

Anti-Tuberculosis Drug Resistance Patterns in Patients with Pulmonary Tuberculosis

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Abstract

Background: In 2022, Indonesia reported a pulmonary tuberculosis (PTB) incidence rate of 354 per 100,000 population, with an estimated 24,666 cases of drug-resistant pulmonary tuberculosis (DR-TB). Nationally, DR-TB case detection coverage reached 50.8%, with 12,531 patients notified—an increase of 17% from the previous year.

Method: This study aimed to examine patterns of Anti-Tuberculosis Drug (ATD) resistance by analyzing internal host-related risk factors using an analytical observational study with a case-control design. The dependent variable was ATD resistance status (resistant and non-resistant). Independent variables included treatment history (new case or previously treated), treatment adherence (adherent or non-adherent), laboratory monitoring (regular or irregular), comorbidities (presence or absence of other diseases), and type of healthcare service unit. Treatment history, laboratory monitoring, and comorbidities were obtained from medical records using checklist forms, while treatment adherence and access to healthcare services were assessed through structured interviews using questionnaires. Data analysis was conducted using chi-square tests and multiple logistic regression.

Result: The chi-square tests revealed significant associations for treatment history ($p = 0.00$, $OR = 71.5$), adherence ($p = 0.00$, $OR = 7.7$), and laboratory monitoring ($p = 0.00$, $OR = 12.0$). No significant associations were found for comorbidities ($p = 0.655$) or service units ($p = 0.171$). Logistic regression identified treatment history as the primary risk factor for DR-TB (adjusted $OR = 47.762$), followed by laboratory monitoring (adjusted $OR = 5.326$).

Conclusion: The resulting regression model indicated a predictive probability of 94.9%, suggesting that treatment history and laboratory monitoring are the key factors contributing to ATD resistance among PTB patients.

Keywords: Comorbidities, Compliance, Laboratory, TB services, Treatment.

INTRODUCTION

Tuberculosis is becoming increasingly widespread. Global surveillance results show that rifampicin and isoniazid-resistant pulmonary tuberculosis or multidrug-resistant tuberculosis (MDR-TB) is found in all countries, including Indonesia.¹ Drug resistance in TB treatment, especially MDR and extensive drug-resistance (XDR), is a major public health problem in numerous countries and serves as an obstacle to the effectiveness of control programs. In addition, the cost of MDR-TB treatment is estimated to be US\$300,000 per patient, much higher than that of regular TB treatment, which is only around US\$300. MDR-TB treatment takes between 18 and 24 months, including eight months of daily injections. In Indonesia, access to resistant TB treatment is inadequate, because some of the necessary drugs are not available.²

MDR-TB is a man-made phenomenon resulting from inadequate TB treatment. First, it results from healthcare providers using inappropriate alloys, not following available alloys, lacking alloys, and lacking appropriate training; additionally, insufficient monitoring of treatment programs and insufficient funding of TB prevention programs play a role. The second problem is drugs: inadequate drug supply or quality, interrupted drug supply, unsafe storage conditions, and/or incorrect drug combinations or under-dosing. Finally, patients contribute to the development of MDR-TB through poor compliance, lack of information, lack of funds, transportation problems, side effect problems, social problems, malabsorption, and dependence on certain substances.³

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The estimated prevalence of all types of TB in Lampung Province is 160 per 100,000 population per year. There were 3,487 new AFB-positive TB cases up to the third trimester in 2022, while MDR-TB was estimated at 140 new cases, and new treatment failure cases reached 159.⁴ The estimated incidence of TB in Bandar Lampung City is 127 per 100,000 population per year. In 2022, there were 956 new AFB+ TB cases, with an estimated 39 new MDR-TB cases. There were also 1,206 pulmonary TB cases, 18 relapses, and 37 dropouts, resulting in an estimated 58 new MDR-TB cases. Meanwhile, 73 MDR-TB cases were recorded at the Health Laboratory Center prior to 2023, and Bandar Lampung City had the highest TB incidence in Lampung Province.⁵

Based on the above phenomena, this study was conducted to analyze patterns of DR-TB occurrence based on internal risk factors such as treatment history, compliance history, laboratory monitoring history, history of comorbidities, and history of treatment service units, to enable efforts to be made immediately to prevent DR-TB.

