RIFAMPICIN RESISTANCE IN TUBERCULOSIS PATIENTS: CAUSE-RELATED FACTORS IN INDONESIA 2017-2018

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Abstract. Drug-resistant tuberculosis (DR TB) is a disease that impacts public health with its increasing number of cases. Using data from the national cross-sectional Anti-Tuberculosis Drug Resistance Survey conducted in 2017-2018, this study aimed to identify factors contributing to Indonesia's high proportion of rifampicin resistance. The independent variables predicted to affect rifampicin-resistant TB occurrence based on the available survey data were: age, gender education, employment status, area of residence, place of residence, have lived with TB patients, and treatment status. The data analysis was done using logistic regression. Among 3,431 smear-positive patients identified with TB, 3,234 were confirmed to be rapid molecular test positive, and 2,956 were *Mycobacterium tuberculosis* (MTB) sensitive. While the other 170 (5.25%) were identified with rifampicin-resistant tuberculosis (RR-TB). Patients with TB retreatment were 8.34 times more likely to have RR-TB, and females were also more likely to have RR-TB 1.38 times more than males (odds ratio (OR) = 1.38; 95% confidence interval (CI): (1.069-1.885), p=0.021). Living with TB patients for at least two years showed no significant difference. Other influential sociodemographic factors, including sex, TB case treatment status, and place of residence, were shown to have a difference in the risk of RR-TB. In conclusion, patients with TB retreatment are at high risk of RR-TB. Therefore, it is crucial to monitor the treatment of new tuberculosis patients to prevent treatment dropout and avoid RR-TB.

Keywords: tuberculosis, rifampicin-resistance, Indonesia

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INTRODUCTION

Drug-resistant tuberculosis (DR TB) is a disease that impacts public health with its increasing number of cases. In 2017-2018, the Ministry of Health Republic of Indonesia conducted the first national anti-TB drug resistance survey (MOH RI, 2020). This was the first survey conducted in Indonesia, and since then, a similar survey has yet to be carried out.

Globally in 2019, an estimated 3.3% of new TB patients and 17.7% of previously treated TB patients were drug-resistant TB patients (MOH RI, 2020). DR TB is a tuberculosis infection caused by the drug-resistant *Mycobacterium tuberculosis* bacteria and attacks the body due to improper treatment.

In Indonesia, the estimated DR TB is 2.4% of all new TB patients and 13% of previously treated TB patients, with an estimated incidence of DR TB cases of 24,000 or 8.8/100,000 population. In 2019, about 11,500 rifampicin-resistant TB (RR-TB) patients were identified and reported, and about 48% of them started second-line TB treatment with a success rate of 45% (WHO, 2020). Based on the 2013-2014 TB Prevalence Survey results, 11 out of 291 specimens with positive smears examined by the rapid molecular test (MR) were RR-TB (MOH RI, 2015).

In 2017-2018, the Health Research and Development Agency conducted a national anti-TB drug resistance survey in collaboration with the Directorate General of Disease Prevention and Control Ministry of Health. The implementation of this survey followed the guidelines for the Anti-TB Drug Resistance Survey from the World Health Organization (WHO, 2015). The survey showed 170 rifampin-resistant cases and 2,956 rifampin-sensitive (RS) cases (MOH RI, 2019). Many factors can cause DR TB. The main factor causing bacterial resistance to anti-TB drugs is the result of inadequate or non-standard treatment of TB patients (MOH RI, 2020). The authors conducted a further analysis based on the available data from the survey. Based on the survey results, this study aimed to determine the determinants that influence the occurrence of TB drug resistance in the community.

MATERIALS AND METHODS

The data analyzed in this paper was obtained from the Anti-Tuberculosis Drug Resistance Survey conducted nationally in 2017-2018 (MOH, 2019). The survey aimed to bring the proportion of anti-TB drug resistance among smear-positive TB cases, including new and retreatment issues in Indonesia. The method used in the study was a cross-sectional design with stratified multi-stage cluster sampling. The sampling frame was all new smear-positive pulmonary TB cases from all regions in Indonesia. Sample selection was systematically performed in stages, using probability proportional to size (PPS) for the provincial, district/city levels, and health service facilities. Participants were selected from 70 selected health facilities spread over 40 districts/cities and 12 provinces in Indonesia. The population in the survey were smear-positive TB patients in selected health facilities with a total sample of 3,235 (94.3%), with details of 2,608 (80.6%) new cases and 627 (19.4%) cases of retreatment.

