# COMPARING THE EFFECTIVENESS OF FIXED-DOSE COMBINATIONS AND SEPARATE-TABLET REGIMENS ON 2-MONTH PULMONARY TUBERCULOSIS SPUTUM CONVERSION

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## ABSTRACT

Background: Tuberculosis (TB) is one of the leading causes of death amongst other non-communicable diseases, accounting for up to 845 thousand cases in 2020 in Indonesia alone. Currently, the WHO recommends the use of anti-tuberculosis fixed dose combinations (FDCs) for treating lung TB. However, before the existence of FDCs, patients rely on the use of anti-TB separate tablets (STs). Both forms offer excellent effectiveness and could be measured objectively through bacterial smear conversion, but different dosages and compliance in each individual may alter the outcomes they offer.
Methods: 5 online databases (Cochrane Central Registers of Trials, Cochrane Database of Systematic Review, Embase Classics, MEDLINE(R) ALL, and Pubmed) were used in finding potential studies. Studies were appraised using the Oxford Center for Evidence-Based Medicine (CEBM) Tool, specifically in the validity, importance, and applicability of the studies.
Result: 24 articles were acquired from literature search, and 3 randomized controlled trials (RCTs) were reviewed. All studies found statistically insignificant results between FDCs and STs in 2-month sputum smear conversion. The negative percentage of patients with a negative 2-month sputum conversion result using FDCs ranges from 88% - 96% and those using STs ranges from 89% - 96%. Relative risk results for all studies are within the 95% CI range, hence precision of results are more certain.
Conclusion: In conclusion, all studies reported FDCs nor STs to have significant effectiveness difference in 2-month sputum smear conversion rate. Future studies should consider doing individual analysis of these forms of anti-TB treatment on bacterial smear conversion with factors that could influence conversion time.
Keywords: fixed dose combinations, separate tablets, 2-month sputum smear conversion, lung tuberculosis

## ABSTRAK

Latar Belakang: Tuberkulosis (TB) merupakan salah satu penyebab kematian utama di antara penyakit tidak menular lainnya, terhitung hingga 845 ribu kasus pada tahun 2020 di Indonesia saja. Saat ini, WHO merekomendasikan penggunaan kombinasi dosis tetap anti-tuberkulosis (FDC) untuk mengobati TB paru. Namun, sebelum adanya FDC, pasien mengandalkan penggunaan tablet lepas (ST). Kedua bentuk menawarkan efektivitas yang sangat baik dan dapat diukur secara objektif melalui konversi apusan bakteri, tetapi dosis dan kepatuhan yang berbeda pada setiap individu dapat mengubah hasil yang mereka tawarkan.
Metode: 5 database online (Cochrane Central Registers of Trials, Cochrane Database of Systematic Review, Embase Classics, MEDLINE(R) ALL, dan Pubmed) dibedah untuk mencari studi potensial dan dievaluasi kelayakannya melalui Oxford Center for Evidence-Based Medicine (CEBM), khususnya dalam validitas, kepentingan, dan penerapan studi.
Hasil: 24 artikel diperoleh dari pencarian literatur, dan 3 uji coba terkontrol secara acak (RCT) ditinjau dalam makalah ini. Semua penelitian menemukan hasil yang tidak signifikan secara statistik antara FDC dan ST dalam konversi sputum 2-bulan. Persentase negatif pasien dengan hasil konversi sputum negatif 2-bulan menggunakan FDC berkisar antara 88% - 96% dan yang menggunakan ST berkisar antara 89% - 96%. Hasil risiko relatif untuk semua studi berada dalam kisaran 95% CI, sehingga presisi hasil lebih pasti.
Kesimpulan: Secara garis besar, semua penelitian melaporkan hasil tidak signifikan pada FDC atau ST dengan efektivitasnya terhadap tingkat konversi apusan dahak dalam 2 bulan. Penelitian selanjutnya harus mempertimbangkan untuk melakukan analisis individu dari bentuk pengobatan anti-TB ini pada konversi apusan dahak dengan faktor-faktor yang dapat mempengaruhi waktu konversi.
Kata Kunci: kombinasi dosis tetap, tablet lepas, konversi dahak 2-bulan, tuberkulosis paru

