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Maria Holly Herawati
Public Health and Nutrition Research Center, Health Organization Research, The National Research and Innovation Agency, mariaholly@gmail.com

Dasuki Dasuki
Public Health and Nutrition Research Center, Health Organization Research, The National Research and Innovation Agency, dasu001@brin.go.id

Dina Bisara Lolong
Public Health and Nutrition Research Center, Health Organization Research, The National Research and Innovation Agency, dina019@brin.go.id

Mirna Widiyanti
Public Health and Nutrition Research Center, Health Organization Research, The National Research and Innovation Agency, mirna.widiyanti@brin.go.id

Betty Roosihermiatie
Public Health and Nutrition Research Center, Health Organization Research, The National Research and Innovation Agency, bett003@brin.go.id

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Maria Holly Herawati, Dasuki Dasuki, Dina Bisara Lolong, Mirna Widiyanti, Betty Roosihermiatie, Ria Yuda Permata, Raflizar Raflizar, Ferry Ahmadi, Hadi Supratikta, and Meita Veruswati

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Utilizing Rapid Molecular Tests (RMT/RIF) in Tuberculosis Drug-Sensitive/Resistant Discovery in Indonesia: A Pilot Study

Maria Holly Herawati[1], Dasuki[1], Dina Bisara Lolong[1], Mirna Widiyanti[1], Betty Roosihermiati[1], Ria Yuda Permata[1], Raflizar[1], Ferry Ahmadi[1], Hadi Supratikta[1], Meita Veruswati[2,3*]

[1]Public Health and Nutrition Research Center, Health Organization Research, The National Research and Innovation Agency, Jakarta, Indonesia, [2]Department of Public Health, Faculty of Health Sciences, University of Muhammadiyah Prof. Dr. HAMKA (UHAMKA), Jakarta, Indonesia, [3]Doctoral Program in Business and Management, Postgraduate School, Management and Science University, Shah Alam – Selangor Darul Ehsan, Malaysia

Abstract

The underdiagnosis and underreporting of tuberculosis (TB) indicators are unresolved problems. The rapid molecular test (RMT) is one of the breakthroughs for TB case finding by using safer and more sensitive equipment; it is even believed to help find drug-resistant TB. The results of several webinars held regularly by a TB program as well as its evaluation and the use of RMT, formed the basis of this study. This initial pilot study aimed to provide an overview of case finding for both drug-sensitive and drug-resistant TB using RMT. A cross-sectional study was conducted on samples in several provinces in Indonesia that have used RMT, both in remote or non-remote island borders areas and fiscal capacity. Regarding the use of RMT for drug-sensitive TB case finding, the largest contributors were males aged above 15 years, while in the drug-resistant TB case finding group, the biggest contributor was the use of RMT in 2017 and 2018. Overall, the findings could only describe the situation in the study area. The use of RMT in drug-sensitive TB case finding would be maximized if the detected cases are males aged above 15 years, while RMT can help find cases of drug-resistant TB.

Keywords: case finding, Indonesia, rapid diagnosis, tuberculosis

Introduction

Indonesia is "The 3rd largest contributor to tuberculosis (TB) prevalence cases in the world after South Africa and Cambodia."[1] The burden of TB disease in Indonesia is relatively high. The prevalence of TB in Indonesia has fluctuated; from 393/100,000 in 2007, 725/100,000 in 2010, 289/100,000 in 2011, 400/100,000 in 2013, and 647/100,000 in 2015, and the TB death rate went from 92/100,000 in 1990 to 27/100,000 in 2011.[2-5] According to the 2014 TB prevalence survey, the number of confirmed bacterial TB cases was 759/100,000, with a positive smear rate of 257/100,000.[6]

Examining the range of case numbers, one can observe that the results of TB control in Indonesia are still in place. Given the limited situation and conditions, TB prevalence data comes from multiple sources, and various measurement methods are performed. The prevalence of TB in Indonesia is still high in terms of culture examination.

World Health Organization (WHO)'s global plan for treating TB cases began with the directly observed treatment short-course (DOTS) Strategy, introduced in 1990.[7] Other strategies include political commitment, case detection by microscopic examination for patients with chronic cough, treatment using standard and brief chemotherapy with direct observation, TB case management, and a good recording and reporting system.[7]

Boehme, *et al.,* found that X-pert MTB/RIF examination could detect 90.3% of TB culture-confirmed cases compared to 67.1% by microscopic examination.[8] X-pert MTB/RIF has a sensitivity and specificity of 76.9% and 99.0%, respectively, for smear-negative positive cultures as well as a sensitivity of 94.4% and a specificity of 98.3% for the rifampin-resistant test.[8] A study in Tanzania on the accuracy of Gen X-pert MTB findings found a sensitivity and specificity of 88.4% and 99%, respectively.[9] In Uganda, analyzing sputum from children aged two months to 12 years for the X-pert MTB/RIF test exhibited a sensitivity of 79.4% and a specificity of 96.5%.[10]

Because MTB/RIF can detect all specimens, the WHO set several policy recommendations for using gen X-pert MTB/RIF.[11] Among others: X-pert MTB/RIF is used as an initial diagnostic test in adults and children suspected of suffering from MDR-TB or HIV-associated TB as a

Correspondence: Meita Veruswati, Department of Public Health, Faculty of Health Sciences, University of Muhammadiyah Prof. Dr. HAMKA (UHAMKA), Jakarta, Indonesia, Limau II Street No. 3, Kebayoran Baru, South Jakarta 12130, Indonesia, E-mail: meitaveruswati@uhamka.ac.id, Phone: +62 858-1300-1500*