METHOD

Participants and Study Design

This study used observational analytics with a case-control design, where the research paradigm is carried out from effect to cause. The research began with a group of sufferers as cases and a group of non-sufferers as controls; then, the two groups were traced back (retrospectively) based on time sequence to identify differences in exposure, using factors suspected of causing the onset of DR-TB. The differences in the experiences of the two groups were then compared to elucidate any cause-and-effect relationships. Treatment history was defined based on medical records, and patients were divided into two groups: those who had previously received TB treatment for more than one month (repetition) and those who were new cases.⁶ Treatment adherence was classified as non-compliant if the patient missed medication for two or more consecutive weeks and compliant if treatment was taken as prescribed. Laboratory monitoring was considered complete if sputum examinations or drug susceptibility tests were conducted according to national guidelines. Comorbidities were identified from recorded diagnoses, and healthcare service units were categorized based on referral status from primary healthcare facilities. The dependent variable (ATD resistance) was obtained from secondary data through a review of medical records and laboratory reports from primary healthcare centers and the Provincial Health Laboratory of Lampung. Primary data for independent variables, including treatment adherence and healthcare access, were collected through patient interviews using structured questionnaires. Secondary data for independent variables, including treatment history, laboratory monitoring, and comorbidities, were obtained from medical records and healthcare unit reports.

Measurements and Procedures

Data collection techniques used questionnaires administered by direct interview with respondents and observation of the results of TB treatment card documentation (TB 01, TB 02, TB 03, and TB 05 cards) with checklists. Data for the dependent variable was collected through observation of the documentation of the M.Tb sensitivity test to ATD at Health Laboratory Center of Lampung Province.

Statistical Analysis

Univariate analysis was presented in the form of a frequency distribution table based on the calculation of percentage (%). Bivariate analysis used statistical analysis of chi-square tests using 95% confidence level (CI). Multivariate analysis used multiple logistic regression analysis with a predictive factor model at the 95% confidence level (CI).

RESULT

Table 1 indicates that in the variable treatment history of pulmonary TB patients, most experienced repetition of treatment (55.3%). The variable compliance history of pulmonary TB patients shows that 67.0% followed the rules during the treatment process. Most laboratory monitoring history results were complete (61.7%). Additionally, most pulmonary TB patients did not experience comorbidities or experienced them only under special circumstances (69.1%), and most patients conducted their initial treatment at the Referral HSU (71.3%).

Table 1. Frequency Distribution of Internal Risk Factors

Variables	Frequency	Percentage
Treatment History		
a. Repetition Occurred	52	55.3%
b. No Repetition Occurred	42	44.7%
Compliance History		
a. Non-Compliant	31	33.0%
b. Compliant	63	67.0%
Laboratory Monitoring History		
a. Incomplete	36	38.3%
b. Complete	58	61.7%
History of Comorbidities		
a. Comorbidities	29	30.9%
b. No Comorbidities	65	69.1%
Service Unit History		
a. No Referral HSU*	27	28.7%
b. Referral HSU	67	71.3%

*Health Service Unit (HSU)

Table 2. Crude Risk Factors Associated with ATD Resistance among Pulmonary Tuberculosis Patients

Independent Variable	Category Variable	Resistance Status				P-Value	OR (95 % CI)
		Resistance Occurs		No Resistance Occurs			
		n	%	n	%		
Treatment History	Repetition Occurred	44	93.6	8	17.0	0.000	71.500
	No Repetition Occurred	3	6.4	39	83.0		
Compliance History	Non-Compliant	25	53.2	6	12.8	0.000	7.765
	Compliant	22	46.8	41	87.2		
Lab Monitoring History	Incomplete	30	63.8	6	12.8	0.000	12.059
	Complete	17	36.2	41	87.2		
History of Comorbidities	Comorbidities	16	34.0	13	27.7	0.655	-
	No Comorbidities	31	66.0	34	72.3		
Service Unit History	No Referral HSU	17	36.2	10	21.3	0.171	-
	Referral HSU	30	63.8	37	78.7		

Table 2 indicates that treatment history, treatment adherence, and laboratory monitoring were significantly associated with anti-tuberculosis drug (ATD) resistance among pulmonary tuberculosis patients ($p < 0.001$). Of the 47 respondents who experienced ATD resistance, 93.6% had a history of treatment repetition, while only 17.0% of non-resistant respondents had such history. Patients with repeated treatment had a markedly higher risk of ATD resistance (OR = 71.5). In addition, non-adherence to treatment was more common among resistant cases (53.2%) than non-resistant cases (12.8%), with non-compliant patients having a 7.765-fold increased risk of resistance. Similarly, incomplete laboratory monitoring was observed in 63.8% of resistant cases compared to 36.2% of

non-resistant cases, indicating a significantly higher risk of ATD resistance for patients with incomplete laboratory examinations (OR = 12.059).