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## SECTION 1
## INTRODUCTION

### 1.1 Case Illustration

A patient came to the Pulmonology Polyclinic for a routine check-up of his TB treatment with an additional complaint of cough since 8 months of SMRS. Phlegm comes and goes, is usually present with the cough, white-colored, and no blood has ever been spotted. Patient had lost some weight, but did not remember how much. In the beginning, the patient admitted to experiencing night sweats and felt feverish but never recorded his body temperature. The patient was diagnosed with TB through clinical symptoms and a chest X-ray result. The patient had a history of not routinely taking medications, but is now regularly taking FDC medication and is currently receiving treatment for the 7th month. A month before hospital admission, the patient underwent a sputum smear test, but the results came back negative. Currently, the patient still complains of coughing, but not as frequent, and phlegm is rarely excreted out. Appetite is getting better and the patient notices weight gain (4 kilograms in 7 months). The patient is currently complaining of red-colored urine (since TB treatment) and a tingling sensation on the tip of his right and left feet.

### 1.2 Background

Tuberculosis (TB) is a communicable disease that is passed on through the exposure of droplets from TB-infected people. Its existence is very abundant in tropical countries due to the survival nature of the M. tuberculosis bacteria. Indonesia is the second highest country in the world with TB cases, accumulating over 845 thousand cases in 2020 from the WHO statistical data. The rate of yearly-TB prevalence has faced a downslope trend, not due to the success of the existing prevention and management programs, but because of the COVID-19 pandemic where attention towards health were mostly shifted to COVID-19.[1] Failure in tracing newly diagnosed TB patients has contributed to the increase in the number of undiagnosed TB cases and worsening of TB mortality rate. The latter problem offers a new challenge to the management of tuberculosis patients.

Tuberculosis pharmacological therapy encompasses five drugs, namely Rifampicin (R), Isoniazid (H/INH), Ethambutol (E), Pyrazinamide (Z), and Streptomycin (S), though the treatment guidelines for every country is different and is variable according to the focus of infection, present comorbidities, and drug resistance. For instance, the treatment guidelines in Indonesia for pulmonary TB is 2RHZE/4RH. If a comorbid is present, such as HIV, the treatment would be adjusted as antiretroviral drugs will be given in addition to the regular TB regimens. Patients suspected with multi drug resistant tuberculosis (MDR-TB) would have a or several drug changes, adjusted accordingly to the ineffective drugs.[2,3] In India, the guidelines in treating tuberculosis is also different, with them relying on the use of Isoniazid, Rifampicin, and Ethambutol for the continuation phase.[4] Another discrepancy in the TB treatment is the length of therapy. The length of therapy is also influenced by similar factors that influenced the regimen. Researches from Taiwan have been found to implement and suggest a 9-month TB treatment program as opposed to the regular 6-month therapy program if Diabetes Mellitus Type 2 (DMT2) is present as a comorbid.[5]

With various considerations needing to be taken into account in the management of a TB case, it generates obstacles relating to patient's compliance. One of the factors that plays a huge role in the adherence of TB treatment is the number of pills. Several organizations, one of which is the World Health Organization (WHO), has recommended the use of fixed-dose combinations (FDCs) to treat TB in hopes that it would further enhance the rate of compliance.[6] The ground theory for this suggestion comes from the assumption that if FDCs offer the same beneficial effects and bioavailability of separated tablet (ST)

formulations, their effectiveness has to be of equal amount.[7]

Diagnostic tools for TB comprises of MTB culture, GeneXpert MTB/RIF assay, conventional polymerase chain reaction (PCR), and acid-fast bacilli (AFB) sputum smear microscopy.[8] Sputum smear is an effortless and rapid test method compared to sputum culture, hence it is frequently adopted as the substitute of sputum culture in evaluating treatment effectiveness and infectivity. Sputum acid-fast bacilli (AFB) smear is consistently checked during the TB therapy period and serves as a valuable indicator of treatment response. Sputum clearance is a cardinal index of treatment effectiveness, and failure to attain sputum clearance conversion in 2 months is thought to indicate a worse treatment outcome.[9] Therefore, documenting sputum smear results is highly suggested.

