duration after completion of treatment:

□Acquired drug resistance
Initial DST done: □ Yes (%) □ No (%)

Secondary Outcomes:

□Death during treatment □Default □Bioavailability
□Compliance □Satisfaction
□Smear/culture conversion after 2 months of treatment □Other:

Outcome results:

Treatment 1: ____ Treated ____ Deaths
_____ serious side effects

____ Denom. F ____ Cured ____ Failed → ____ SENS ____ SDR
____ PDR ____ MDR

____ Denom. R ____ Relapse→____ SENS ____ SDR
____ PDR ____ MDR

Treatment 2: ____ Treated ____ Deaths
_____ serious side effects

____ Denom. F ____ Cured ____ Failed → ____ SENS ____ SDR
____ PDR ____ MDR

____ Denom. R ____ Relapse→____ SENS ____ SDR
____ PDR ____ MDR

Treatment 3: ____ Treated ____ Deaths
_____ Serious side effects

____ Denom. F ____ Cured ____ Failed → ____ SENS ____ SDR
____ PDR ____ MDR

____ Denom. R ____ Relapse→____ SENS ____ SDR
____ PDR ____ MDR

Treatment 4: ____ Treated ____ Deaths
_____ Serious side effects

____ Denom. F ____ Cured ____ Failed → ____ SENS ____ SDR
____ PDR ____ MDR

____ Denom. R ____ Relapse→____ SENS ____ SDR
____ PDR ____ MDR

Treatment 5: ____ Treated ____ Deaths
_____ Serious side effects

____ Denom. F ____ Cured ____ Failed → ____ SENS ____ SDR
____ PDR ____ MDR

____ Denom. R ____ Relapse→____ SENS ____ SDR
____ PDR ____ MDR

Treatment 6: ____ Treated ____ Deaths
_____ Serious side effects

____ Denom. F ____ Cured ____ Failed → ____ SENS ____ SDR
____ PDR ____ MDR

____ Denom. R ____ Relapse→____ SENS ____ SDR
____ PDR ____ MDR

Other outcome results:

Acquired drug resistance:

	Yes	No
FDC		
SDF		

Point estimate: 95% CI:

Adherence:

	Non-compliant	Compliant
FDC		
SDF		

Point estimate: 95% CI:

Smear/culture conversion after 2 months of treatment:

	+ve smear/culture after 2 m.	- ve smear/culture after 2 m.
FDC		
SDF		

Point estimate: 95% CI:

Treatment satisfaction:

	Unfavorable	favorable
FDC		
SDF		

Point estimate: 95% CI:

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