In contrast, comorbidity history and healthcare service unit referral status were not significantly associated with ATD resistance. Among resistant patients, 34.0% had comorbidities, compared to 27.7% in the non-resistant group (p = 0.655). Likewise, patients treated at non-referral primary healthcare units accounted for 36.2% of resistant cases and 21.3% of non-resistant cases; this difference was not statistically significant (p = 0.171). These findings indicate that treatment repetition, medication adherence, and laboratory monitoring are key host-related risk factors for ATD resistance, whereas comorbidities and service unit types do not appear to have a significant effect.

Table 3. Analysis of Independent Variables with the Occurrence of ATD Resistance

Variables	P-Value	Description
Treatment History	0.000	Candidate
Compliance History	0.000	Candidate
Laboratory Monitoring History	0.000	Candidate
History of Comorbidities	0.503	Not a Candidate
Service Unit History	0.114	Candidate

Table 3 shows that of the five independent variables, four have p-values < 0.25. Therefore, these four independent variables—namely treatment history, compliance history, laboratory monitoring history, and service unit history—are candidates for inclusion in multivariate modeling using predictive model logistic regression analysis. One variable—namely the history of comorbidities—has a p-value > 0.25, so it is not a candidate; however, in substance this variable is strongly associated with the incidence of ATD resistance, so it was still included in multivariate modeling.

Table 4. Model of the Occurrence of ATD Resistance

Variables	B	Standard Error	P-Value	OR-Adjusted	95.0% CI	
					Lower	Upper
Medicine	3.866	0.733	0.000	47.762	11.348	201.018
Laboratory	1.673	0.720	0.020	5.326	1.298	21.853
Constant	-2.615	0.635	0.000	0.073		

The final modeling of logistic regression analysis shows that two independent variables, namely treatment history (p-value = 0.000) and laboratory monitoring history (p-value = 0.020), have p-values < 0.05, without any substantial interaction. Thus, it can be concluded that treatment history and laboratory monitoring history are the main internal risk factors for ATD resistance, while adherence history, history of comorbidities, and history of service units are confounding variables. The OR-Adjusted value of 47.762 for treatment history indicates that the risk of ATD resistance is 47.762 times greater in patients with pulmonary TB who experience repetition in treatment than in patients with pulmonary TB who do not experience repetition in treatment, making this the main internal risk factor for detecting early occurrence of ATD resistance. Furthermore, the logistic regression model equation was tested as follows:

$$\begin{aligned}
 Z &= \alpha + \beta_{(1)} X_{(1)} + \beta_{(2)} X_{(2)} \\
 Z &= -2.615 + 3.886 * 1 + 1.673 * 1 \\
 f(Z) &= 0.949 / 94.9\%
 \end{aligned}$$

Therefore, it can be concluded that the occurrence of ATD resistance is 94.9% due to the pattern of repetition history in treatment and laboratory monitoring history.

DISCUSSION

Treatment History with Occurrence of ATD Resistance

The results of the final multivariate modeling analysis show a p-value of 0.000 for treatment history, indicating that the treatment history pattern is an internal risk factor for ATD resistance. As mentioned above, the OR-Adjusted value for treatment history indicates that it is the most important variable for the occurrence of ATD resistance.