An eligible population was the target population in selected health facilities that met the inclusion and exclusion criteria. The inclusion criteria were smear-positive TB patients, children under 15 years old who had smear-positive TB, and new cases or cases of TB retreatment (relapse, failure, return after discontinuation of treatment, chronic patients) diagnosed during the data collection period. The exclusion criteria were extrapulmonary TB cases and TB cases that had received treatment for more than one week during data collection.

For this paper, the selected sample is all Anti-Tuberculosis Drug Resistance Survey participants examined by rapid molecular test, which were rifampicin sensitive and rifampicin-resistant. Patients who tested negative for the rapid molecular test were excluded from the sample count (Fig 1). Furthermore, the determinants that affect the occurrence of drug-resistant TB were analyzed. The independent variables predicted to affect rifampicin-resistant TB occurrence based on the available survey data were: age (grouped into three: <35 years, 35-54 years, and ≥55 years), gender (female

and male), education (junior high school and below, and senior high school), employment status (working and not working), area of residence (consisting of three areas: Sumatra Region: North Sumatra, West Sumatra, South Sumatra, and Lampung; Java-Bali Region: DKI Jakarta, West Java, Central Java, and East Java; and Eastern Region of Indonesia areas: West Kalimantan, North Sulawesi, South Sulawesi, and Papua), place of residence (rural and urban), have lived with TB patients (yes and no), and treatment status of TB patients (new TB cases and recurrent TB patients. Univariate analysis was used to obtain an overview of the frequency distribution or the magnitude of the proportion according to the characteristics studied of all research variables. Logistic regression analysis was carried out to see the relationship between two variables: the dependent variable and the independent variable.

Data analysis was conducted using STATA V.14.0 (StataCorp LLC, College Station, TX). Before the examination, data cleaning was performed, and the recording was completed according to the purpose of the study. The statistical analysis program was used for the univariate, bivariate, and multivariate analyses. The univariate analysis aimed to describe the characteristics and sociodemographics of respondents, the bivariate analysis aimed at the relationship between the dependent and independent variables, and the multivariate analysis aimed to see the most influential factors in the occurrence of TB drug resistance.

This research has received ethical approval from the Health Research Ethics Commission of the Health Research and Development Agency with letter number LB. 5.2/KE 2545/2016 dated Jul 28, 2016.

RESULTS

In Fig 1, out of the total of 3,431 study samples (positive smear), 141 (4.11%) were lost to follow-up in the 2017-2018 survey, 55 (1.60%) refused to be interviewed during the 2017-2018 survey, and one (0.03%) empty sputum pot. The total number of patients analyzed in this study? Was 3,234.

