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COMPARISON OF MIDDLEBROOK 7H9 CULTURE AND XPERT MTB/XDR FOR DETECTING ISONIAZID AND FLUOROQUINOLONE RESISTANCE

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ABSTRAK

Abstract:
Drug-resistant tuberculosis (DR-TB) remains a major public health challenge in Indonesia, necessitating rapid and accurate detection of resistance to key anti-tuberculosis drugs. This quantitative descriptive analytic cross-sectional study evaluated the concordance of *Mycobacterium tuberculosis* resistance detection between phenotypic Middlebrook 7H9 liquid culture and genotypic TCM XDR in 44 DR-TB patients, focusing on isoniazid (H) and fluoroquinolone/levofloxacin (FQ/Lfx) resistance. Data were analyzed using the McNemar test methode. High-concentration H resistance was detected in 68.2% by culture and 65.9% by TCM XDR, while FQ/Lfx resistance was identified in 18.2% and 15.9%, respectively. No significant differences were observed between methods for high-concentration H and FQ/Lfx resistance detection (P=1.000), indicating high concordance with cappa values 0,74 isoniazid for and 0,86 for FQ/Lfx resistance. In contrast, a significant discrepancy was found for low-concentration H resistance (P=0.001), with a discordance rate of 25%, potentially attributable to HA promoter mutations not included in the TCM XDR panel or non-genetic adaptive mechanisms.

***Abstrak*:**
Tuberkulosis Resisten Obat (TBC RO) merupakan masalah kesehatan masyarakat serius di Indonesia sehingga diperlukan metode diagnosis resistensi obat yang cepat dan akurat, khususnya terhadap isoniazid (H) dan fluoroquinolone (FQ), untuk menunjang penatalaksanaan yang efektif. Penelitian kuantitatif deskriptif analitik dengan desain potong lintang ini bertujuan menganalisis kesesuaian hasil deteksi resistensi Mycobacterium tuberculosis menggunakan metode fenotipik Kultur Media Cair Middlebrook 7H9 dan metode genotipik TCM XDR pada 44 pasien TBC RO. Analisis data dilakukan dengan Uji McNemar. Hasil menunjukkan resistensi H konsentrasi tinggi sebesar 68,2% pada kultur dan 65,9% pada TCM XDR, serta resistensi FQ/Lfx masing-masing 18,2% dan 15,9%. Tidak terdapat perbedaan bermakna antara kedua metode dalam mendeteksi resistensi H konsentrasi tinggi dan FQ/Lfx (P=1,000), yang menandakan kesesuaian tinggi dengan nilai Cappa 0,74 untuk resistensi isoniazid dan 0.86 untuk resistensi FQ/Lfx. Namun, ditemukan perbedaan bermakna pada deteksi resistensi H konsentrasi rendah (P=0,001) dengan ketidaksesuaian 25%.

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INTRODUCTION

Drug-resistant tuberculosis (DR-TB) remains a major challenge to tuberculosis (TB) control, particularly in high-burden countries such as Indonesia.[1] Accurate and timely detection of drug resistance is essential to guide appropriate treatment and prevent further transmission of resistant *Mycobacterium tuberculosis* strains[2] Effective management of DR-TB relies heavily on the rapid and accurate detection of resistance to first- and second-line anti-tuberculosis drugs. Resistance to isoniazid (H) and fluoroquinolones (FQ), particularly levofloxacin, is of critical concern because these drugs form the backbone of both drug-susceptible and drug-resistant TB treatment regimens. Delayed or inaccurate identification of drug resistance can lead to inappropriate therapy, prolonged infectiousness, poor treatment outcomes, and further transmission of resistant strains[3].

Phenotypic drug susceptibility testing (DST) using culture-based methods remains an important reference method for determining drug resistance [4]. Liquid culture systems, including Middlebrook 7H9-based methods, can assess bacterial growth in the presence of anti-tuberculosis drugs and provide phenotypic evidence of resistance. However, culture-based DST requires considerable time, technical expertise, and laboratory resources, which may delay treatment decision.[5]

Rapid molecular testing, such as the Xpert MTB/XDR assay, enables detection of genetic mutations associated with resistance to isoniazid (H) and fluoroquinolones (FQ), allowing earlier identification of resistance and supporting timely treatment decisions [6][7][8]

Nevertheless, molecular and phenotypic DST may produce discordant results, particularly in cases of low-level isoniazid resistance. Such discordance may be related to mutations outside the targets detected by the assay or to differences in the biological and methodological principles of molecular and phenotypic testing [9][10][11].