The results of the analysis support the theoretical concept that drug resistance is related to previous treatment history; in patients with a previous treatment history, the possibility of resistance is four times greater, and the occurrence of MDR-TB is ten times or more greater than in patients who have never been treated.² The overall prevalence of drug immunity is related to the number of previously treated patients in the country. MDR-TB patients are often asymptomatic and can transmit the disease before they become ill. Therefore, the prevalence of MDR-TB can be three times greater than the incidence, approaching or exceeding 1 million.⁷

The findings of this study are supported by previous empirical research. Heriqbaldi et al. reported that among 239 pulmonary tuberculosis patients with first-line anti-tuberculosis drug resistance treated at Dr. Soetomo General Hospital, Surabaya, the incidence of resistance was highest for rifampicin (94.14%) and isoniazid (79.08%), followed by ethambutol (25.94%) and streptomycin (20.08%). The most common resistance patterns were HR (42.26%), R (18.83%), and HRE (12.55%).⁸ Wu et al. reported comparable resistance patterns, with the highest resistance observed for isoniazid (18.51%), followed by streptomycin (15.49%), rifampicin (12.36%), and ethambutol (5.13%). Both studies demonstrated significantly higher drug resistance among previously treated patients than among new cases.⁹

Further support is drawn from Yinke and Sinaga, who found that all MDR-TB patients had a history of anti-tuberculosis drug use exceeding one month. Among these patients, 21.43% had been treated once, 42.86% twice, and 35.71% three times. In terms of treatment regularity, all patients (100%) had experienced irregular treatment, reinforcing the strong association between inadequate therapy and resistance development.¹⁰

According to the WHO, TB patients who meet the criteria to be suspected of ATD resistance are those who have a history of repetition in treatment, such as chronic pulmonary TB cases or pulmonary TB patients failing category 2 treatment, pulmonary TB patients with sputum examination results remaining positive after the third month of category 2 treatment, TB patients who have been treated with second-line ATDs such as quinolones and kanamycin, pulmonary TB patients who have failed category 1 treatment, pulmonary TB patients whose sputum smears remain positive after category 1 insertion, relapsed pulmonary TB cases, TB patients who have returned after defaulting on category 1 and/or category 2 treatment, TB suspects living close to MDR-TB patients, and health workers on duty in MDR-TB wards.¹¹

The occurrence of ATD resistance is essentially a man-made phenomenon resulting from inadequate TB treatment. Inadequate TB therapy leads to mutations, which can be resistant to first-line ATD. Prolonged infectious periods due to delayed diagnosis also lead to the spread of drug-resistant strain.¹² This spread is not only to patients in the hospital but also to hospital staff, dormitories, prisons, and patients' families. Patients with MDR-TB treated with short-term ATD will not recover and will spread the disease. MDR-TB is difficult to treat and requires long-term, expensive treatment. Patients with ATD-resistant tuberculosis germs who receive short-term treatment with monotherapy will develop more ATD-resistant bacteria (the amplifier effect). This leads to selection of resistant mutations.¹³

The relationship between treatment history and the occurrence of ATD resistance aligns with the classification of TB resistance put forward by the WHO, which names three types of resistance: 1) primary resistance, in which the patient has never previously received ATD treatment or has received ATD treatment for less than one month; 2) initial resistance, in which it is not known whether the patient has a history of previous ATD treatment; and 3) secondary resistance, in which the patient has had a history of ATD treatment for at least one month.¹

In addition to being in accordance with several theoretical concepts, these findings also align with data from a first-line ATD resistance study conducted in Central Java, which showed a low MDR-TB rate in new cases (1–2%), which increased in previously treated patients (15%). One-third of MDR-TB cases were resistant to ofloxacin, and one case of XDR-TB was found among 24 MDR-TB cases.² Additionally, the pattern of MDR-TB in Indonesia, especially in Friendship Hospital from 1995 to 1997,

showed primary resistance at 4.6%–5.8% and secondary resistance at 22.95%–26.07%. This shows an increase in prevalence that should be monitored.¹⁴

This relationship is also supported by the results of the analysis of treatment history. In the case group, who experienced repeated treatment, 44 patients (93.6%) were resistant, while in the control group, who did not experience repeated treatment (83.0%) were not resistant. In addition, the characteristics of respondents support the relationship between treatment history and ATD resistance. The education level of respondents is mostly primary and secondary education (88.3%), with only 11.7% having higher education. Most respondents, namely 89 people (94.7%), are employed. The average age of respondents is 40-45 years, and most are men (68.1%).

However, 17.0% of respondents in the control group experienced repetition of treatment but no resistance. This could be because the patients completed category 2 treatment in accordance with the guidelines or an increase in drug dose, an extension of the treatment period, or an increase in body resistance, and bacteria were still sensitive to the addition of drugs. In the case group, 6.4% did not repeat treatment but experienced resistance. This result could be due to insufficient monitoring of treatment results limiting our knowledge of treatment progress or could be caused by pulmonary TB transmission from patients who were resistant.