Considering that TB treatment requires adherence, and FDCs and ST regimens are elements that greatly determine non-adherence and effectivity of bacterial clearance which is monitored objectively by sputum smear conversion, it may be necessary to determine which set of TB drug formulations offer the highest efficacy rate in eliminating M. tuberculosis bacteria. This review aims to present a comprehensive review of the effectiveness of FDCs and ST regimens in the conversion of a 2-month follow up sputum smear result following lung TB diagnosis.

### 1.3 Clinical Question

In pulmonary tuberculosis patients, will the use of FDC (fixed-dose combination) increase the 2-month sputum smear conversion rate if compared to separate tuberculosis tablet regimens?

| **Patient/Problem (P)** | **Intervention (I)** | **Comparison (C)** | **Outcome (O)** |
|---|---|---|---|
| Patients with lung tuberculosis | Fixed-dose combination | Separate tablets | 2-month sputum smear conversion |
| **Type of Clinical Question** | Interventions | | |
| **Study Design** | Systematic review of randomized controlled trials<br>Randomized controlled trials | | |

**Table 1.** PICO Framework.

## SECTION II
## METHOD

### 1.4 Searching Strategy

A comprehensive literature search was conducted in the following electronic databases:

- MEDLINE
- Embase Classics
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Review
- Pubmed

The main keywords utilized to be expanded were, “adult”, “lung tuberculosis”, “fixed-dose combinations”, “separate tablets”, and “sputum smear conversion”. After database-oriented literature search was conducted, hand searching for additional relevant literature was done. The specific search strategy is displayed in *Table 2*.

| **Database** | **Search Strategy** | **Temuan** |
|---|---|---|

| | | |
|---|---|---|
| Ovid – 20/06/2022 | | |
| Cochrane Central Register of Controlled Trials<br><br>Cochrane Database of Systematic Review<br><br>Embase Classics<br><br>MEDLINE(R) ALL | Adult* OR elder* OR geriatric* NOT child* OR adolescen*<br>Lung tuberculosis OR lung TB OR lung M tuberculosis infection* OR lung MTBI OR lung TBI OR lung tuberculosis infection* OR lung mycobacterium tuberculosis infection* OR lung TB infection* OR pulmonary tuberculosis OR pulmonary TB OR pulmonary M tuberculosis infection* OR pulmonary MTBI OR pulmonary TBI OR pulmonary tuberculosis infection* OR pulmonary mycobacterium tuberculosis infection* OR pulmonary TB infection*<br>Fixed-dose combination* OR fixed-dose combination tuberculosis OR fixed-dose tuberculosis combination OR fixed-dose TB combination OR fixed-dose drug combination* OR fixed-dose TB drug combination OR FDC* OR FDC TB<br>Separate TB tablet* OR ST* OR Separate tablets tuberculosis OR ST TB OR Separate TB drug* OR Separate tablet* OR Separate drug* OR split tablet* OR split TB tablet* OR split tablets tuberculosis OR split tablets TB OR separate pill* OR separate TB pill* OR separate tuberculosis pill* OR separate drug formulation* OR separate TB drug formulation* OR separate tuberculosis drug formulation* OR loose formulation TB treatment regimen* OR loose TB regimen formulation* OR LF TB regimen* OR LF TB OR LF tuberculosis regimen* Sputum OR sputum culture* OR sputum culture conversion* OR sputum conversion* OR sputum negative* OR sputum smear* OR smear conversion* OR 2-month TB sputum-culture conversion* OR culture conversion* OR 2-month TB culture conversion OR acid-fast bacill* Systematic review/ OR randomized controlled trial/ OR RCT* OR meta analysis/ NOT prospective cohort study/ NOT retrospective cohort study/ NOT case-control study/ NOT case report/ NOT review/ NOT cross-sectional study/ 1 AND 2 AND 3 AND 4 AND 5 AND 6 | 21 |
| Pubmed – 20/06/2022 | (((((Adult* OR elder* OR geriatric* NOT child* NOT adolescen*) AND (Lung tuberculosis OR lung TB OR lung M tuberculosis infection* OR lung MTBI OR lung TBI OR lung tuberculosis infection* OR lung mycobacterium tuberculosis infection* OR lung TB infection* OR pulmonary tuberculosis OR pulmonary TB OR pulmonary M tuberculosis infection* OR pulmonary MTBI OR pulmonary TBI OR pulmonary tuberculosis infection* OR pulmonary mycobacterium tuberculosis infection* OR pulmonary TB infection*)) AND (Fixed-dose combination* OR fixed-dose combination tuberculosis OR fixed-dose tuberculosis combination OR fixed-dose TB combination OR fixed-dose drug combination* OR fixed-dose TB drug combination OR FDC OR FDC TB)) AND (Separate TB tablet* OR ST OR Separate tablets tuberculosis OR ST TB OR Separate TB drug* OR Separate tablet* OR Separate drug* OR split tablet* OR split TB tablet* OR split tablets tuberculosis OR split tablets TB OR separate pill* OR separate TB pill* OR separate tuberculosis pill* OR separate drug formulation* OR separate TB drug formulation* OR separate | 3 |