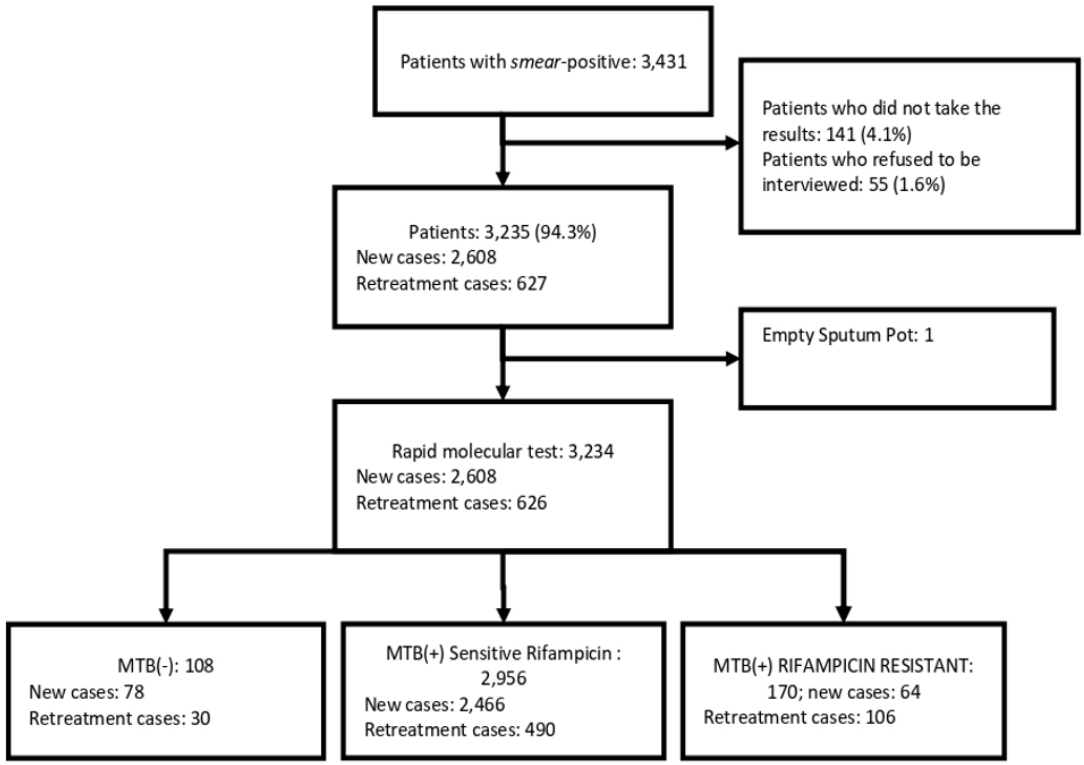

Fig 1 - Specimen collection flow

MTB(-): *Mycobacterium tuberculosis* negative by molecular rapid test; MTB(+): *Mycobacterium tuberculosis* positive by molecular rapid test

Table 1 shows that most TB participants are in the 35-54 age group, male, with junior high school education, working, and living in the Java-Bali, and rural areas. All variables in the bivariate analysis with a *p*-value <0.25 or substantially affecting the occurrence of RR-TB were included in the initial model. The eight variables in Table 1 were simultaneously entered into the model.

Table 2 describes significant variables of rifampicin resistance. Variables with a *p*-value >0.05 in multivariate analysis were removed from the model to get a fit model. Those variables which were removed are age group, education, employment status, region, place of residence, and living with TB patients.

Table 1

Distribution and relationship of rifampicin-resistant TB with respondent characteristics, socio-demography, and other factors related to TB patients

Variable	MTB RIF sensitive, *n* (%)	MTB RIF resistant, *n* (%)	OR (95% CI)	*p*-value
Age group				
<35 years (N = 1,131)	1,075 (94.88)	56 (5.12)	1.05 (0.653-1.685)	0.824
35-54 years (N = 1,244)	1,170 (93.83)	74 (6.17)	1.31 (0.877-1.956)	0.162
Gender				
Male (N = 2,002)	1,903 (95.05)	99 (4.95)	1.00	
Female (N = 1,124)	1,053 (93.68)	71 (6.32)	1.28 (0.971-1.674)	0.074
Education				
Junior High School (N = 1,985)	1,881 (94.76)	104 (5.24)	1.00	
Senior High School (N = 1,141)	1,075 (94.22)	66 (5.78)	1.08 (0.764-1.516)	0.636
Employment status				
Not working (N = 1,440)	1,364 (94.72)	76 (5.28)	1.00	
Working (N = 1,686)	1,592 (94.42)	94 (5.58)	1.08 (0.832-1.400)	0.523
Region				
Sumatera (N = 965)	921 (95.44)	44 (4.56)	1.00	
Java-Bali (N = 1,276)	1,206 (94.51)	70 (5.49)	1.24 (0.517-2.966)	0.592
Eastern Indonesian area (N = 885)	829 (93.57)	56 (6.33)	1.46 (0.527-4.014)	0.424

Table 1 (cont)

Variable	MTB RIF sensitive, *n* (%)	MTB RIF resistant, *n* (%)	OR (95% CI)	*p*-value
Place of residence				
Rural area (N = 1,834)	1,753 (95.58)	81 (4.42)	1.00	
Urban area (N = 1,292)	1,203 (93)	89 (6.89)	1.61 (1.029-2.524)	0.039
Living with TB patients				
No (N = 2,672)	2,527 (94.57)	145 (5.43)	1.00	
Yes (N = 454)	429 (94)	25 (5.51)	1.01 (0.689-1.472)	0.964
TB treatment status				
New case (N = 2,530)	2,466 (97.47)	64 (2.53)	1.00	
Case of TB retreatment (N = 596)	490 (82.21)	106 (17.79)	8.23 (4.815-14.077)	0.000

CI: confidence interval; MTB RIF resistant: *Mycobacterium tuberculosis* rifampicin resistant; MTB RIF sensitive: *Mycobacterium tuberculosis* rifampicin sensitive; OR: odds ratio; TB: Tuberculosis

Table 2
Initial rifampicin-resistant modeling with several independent variables

Variable	OR (95% CI)	*p*-value
Age group		
<35 years	0.99 (0.536 - 1.830)	0.974
35-54 years	1.18 (0.736 - 1.897)	0.445
Gender		
Female	1.58 (1.063 - 2.332)	0.028
Education		
Senior High School	1.07 (0.745 - 1.532)	0.686
Employment status		
Working	1.26 (0.745 - 1.532)	0.227
Region		
Java-Bali	1.23 (0.664 - 2.260)	0.471
Eastern Indonesia area	1.60 (0.748 - 3.401)	0.196
Place of residence		
Urban area	1.45 (0.978 - 2.152)	0.061
Living with TB patients		
Yes	0.79 (0.515 - 1.204)	0.235
TB treatment status		
Case of tuberculosis retreatment	34.00 (9.747 - 118.595)	<0.001

CI: confidence interval; OR: odds ratio: TB: Tuberculosis

The results of the final multivariate analysis model showed that the dominant variables influencing the occurrence of RR-TB were gender and TB treatment status of the patients (Table 3). Participants with repeated TB treatment status had an 8.34 times greater risk of developing RR-TB than those with new TB status. Based on gender, women had a 1.38 times higher chance for the occurrence of RR-TB when compared to men (odds ratio (OR) = 1.38; 95% confidence interval (CI): (1.069-1.885), p=0.021).