According to the WHO, prevention efforts must include appropriately classifying cases of TB, providing adequate drug regimens for all categories of patients, and providing early identification and adequate treatment for resistant TB cases. Integrating the DOTS program with treatment of resistant TB will work synergistically to eliminate potential sources of transmission and infection control.¹⁵ In addition, TB management must follow guidelines for dosing, regimen, and duration of treatment and apply the DOTS strategy. This will increase the cure rate and prevent resistance. If a suspected resistant case is found, a culture examination and sensitivity test should be conducted immediately. MDR-TB treatment must apply the DOTS-PLUS strategy. The national TB program should include aggressive case identification, rapid and appropriate diagnosis, and continuous provision of second-line ATD. Facilities and infrastructure for supporting examinations, especially culture and sensitivity tests, should be available in all regions.¹⁶

History of Laboratory Monitoring with Occurrence of ATD Resistance

The results of the final multivariate modeling analysis show a p-value of 0.020 for laboratory monitoring, indicating that laboratory monitoring history is an internal risk factor for the early detection of ATD resistance. The OR-Adjusted value of 5.326 indicates that patients with pulmonary TB with incomplete laboratory monitoring history have a 5.326 times greater chance of experiencing ATD resistance than those with complete laboratory monitoring history.

The results of this analysis support the theoretical concept that monitoring treatment progress through microscopic sputum re-examination is essential, especially in adults. Microscopic sputum examination is superior to radiological examination for monitoring treatment progress. ESR is not used for this purpose, as it is not specific for TB. To monitor treatment progress, two specimens (during and in the morning) are examined at the end of the intensive treatment phase, one month before the end of the advanced treatment phase, and at the end of the advanced treatment phase. The result is negative if both specimens are negative.¹⁷ If one of the specimens is positive or both are positive, the result of the sputum re-examination is declared positive. If the monitoring of treatment progress is not carried out completely, the treatment results are unknown, and resistance may develop.¹⁸

The present findings are also consistent with Munir *et al.*'s study, which reported that MDR-TB monitoring consists of two phases: the intensive phase and the continuation phase. During the intensive phase, patient visits every 2–4 weeks showed a positive impact on disease management by enabling close supervision of patient condition and early detection of side effects from injectable drugs. During the continuation phase, most patients attended follow-up visits at the same interval (70.5%). Additionally, 69.2% of patients underwent sputum examinations every 2–4 weeks during the intensive phase. This high monitoring frequency allowed timely detection of culture conversion and appropriate clinical decision-making. In the continuation phase, sputum examinations were conducted every 2–4 weeks in 50.8% of patients and every two months in 49.2%. These findings emphasize the importance of regular laboratory monitoring in preventing treatment interruption, enabling early detection of therapeutic failure, and identifying MDR-TB cases promptly.¹⁴

The appropriate selection of drugs and the correct administration of drugs by health workers is insufficient to guarantee the success of a therapy if it is not supported by adequate laboratory facilities and infrastructure. The absence of complete laboratory monitoring can have a significant negative effect because sputum examination in TB patients serves to establish a diagnosis, assess the success of treatment, and determine the potential for transmission.¹⁹

This relationship is also supported by the results of the analysis of laboratory monitoring history. In the case group with incomplete monitoring history, 63.8% are resistant, while in the control group with complete laboratory monitoring history, 87.2% are not resistant. Notably, in the control group with incomplete monitoring history, 12.8% are not resistant. This may be due to high levels of compliance in patients taking ATD, preventing repetition in treatment and keeping bacteria sensitive to the type of drug given.

In the case group, 36.2% with complete laboratory monitoring history experienced resistance. This may be due to low levels of compliance in patients taking ATD, leading to repetition in treatment and causing the bacteria to lose sensitivity to the type of drug given. It could also be caused by pulmonary TB transmission from a resistant patient.¹⁶

The WHO's global plan recommends implementing a rational case-finding strategy that is accurate and timely using quality-assured culture and sensitivity tests, implementing standardized recording and reporting systems for sputum laboratory examinations, and performing culture tests to monitor treatment progress.¹¹ Laboratory examinations should begin with sputum testing using the morning–spot–morning (MSM) method for initial diagnosis, followed by sputum tests at the end of the second month using the spot–morning (SM) method, and continuing with sputum testing (SM) at the end of the fifth month and once more at the end of the treatment period.¹⁷

Adherence History with Occurrence of ATD Resistance

The results of the bivariate analysis show that a p-value of 0.000 ($p\text{-value} < \alpha 0.05$) for compliance history, indicating that this variable is an internal risk factor for early detection of ATD resistance. It has an OR-Adjusted value of 7.765, meaning that patients with pulmonary TB who are not compliant with their treatment have a 7.765 times greater risk of ATD resistance than those who are compliant.