| | | |
|---|---|---|
| | tuberculosis drug formulation* OR loose formulation TB treatment regimen* OR loose TB regimen formulation* OR LF TB regimen* OR LF TB OR LF tuberculosis regimen*)) AND (Sputum OR sputum culture* OR sputum culture conversion* OR sputum conversion* OR sputum negative* OR sputum smear* OR smear conversion* OR 2-month TB sputum-culture conversion* OR culture conversion* OR 2-month TB culture conversion OR acid-fast bacill*)) AND (Systematic review/ OR randomized controlled trial/ OR RCT OR meta analysis/ NOT prospective cohort study/ NOT retrospective cohort study/ NOT case-control study/ NOT case report/ NOT review/ NOT cross-sectional study/) | |

**Table 2.** Literature Search Strategy.

### 1.5 Eligibility Criteria

*1.1.5. Inclusion criteria*

Inclusion criteria include:

- Male and female participants who were eighteen years old or older,
- Participants complained of any lung tuberculosis signs and symptoms, and later validated by a doctor's diagnosis,
- Participants had taken anti-tuberculosis drugs during the trial period and had never stopped,
- Patients had never been diagnosed with tuberculosis before,
- The study focuses on discussing about the efficacy of anti-tuberculosis drugs, measured objectively by a 2-month sputum smear conversion result
- Study design of randomized controlled trial (RCT) or systematic review with or without meta-analysis

*2.1.5. Exclusion criteria*

Cross-sectional, case report, cohort, conference, and protocol studies were excluded from this review. Articles including participants younger than 18 years old or drugs other than Rifampicin (R), Isoniazid (I), Pyrazinamide (Z), Ethambutol (E), and Streptomycin (S) were excluded. Reports written in languages other than English or without accessibility to a full-text on the Internet were excluded.

### 1.6 Article Selection

Literature search results were imported into Covidence, an online-based review software (Veritas Health Innovation, Melbourne, 2021), for literature screening. Preferable study designs include randomized controlled trials (RCTs) and systematic reviews with or without meta-analysis (SR only or SR-MA). After removal of 8 duplicate articles, titles and abstracts were screened from 16 articles for superficial eligibility. 9 articles went for a full-text screening for the selection of papers that matched the inclusion and exclusion criteria of this review. 7 articles were excluded due to inaccessible full text, wrong outcome or population, and not written in English. Two articles were chosen for data synthesis from the result of literature screening, and one additional article was added through hand searching and after screening being screened for eligibility criteria. A PRISMA flow chart which depicts the complete process of literature selection is included below.