Comparing Xpert MTB/XDR with culture-based DST is therefore important to determine the level of agreement between the two methods and to clarify their complementary roles in detecting drug resistance. This study aims to evaluate the agreement between phenotypic culture/ DST and Xpert MTB/XDR for the detection of isoniazid and fluoroquinolone resistance, thereby providing evidence for their appropriate integration in the diagnostic management of DR-TB in high-burden settings such as Indonesia[12].

RESEARCH METHOD

This study employed a quantitative descriptive analytic approach with a cross-sectional design to evaluate the concordance of drug resistance detection results in *Mycobacterium tuberculosis*. The research was conducted at a tuberculosis referral laboratory that routinely performs both phenotypic and genotypic drug susceptibility testing for drug-resistant tuberculosis (DR-TB). The study period covered routine diagnostic examinations performed within the defined timeframe of data collection. Located in RS Paru H.A. Rotinsulu periode 2024 with sputum sample from TBC suspected patient and has an ethical approved from KEPK Poltekkes Kemenkes Bandung.

The study population consisted of confirmed DR-TB patients whose clinical specimens met the inclusion criteria. A total of 44 samples were included using a total sampling technique. Inclusion criteria were specimens from patients diagnosed with DR-TB that underwent both phenotypic drug susceptibility testing using liquid culture and genotypic testing using the TCM XDR assay. Samples with incomplete test results or contaminated cultures were excluded from the analysis.

Phenotypic drug susceptibility testing was performed using liquid culture media based on Middlebrook 7H9. The method was used to assess resistance to isoniazid at both low and high concentrations, as well as resistance to fluoroquinolones,

specifically levofloxacin. Culture results were interpreted according to established laboratory standard operating procedures, with resistance determined based on growth comparison between drug-containing and control media.

Genotypic testing was conducted using the TCM XDR assay, a rapid molecular diagnostic method designed to detect genetic mutations associated with resistance to first- and second-line anti-tuberculosis drugs. The assay was performed according to the manufacturer's instructions, and results were interpreted based on the detection of specific resistance-associated genetic targets. No modifications were made to the standard testing protocol.

Data obtained from both testing methods were recorded and categorized according to resistance profiles for isoniazid and fluoroquinolones. The concordance between phenotypic and genotypic results was evaluated by comparing paired outcomes from the same samples.

Statistical analysis was performed using the McNemar test to assess differences in resistance detection between the two methods. A p-value of less than 0.05 was considered statistically significant. The analysis focused on determining the level of agreement and identifying potential discrepancies between phenotypic and genotypic drug resistance detection methods.

RESULT AND ANALYSIS

This section contains the results of the study and its discussion. All figures and tables are numbered sequentially which refers to the text. The discussion can be given in several sections;

1. Respondent Characteristics

The respondent characteristics of study samples are presented in Table 1.

Table 1.
Respondent Characteristic

Characteristics	n	%
Gender		
Men	22	50%
Woman	22	50%
Age		
18-30 Years Old	14	31,8
31-45 Years Old	15	34,1
46-60 Years Old	9	20,5
>60 Years Old	6	13,6
Total	**44**	**100**

Based on the table above, the largest proportion of patients undergoing treatment for drug-resistant tuberculosis (DR-TB) was in the 31–45-year age group (34.1%), followed by those aged 18–30 years (31.8%), 46–60 years (20.5%), and over 60 years (13.6%). Regarding sex distribution, the study population was evenly divided, with males and females each accounting for 50% of DR-TB cases. This finding indicates a balanced gender distribution among DR-TB patients in the study population, suggesting that drug-resistant tuberculosis affects both sexes at a comparable rate in this cohort.

2. Mc Nemar Statistic Results H^+

The Mc Nemar statistic result H^+ are presented in Table 2.

Table 2.
McNemar H^+ Results

	Culture H^+	
TCM H^+	**Sensitive**	**Resistent**
Sensitive	14	1
Resistent	0	29

Among the study participants, 14 patients showed isoniazid (H)–susceptible results by both Middlebrook 7H9 liquid culture and TCM XDR testing. One patient demonstrated isoniazid resistance by Middlebrook 7H9 liquid culture but susceptibility by TCM XDR. No patients were found to be susceptible to isoniazid by Middlebrook 7H9 liquid culture while

being resistant according to TCM XDR. Additionally, 29 patients were identified as isoniazid-resistant by both Middlebrook 7H9 liquid culture and TCM XDR. In this result has a Cappa Value's 0,74 thats mean has a substansial agreement.