The results of the analysis indicate that patient compliance is necessary to achieve therapeutic success, especially in infectious and non-communicable disease therapy. Patient non-adherence can have a significant negative effect. It is important to remember that compliance is a multidimensional phenomenon determined by five interrelated dimensions—namely patient factors, therapeutic factors, health system factors, environmental factors, and socio-economic factors.¹⁹

Economic factors related to TB disease usually affect people from weak economic backgrounds. Inadequate social support and instability create an unsupportive environment for patient adherence. Factors such as age, gender, ethnicity/race, knowledge about TB disease, and belief in the efficacy of the drugs will influence the patient's decision to complete their therapy. Regimen complexity factors are related to the number of drugs to be taken and their toxicity and effects. Support and empathy from healthcare workers increases patient satisfaction, and the integrated system of health care should support patients' willingness to comply with their therapy.¹⁶

This relationship is supported by the results of the analysis of compliance history. In the case group, who had a history of non-compliance in carrying out treatment, 53.2% experienced resistance, while in the control group, who had a history of compliance, 87.2% did not experience resistance. In addition, the characteristics of respondents, presented above, support the relationship between compliance history and the occurrence of ATD resistance.

In the control group, 12.8% had a history of non-compliance but experienced no resistance. This could be because the *mycobacterium tuberculosis* bacteria is very sensitive to this type of ATD, or it could result from increased activity in the patient's immune system. In the case group, 46.8% who had a history of being compliant in treatment but experienced resistance. This could be due to inadequate monitoring of treatment results reducing our knowledge of treatment progress, or it could be caused by pulmonary TB transmission from a resistant patient.¹⁸

History of Comorbidities and Service Unit History with Occurrence of ATD Resistance

The results of the bivariate analysis show a p-value of 0.655 for history of comorbidities, indicating that this variable is not an internal risk factor for the early detection of ATD resistance; similarly, the results show a p-value of 0.171 for history in service units, meaning indicating that this is not an internal risk factor for ATD resistance.

These results support the theoretical concept that resistance is a multidimensional man-made phenomenon with various causes. The first category of these causes relates to healthcare workers, who affect resistance by using inappropriate alloys, not following available alloys, lacking alloys, receiving poor training, insufficiently monitoring treatment programs, and receiving insufficient funding for TB control programs. The second category relates to drugs. Resistance is affected by inadequate drug supply or quality, poor drug quality, interrupted drug supply, unsecured storage conditions, and incorrect drug combinations or under-dosing. Finally, the third category of causes involves patients. Resistance is affected by poor patient compliance, lack of information, insufficient funds, transportation problems, side effect problems, social problems, malabsorption, and dependence on certain substances.³

CONCLUSION

Treatment history and laboratory monitoring are highly useful indicators for early detection of ATD resistance in patients with pulmonary TB. The results of this study enable national pulmonary TB programs to detect the occurrence of DR-TB earlier and allow pulmonary TB patients to prevent the occurrence of chronic pulmonary TB disease.

ETHICS APPROVAL

Ethical approval was not required for this study because it analyzed secondary data that is publicly available and completely anonymized. No identifiable personal information was accessed or used in this research.

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COMPETING INTEREST

All authors declare no conflicts of interest.

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UNDERLYING DATA

The data that support the findings of this article are derived from direct interviews using questionnaires and observation of TB treatment card documentation (TB 01, TB 02, TB 03, and TB 05) at the Health Laboratory Center of Lampung Province.

DECLARATION OF ARTIFICIAL INTELLIGENCE USE

The authors declare that no artificial intelligence tools were used at any stage of the preparation, writing, or editing of this manuscript. All content was written, reviewed, and validated solely by the authors, who take full responsibility for the accuracy and integrity of the published work.

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