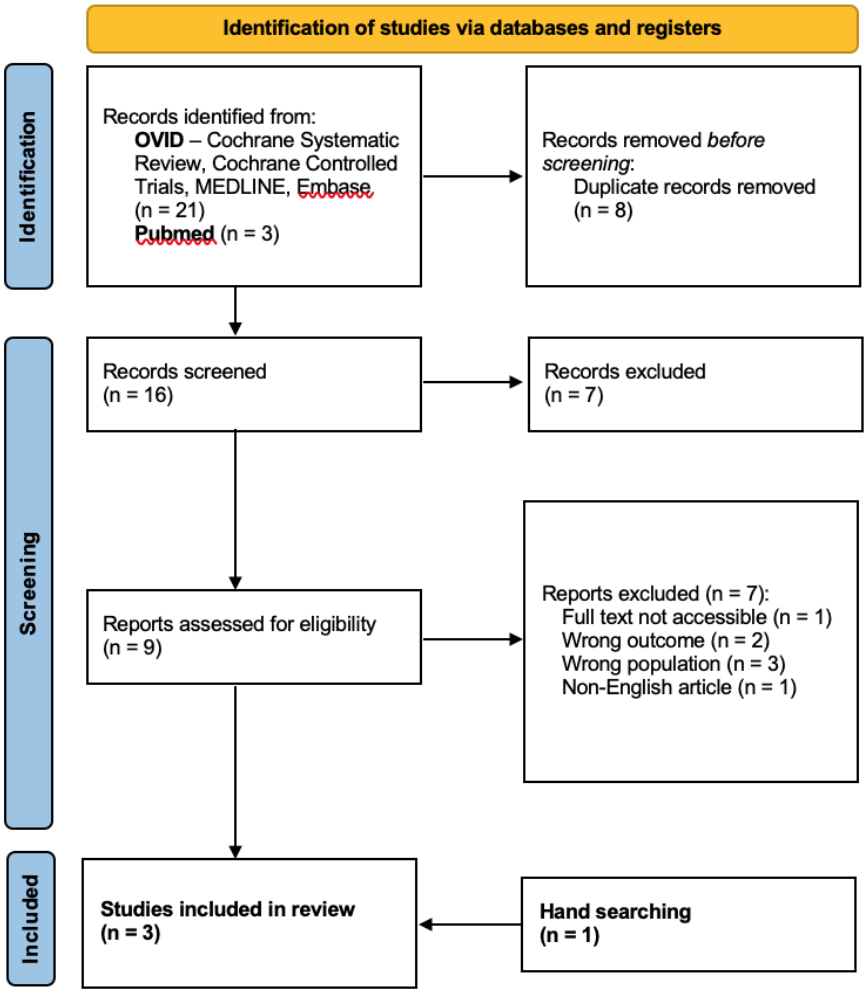


**Figure 1.** PRISMA flowchart.

## SECTION III
## RESULT

### 1.7 Study Characteristics

Final screening yielded three papers to be reviewed, extracted, and described in Table 3. The reported characteristics are arranged based on the study quality, patient demographics (number of subjects and age of enrollment), intervention (name of regimen and dosage), and comparator description (if available), and targeted outcomes. Out of the three papers included, Su et al. and Wu et al. acquired similar eligibility criterias, whereas Gravendeel et al. had less-detailed information about their eligibility criteria.

| Author (Year) | Length of Study | Study Design | Population | Intervention | | Comparison | | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | | Drugs & Dose | Total participants | Drugs & Dose | Total participants | |
| Su et al. (2002)[10] | 18 months | RCT | 108 enrolled, 51 analysed<br><br>≥ 18 years old and confirmed TB diagnosis (smear or culture) | 30-39 kg: 3 Rifater tablets + EMB<br><br>40-49 kg: 4 Rifater tablets + EMB<br><br>≥50 kg: 5 Rifater tablets + EMB<br><br>*Rifater: R 120 mg + H 50 mg + Z 250 mg* | 23/26 | <50 kg: R 450 mg, H 300 mg, Z 1500 mg, E 1200 mg<br><br>≥50 kg: R 600 mg, H 300 mg, Z 1500 mg, E 1200 mg | 24/25 | 1. Adverse reactions<br>2. Smear and culture conversions<br>3. Drug resistance rate<br>4. Rate of relapse<br>5. Patient compliance<br>6. Treatment failure |
| Gravendeel et al. (2003)[11] | 6 months | RCT | 360 enrolled, 358 analysed<br><br>Patients with new smear-positive result and with body weight between 33-50kg | Isoniazid 75 mg<br>Rifampicin 150 mg<br>Pyrazinamide 400 mg<br>Ethambutol 275 mg<br><br>3x/day | 186/198 | Isoniazid 1x300 mg<br>Rifampicin 1x450 mg<br>Pyrazinamide 3x500 mg<br>Ethambutol 3x250 mg | 143/160 | 1. Complaints during intensive phase<br>2. Sputum smear and culture conversion<br>3. Death and treatment failure rates |
| Wu et al. (2015)[12] | 13 months | RCT | 161 enrolled, 98 analysed<br><br>≥ 18 years old and suspected TB diagnosis by a clinician (smear, culture, chest x-ray, and CT) | 30-39 kg: 3 Rifater tablets + EMB<br><br>40-49 kg: 4 Rifater tablets + EMB<br><br>≥50 kg: 5 Rifater tablets + EMB<br><br>*Rifater: R 120 mg + H 80 mg + Z 250 mg* | 47/49 | R: 10 mg/kgBW<br>H: 5 mg/kgBW<br>Z: 15-30 mg/kgBW<br>E: 15-25 mg/kgBW | 47/49 | 1. Smear conversion at 2, 4, and 6 months<br>2. Liver function fluctuation during treatment<br>3. Treatment failure.<br>4. Relapse.<br>5. Adverse events<br>6. Death. |