3. Mc Nemar Statistic Results H*Low*

The Mc Nemar statistic result HLow are presented in Table 3.

Table 3.
McNemar H *Low* Results

	Culture H^+	
TCM H*Low*	**Sensitive**	**Resistent**
Sensitive	0	11
Resistent	0	33

No patients demonstrated low-concentration isoniazid (H low) susceptibility by both Middlebrook 7H9 liquid culture and TCM XDR. Eleven patients were identified as resistant to low-concentration isoniazid by Middlebrook 7H9 liquid culture but susceptible according to TCM XDR. There were no patients who showed susceptibility to low-concentration isoniazid by Middlebrook 7H9 liquid culture while being resistant by TCM XDR. In addition, 33 patients were classified as resistant to low-concentration isoniazid by both Middlebrook 7H9 liquid culture and TCM XDR. In this result has a Cappa Value's 0,86 thats mean has a substansial agreement.

4. Mc Nemar Statistic Results FQ and Lfx

The Mc Nemar statistic result FQ and Lf are presented in Table 4.

Table 4.
McNemar FQ and LFx Results

	Culture LFx	
TCM FQ	**Sensitive**	**Resistent**
Sensitive	36	1
Resistent	0	7

Among the study participants, 36 patients were identified as susceptible to levofloxacin (Lfx) by Middlebrook 7H9 liquid culture and were also classified as fluoroquinolone (FQ) susceptible by TCM XDR. One patient showed levofloxacin resistance by Middlebrook 7H9 liquid culture but was categorized as fluoroquinolone susceptible by TCM XDR. No patients demonstrated levofloxacin susceptibility by Middlebrook 7H9 liquid culture while being classified as fluoroquinolone resistant by TCM XDR. Additionally, seven patients were identified as resistant to levofloxacin by Middlebrook 7H9 liquid culture and resistant to fluoroquinolones by TCM XDR.

5. Mc Nemar Statistic Results FQ*Low* and MFx

The Mc Nemar statistic result FQLow and MFx are presented in Table 5

Table 5.
McNemar FQ*Low* and MFx Results

	Culture LFx	
TCM FQ	**Sensitive**	**Resistent**
Sensitive	36	0
Resistent	0	8

Among the study participants, 36 patients were found to be susceptible to low-concentration moxifloxacin (Mfx low) by Middlebrook 7H9 liquid culture and were also classified as susceptible to low-concentration fluoroquinolones (FQ low) by TCM XDR. No patients demonstrated resistance to low-concentration moxifloxacin by Middlebrook 7H9 liquid culture while being classified as susceptible by TCM XDR. Likewise, no patients showed susceptibility to low-concentration moxifloxacin by Middlebrook 7H9 liquid culture but resistance according to TCM XDR. In addition, eight patients were identified as resistant to low-concentration moxifloxacin by Middlebrook 7H9 liquid culture and resistant to low-concentration fluoroquinolones by TCM XDR.

6. Mc Nemar Statistic Culture and TCM Results

The Mc Nemar statistic Culture and TCM are presented in Table 6.

Table 6.
McNemar Results

	TCM H$^+$ Kultur H$^+$	TCM H*Low* & Kultur H*Low*	TCM FQ & Kultur Lfx	TCM FQLow & Kultur Mfx*Low*
N	44	44	44	44
Exact Sig. (2-tailed)	1.000[b]	0,001[b]	1.000[b]	1.000[b]

For isoniazid (H) resistance, the significance value (P = 1.000 > 0.05) indicates that there was no statistically significant difference between the Middlebrook 7H9 liquid culture method and TCM XDR in detecting isoniazid resistance among patients with drug-resistant tuberculosis (DR-TB). In contrast, for low-concentration isoniazid (H low), a significant difference was observed between the two methods (P = 0.001 < 0.05), demonstrating discordant detection of low-level isoniazid resistance. Regarding fluoroquinolone (FQ) and levofloxacin (Lfx) resistance, no significant difference was identified between Middlebrook 7H9 liquid culture and TCM XDR (P = 1.000 > 0.05). Similarly, no statistically significant difference was found in the detection of low-concentration fluoroquinolone (FQ low) and moxifloxacin (Mfx low) resistance between the two methods (P = 1.000 > 0.05).