Table 3
Model fitting in modeling the influence of rifampicin-resistant tuberculosis

Variable	OR (95% CI)	*p*-value
Female	1.38 (1.069-1.885)	0.021
Case of TB retreatment	8.34 (9.24-10.721)	0.001

CI: confidence interval; OR: odds ratio

DISCUSSION

After being controlled with several variables, the results showed that three variables contributed to the occurrence of RR-TB. Patients who had the most significant risk of developing rifampin-resistant TB were those who received TB retreatment (after controlling variables of treatment status and gender).

In some other research results, it was found that many people living with male acquired immune deficiency syndrome (AIDS) patients experienced rifampicin-resistant TB (Ukwamedua *et al*, 2019, Mohr *et al*, 2018, Audu *et al*, 2017, Jaleta *et al*, 2017, Araya *et al*, 2020), although the findings of McQuaid *et al* (2020) found no difference in risk between male and female groups for the incidence of rifampin-resistant TB.

Although no significant association was found in this study, Jaleta *et al* (2017) discovered rifampicin-resistant *Mycobacterium tuberculosis* in HIV seropositive (14, 18.7%), males (45, 17.3%) and previously treated tuberculosis patients (61, 16.5%). Araya *et al* (2020) found that for the 18-29 years age group, HIV positivity and previous TB treatment history were significantly associated with high MTB, whereas gender (being female) was associated with low MTB. While rifampicin resistance tuberculosis (RR-TB) was more prevalent among relapse and failure cases, it was lower among the 30-39 age group. The strong association of MTB and rifampicin resistance-*Mycobacterium*

tuberculosis (RR-MTB) with previous treatment highlights the need for more attention to TB treatment and monitoring programs in the study area.

The risk of rifampicin resistance found in the group who had received TB treatment was also revealed in the studies by Asfaw *et al* (2018), Gebrehiwet *et al* (2019), Chen *et al* (2019), Sah *et al* (2020) Gautam *et al* (2018), Ragonnet *et al* (2017), Mulu *et al* (2017) and Wasihun *et al* (2021).

Human immunodeficiency virus or acquired immune deficiency syndrome (HIV/AIDS), according to the studies by Cox *et al* (2021) and Jaleta *et al* (2017), was identified as one of the most significant risk factors for rifampicin resistance in patients.

Drug-resistant TB can be cured if the patient completes the treatment. Most DR TB is not curable. The main factor causing bacterial resistance to anti-TB drugs is inadequate or non-standard treatment for TB patients. The following four factors can cause anti-TB drug resistance: (1) TB sufferers do not complete treatment ultimately, (2) there is an unavailability of TB drugs, (3) service providers (health workers) make the incorrect diagnosis, and (4) service providers (health workers) do not use the right drug combinations in treating TB (WHO, 2018). This logic is corroborated by the findings of Liu *et al* (2020), Cox *et al* (2020), and Mohr-Holland (2022).

There is a risk of developing rifampicin resistance in respondents who live in the same house with a TB patient, as supported by the results of the studies by Olatunji *et al* (2022), Rossetti *et al* (2020), Asfaw *et al* (2018) and Gebrehiwet *et al* (2019).

Another research showed that of the 423 pulmonary tuberculosis (PTB) suspected patients, 38 (8.98%) were identified as having PTB by GeneXpert, where 2/38 (5.3%) were resistant to rifampicin, and 3/38 (7.89%) were co-infected with HIV. Participants aged between 18 and 24 and between 25 and 34 years, weight loss, chest pain, having a history of contact with confirmed PTB cases, utilization of congested transportation, and a history of imprisonment were significantly associated with the prevalence of PTB (Gebretsadik *et al*, 2020).

In conclusion, patients with TB retreatment have more than eight times higher risk of RR-TB. Also, women had a 1.38 times higher chance for the occurrence of RR-TB when compared to men. Therefore, it is crucial to monitor the treatment of new tuberculosis patients to prevent treatment dropout and avoid RR-TB.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare that they have no competing interests.

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