**Table 3.** Study Characteristics.

## 1.8 Critical Appraisal

Critical appraisal was carried out using the guidelines from the Center of Evidence Based Medicine (CEBM) Oxford University. Every appraised article was reviewed by assessing the validity, importance, and applicability aspects.

| Components | Questions | Study | | |
|---|---|---|---|---|
| | | Su et al. (2002)[10] | Gravendeel et al. (2003)[11] | Wu et al. (2015)[12] |
| Validity | Was the assignment of patients to treatments randomised? | Yes | Yes | Yes |
| | Were the groups similar at the start of the trial? | Yes | **Unclear** | Yes |
| | Aside from the allocated treatment, were groups treated equally? | Yes | Yes | Yes |
| | Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised? | **No** | Yes | Yes |
| | Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received? | **Unclear** | Yes | **No** |
| Importance | How large was the treatment effect? | % FDC: 88%<br>% ST: 96%<br><br>RR: 0.92<br>RRR: 0.08<br>NNT: 12.5 | % FDC: 94%<br>% ST: 89%<br><br>RR: 1.05<br>RRR: 0.30<br>NNT: 3.3 | % FDC: 96%<br>% ST: 96%<br><br>RR: 1.00<br>RRR: 0<br>NNT: - |
| | How precise was the estimate of the treatment effect? | 95% CI: [0.79,1.08]<br><br>P > 0.05 | 95% CI: [0.22, 1.88]<br><br>P = 0.23 | 95% CI: [0.92,1.09]<br><br>P > 0.05 |
| Applicability | Will the results help me in caring for my patient? | Yes | Yes | Yes |
| Level of Evidence | | **2** | **2** | **2** |

*% = percentage of negative sputum smear result within the group*

**Table 4.** Critical Appraisal of Included Studies

### 1.8.1 *Validity*

In accordance with the Oxford Level of Evidence appraisal tool, three parameters are evaluated. No studies fulfilled all the parameters for validity, suggesting potential risk of bias in the results and probability of inconsistency with the real variations of the general population's characteristics. Upon further inspection, the study by Su et al. and Wu et al. conducted their research under an unclear or unblinded circumstance, where and there was no clarity whether the allocation of FDCs and STs were done without prior knowledge of the examiners and patients.[10,12] Blinding refers to disguising the treatment allocation from participants, including investigators, to avoid influencing the trial's outcomes, and is especially important for interventional research as it could help prevent outcome contamination (i.e. where participants seek additional therapy from outside to enhance their outcomes).[13] Therefore, absence of that means the representation of unbiased patient outcome is unmet. In addition to blinding, Su et al. found an obscurity in the rate of participants loss to follow up, where more than 50% participants were gone by the end of the trial.[12] Gravendeel et al. provided unclear participant inclusion criteria descriptions, hence only one sub-parameter is unmet and validity is still met for their research.[11]

### 1.8.2 *Importance*

Gravendeel et al. is the only study to provide a 2x2 table to enable calculations of relevant parameters needed to evaluate intervention effect measures. However, despite not providing any relevant tables, outcomes from Su et al. and Wu et al. were reported and able to be calculated as well. Study by Gravendeel et al. reported 94% participants with a 2-month negative sputum smear conversion result from the FDC group, whereas a negative result was acquired by 89% of the participants from the ST group.[11] Study by Su et al. generated a contradictory percentage, where ST group had a 96% negative sputum smear conversion in 2 months and FDC group produced a 88% conversion rate, but the number of participants in the ST group is smaller than the FDC group, although not by a huge difference.[10] Wu et al. generated a unique result, where both groups had the same amount of participants, and the same negative-to-positive 2-month smear conversion results. Regardless of the three different results, all studies generated a p-value of more than 0.05, thus making the results insignificant.