DISCUSSION

The findings of this study highlight the continuing challenge of drug-resistant tuberculosis (DR-TB) in Indonesia, particularly given the substantial burden of drug-resistant disease in high-burden settings. Environmental and community factors, including population density, inadequate ventilation, population mobility, and poor sanitation, may contribute to TB transmission and the persistence of drug-resistant strains [13] [14]. The proportion of isoniazid and fluoroquinolone resistance observed in this study is also consistent with the continuing global and national concern regarding resistance to key anti-tuberculosis drugs[15].

In this study, no significant difference between phenotypic Middlebrook 7H9 liquid culture and Xpert MTB/XDR was observed in the detection of high-concentration isoniazid resistance and fluoroquinolone resistance based on the McNemar test. This finding indicates that the two methods produced comparable classifications of resistance within the study population. The result is consistent with previous studies reporting the potential utility of rapid molecular assays for detecting clinically relevant drug resistance [16][17]. However, the absence of a statistically significant difference should not be interpreted as complete equivalence or diagnostic accuracy of the two methods, particularly because agreement between methods may be influenced by the characteristics and size of the study population.

Recent evidence highlights significant challenges in drug susceptibility testing (DST) for Tuberculosis, particularly in regions with a high prevalence of fluoroquinolone resistance[18]. A study by Francesco Saluzzo et al. (2024) demonstrated that increasing resistance to key components of newer treatment regimens, such as BPaLM, poses a substantial threat to treatment efficacy and TB control programs. In this context, the implementation of rapid and accurate diagnostic approaches becomes essential. Molecular-based methods have been shown to provide faster detection of drug resistance compared to conventional phenotypic techniques, thereby facilitating timely clinical decision-making and improving patient management [19].

Furthermore, the study emphasized that reliance solely on standard treatment protocols without comprehensive DST confirmation may lead to inappropriate therapy, particularly in high-resistance settings[19]. This is particularly relevant in settings with increasing fluoroquinolone

resistance, where delayed identification of resistance may affect the selection of appropriate treatment regimens. However, phenotypic DST remains valuable because it assesses the functional response of *Mycobacterium tuberculosis* to anti-tuberculosis drugs and can provide additional information when molecular and phenotypic results do not agree [20][22].

The most notable discordance in this study was observed for low-concentration isoniazid resistance, where phenotypic testing identified resistant isolates that were not detected by Xpert MTB/XDR. This finding should be interpreted cautiously. Xpert MTB/XDR includes detection of the *inhA* promoter and other established genetic targets associated with isoniazid resistance. Therefore, the discordance cannot simply be attributed to the absence of *inhA* promoter detection. Possible explanations include resistance-associated mutations located outside the targets covered by the assay, technical factors affecting either testing method, heteroresistance within the bacterial population, or differences between molecular detection of specific resistance-associated mutations and phenotypic assessment of drug susceptibility [23] [24] [25]. Because this study did not include sequencing or another independent reference method, the underlying cause of the discordant results could not be definitively determined.

Differences in the biological principles of the two methods may also contribute to discordant findings. Molecular assays detect predefined genetic markers associated with resistance, whereas phenotypic DST determines whether the organism demonstrates growth in the presence of a particular drug concentration. Consequently, a phenotypic result may not always correspond directly to the detection of a known resistance-associated mutation. However, the present study cannot establish that phenotypic testing is more sensitive for low-concentration isoniazid resistance because sensitivity and specificity were not assessed against an independent reference standard [26][27]

Overall, the findings support the use of Xpert MTB/XDR as a rapid tool for detecting resistance and supporting early treatment decisions, while recognizing that molecular and phenotypic methods may produce discordant results. Culture-based DST remains useful for investigating discordant or unclear results and for providing complementary phenotypic evidence of drug susceptibility [28]

Therefore, the two methods should be considered complementary rather than interchangeable. Further studies using larger sample sizes and independent reference methods, including targeted sequencing, are needed to better characterize the causes and clinical significance of discordant results, particularly for low-concentration isoniazid resistance[29][30].

CONCLUSION

In this study involving 44 patients with drug-resistant tuberculosis, no statistically significant differences were observed between Middlebrook 7H9 liquid culture and TCM XDR in the detection of high-concentration isoniazid and fluoroquinolone/levofloxacin resistance. However, discordant results were identified for low-concentration isoniazid resistance. These findings indicate that TCM XDR may provide a rapid approach for detecting key drug resistance patterns, whereas phenotypic culture-based DST remains valuable for evaluating discordant or complex results. Further studies with larger sample sizes and comprehensive measures of agreement and diagnostic accuracy are warranted to better characterize the complementary roles of these methods.

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