### 1.8.3 *Applicability*

All studies fulfill this review's eligibility criteria, except for Gravendeel et al. and its vagueness in their participants' age. The treatment of tuberculosis has been integrated into the primary health care system of Indonesia and all studies included similar intensive-phase tuberculosis treatment regimens which increases the applicability of outcomes in countries with tuberculosis disease problems. Future replication of study is guaranteed for all studies except the study by Gravendeel et al., due to the ambiguity surrounding its eligibility criteria. One important value in the study by Gravendeel et al. is its location, where their research was conducted in Indonesia, thus their results might be more reflective and applicable to the author's place of living.

## SECTION IV
## DISCUSSION

FDCs have been suggested as a routine anti-TB therapy regimen due to its non complex property; administration becomes easier and limits the emergence of drug resistance.[14] Unfortunately, the composition and dosage instructions for FDCs are distinctive from those for STs, thus creating a major concern amongst clinicians.[15,16] Therefore, this case report aims to assess the impact of FDCs and STs negative sputum smear proportion rate. This report included 3 RCTs with a total of 629 participants, and generally did not find any significant difference in the 2-month smear conversion rate between fixed-

dose combinations (FDC) and separate-tablet (ST) formulations in treating pulmonary tuberculosis (P > 0.05). However, considerations have to be made as each study generated a different leading group in having a negative sputum smear conversion result.

The study by Wu et al. is considered to be of high quality evidence, as it fulfills every criteria of validity, importance, and applicability, except for blinding. However, the outcomes were unlikely to be influenced by a lack of blinding as only objective and measurable outcomes were reported. Their results showed the same number of participants (47/49) tested negative on their sputum smear result after 2-months of routine tuberculosis drugs consumption, hence their relative risk equals one, implying whether the exposure took place or not it would not make a difference to the occurrence.[12,17] In their analysis, it was discovered that when anti-TB treatment was monitored using the directly observed treatment short-course strategy (DOTS), the incidence rates of side effects and sputum conversion proportion rate were not substantially different between the FDC and the ST formulations. During therapy in the per-protocol group, only the occurrence of transient hyperbilirubinemia differed substantially between patients treated with the FDCs and those treated with the ST formulations.[12]

Evidence from Gravendeel et al. reported no statistically significant difference in sputum conversion between the two regimens (P = 0.23). The relative risk is 0.70, meaning that lung TB patients given the FDCs are .70 times as likely as lung TB patients given the ST formulations to have a negative sputum smear results in 2 month after the start of treatment.[11] This was consistent with findings from studies by Bellabas et al. and Zhu et al., where despite statistically insignificant findings, FDCs gave rise to a higher percentage of patients with a negative sputum smear result after two months of treatment as opposed to those in the STs group.[18,19] One explanation to the lower percentage of the STs group might be attributed by lack of adherence to consuming more than two drugs. A study investigated several key factors into non-adherence in anti-TB drugs, such as a family history of tuberculosis treatment, younger age, healthcare access difficulties (e.g. cost, distance, etc.), treatment experiences (e.g. ST drugs vs FDCs), and knowledge about TB (consequences of incomplete TB treatment, transmission of TB pathogens, and causes of TB).[20] This vouches for the result from Gravendeel et al. and may explain why the FDCs group might take a farther lead than the STs group.

Another study by Su et al. is slightly less convincing upon critical appraisal, mainly due to the study's high loss of participants to follow-up and unspecified blinding method. Overall, the statistical finding from this study is consistent with the other two studies (P > 0.05), but it was reported that the STs group had higher negative sputum smear results as opposed to the FDCs group. This is not the first to report such a result, as studies by Munteau et al. and Bartacek et al. had reported statistical results favoring single drug formulations as opposed to the fixed dose combinations.[21,22] These results may indicate higher patient compliance rate in the ST groups as ST formulations have been proven to show excellent effectiveness if patients have good adherence.[23]

Historically, the use of FDCs have raised several concerns in middle- and lower-income countries, such as South Africa, Indonesia, and India. FDCs have been suggested to elevate drug-drug interactions or adverse drug reactions, increased toxicity and reduced effectiveness if inappropriately manufactured, a higher loss of treatment effectiveness if patients forget to take their FDC compared to just one of the individual components, and arise difficulty in titrating individual doses according to the specific needs of each patient.[24] Therefore, doors are

open for clinicians to determine which set of therapy is best for their patients. In fact, several systematic reviews and meta analysis have reported no statistically significant differences between the use of FDCs and ST groups, which aligns with the evidence from the three studies included in this review. Systematic reviews by Gallardo et al. and Lima et al. suggested that four-medicine FDCs did not improve bacterial conversion rates after 2 and 6 months of treatment when compared to the separate medicines.[23,25] Having said this, five FDCs for the treatment of TB are currently endorsed by the WHO in its Essential Medicine List (EML).[26]

Insignificant results in the bacterial conversion rates might be generated due to several factors. In a study, bacillary load, erythrocyte sedimentation rate, hemoglobin levels post treatment, and duration of symptoms at the time of diagnosis played a huge role in the conversion rate of their patients. Probability of remaining sputum positive is enhanced if patients have longer duration of symptoms at the time of diagnosis, no improvement in post-treatment hemoglobin levels, high baseline erythrocyte sedimentation rate, and high bacillary load.[27] Gender, specifically females, was considered to be a factor in their study, but another study found males to be more at risk.[27,28] These factors were not individually reported nor assessed by included studies, thus unclarity arises as to which factors played a role in the insignificance of the results.

Overall, fixed dose combinations offer simplified therapy regimens, which may be essential in some patients. Several studies have also suggested the combination of FDCs and directly observed treatment short-course strategy (DOTS) in chosen patients to aid in managing potential pharmacological adverse effects and detecting early non-adherence.[29] However, directly observed treatment short-course strategy (DOTS) is less likely to be available in most lower-to-middle income countries. Opening new treatment facilities and community outreach centers in remote regions where access is an issue are among the strategies to further increase adherence rates.[30] This expands on initiatives to give free, standardized anti-TB FDC regimens to all TB-diagnosed patients while being closely monitored, along with additional initiatives like patient support, in order to enhance patient outcomes.[31,32]

Strengths and Limitations

This EBCR has several strengths. First, all studies included in this report are randomized controlled trials, which are highly suitable for interventional studies. Moreover, every study included in this report applied randomization and allocation. Second, since FDCs have been endorsed by the WHO, they are accessible to any population and are cost-effective, hence results from this report are relevant and useful for our patients in Indonesia. Nonetheless, limitations are noted from this report. All studies included have flaws in validity, thus it may jeopardize the generalizability of the results to our patients. Furthermore, different doses are used between each study, leading to reduced comparability of methodology between the three studies. Lastly, no studies assessed FDCs and STs effectiveness with or without the factors that may influence bacterial conversion rate and indirectly cause insignificant results.

## SECTION V
## CONCLUSION

### 1.9 Conclusion

In conclusion, the included studies suggest that FDCs or STs do not produce significant effects on 2-month sputum smear conversion rate. The treatment effectiveness of FDCs were shown to be just as efficacious as ST regimens. Furthermore, FDCs and STs have their own benefits and potential harms, but FDCs are now the suggested standard set of therapy by the WHO. Therefore, this should

make FDCs highly appealing and become the regimen of choice to clinicians in Indonesia.

### 1.10 Recommendation

Future researchers should compare the effect of STs and FDCs in bacterial conversion rates, with individual assessment of factors that could potentially influence the conversion time, namely bacillary load, baseline ESR, duration of symptoms at the time of diagnosis, and other relevant factors. Another aim is to review the impact of combining FDCs and DOTS on treatment relapse, sputum smear and culture conversion at several months, adverse effects, and patient satisfaction. This may offer better treatment results for TB patients residing anywhere in the world. Patients with comorbidities, such as diabetes mellitus type 2 and HIV, should also be included in the studies with separate analysis and tables to enhance views on whether these may affect the compliance and efficacy of the offered drug.

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