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strong recommendation, and X-pert MTB/RIF can be used as the initial diagnostic test in all adults and children suspected of having TB as a conditional recommendation rather than conventional microscopy and culture. The Indonesian Minister of Health Regulation No. 67 of 2016 states that one of the ways to diagnose TB cases is by examining gen X-pert MTB/RIF.[11]

In 2014–2015, X-pert machines were distributed in 59 cities and districts in Indonesia. Then at the end of December 2016, X-pert MTB/RIF machines were distributed and installed in 142 health facilities in Indonesia. Until the end of 2017, X-pert MTB/RIF machines were distributed to 600 health facilities.[12] Along with the distribution of the MTB/RIF tool, TB cases in several health facilities have increased. In 2016, the number of TB cases was 360,565; this increased to 568,987 in 2019 but was still far from the estimated incidence.[13] Thus, this initial pilot study aimed to provide an overview of the use of RTM and RIF in the case finding of rifampicin-sensitive and rifampicin-resistant TB, considering the abovementioned problem. This study would be evidence for introducing one of the breakthroughs for TB case finding by using safer and more sensitive equipment.

Method

This sub-national representative study was carried out cross-sectionally by looking at the use of RTM/RIF from 2014 until 2018. The total sample was 43 health facilities, consisting of 41 hospitals and 2 primary health care using RTM/RIF in 42 districts in Indonesia. TB case report data was taken for further processing. The RTM/RIF results shown were rifampicin-sensitive TB and rifampicin-resistant TB.[14] The regional status variables consist of high fiscal lagging regions, moderate fiscal lagging regions, low fiscal lagging regions, high fiscal non-lagging regions, moderate fiscal non-lagging regions, low fiscal non-lagging regions, sex, age group (<15 years), and year of use of RTM/RIF (from 2014 until 2018). The data analyses were univariate and multivariate and were conducted using software for advanced statistical analysis.

Results

The distribution of MTB/RIF results showed five categories: negative, rifampin sensitive, rifampicin-resistant, intermediate, and failed. Table 1 shows that after examination with the RMT, the mean rifampicin-sensitive cases were 0.27, while the mean rifampicin-resistant cases were 0.03. While, in the distribution of years of use of RTM/RIF, there was an increase in the use of MTB/RIF in the detection of suspected TB cases. The use of RTM/RIF was still dominant in determining cases in the age group of 15 years and older, and the male group had a higher proportion of suspected TB cases than the female group.

Table 2 shows the status of the sample areas using RTM/RIF. The sample areas were not evenly distributed in the medium to minimum capacity areas. The most sampled areas were both in remote or non-remote island borders areas. The relationship between case finding and regional status was not statistically significant.

The final results of the linear regression produced two outputs: the results of RTM/RIF-sensitive and resistant rifampicin. The R square values were around 0.44 and 0.32, showing a weaker relationship, although a significant relationship was detected, 0.00 and 0.02, with R (0.66 and 0.57). Also, it contributed the most to the case findings, with both drug-sensitive and drug-resistant rifampicin. In contrast, the age group of less than 15 years old barely contributed to the TB case findings, as did the female sex group.

The use of RTM/RIF in the case finding of rifampicin-sensitive TB was the most effective in the male group, followed by the age group of over 15 years old, while the

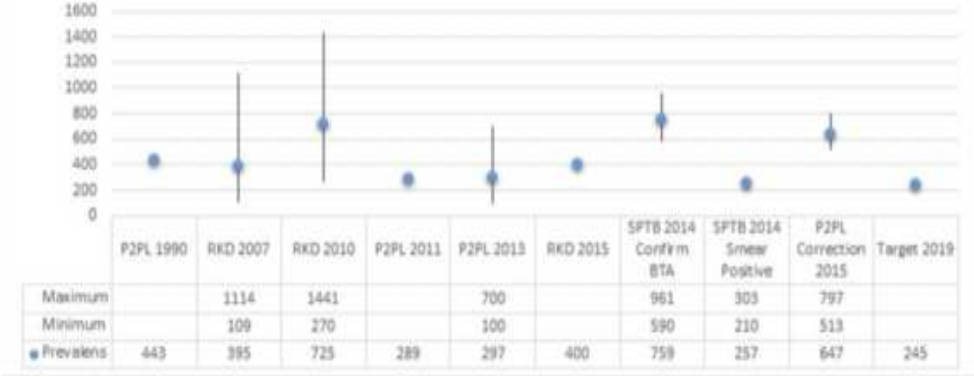

Figure 1. Prevalence of Tuberculosis in 1990–2015 and Projected Prevalence in 2019

Table 1. Distribution of Rapid Molecular Test Results of Suspected TB Cases in 43 Health Facilities in 2018 in Indonesia

Variable	Category	n	Mean	SD	Min–Max
RTM/RIF result	Negative	43	0.69	0.07	0.5–0.8
	Rifampicin-sensitive	43	0.27	0.06	0.18–0.45
	Rifampicin-resistant	43	0.03	0.02	0–0.09
	Intermediate	43	0.00	0.00	0–0.01
	Failed	43	0.01	0.01	0–0.05
Year	2014	43	0.00	0.01	0–0.03
	2015	43	0.01	0.02	0–0.08
	2016	43	0.04	0.07	0–0.30
	2017	43	0.35	0.14	0–0.56
	2018	43	0.60	0.18	0.3–1
Age	<15 years	43	0.03	0.03	0–0.16
	≥15 years	43	0.97	0.03	0.84–1
Sex	Male	43	0.60	0.05	0.48–0.73
	Female	43	0.40	0.05	0.27–0.52

Table 2. Relationship between Rapid Molecular Test Results (Sensitive and Resistance of Rifampicin) Case Findings with Regional Status

	Area	n	%	Mean	SD	95% CI	Sig.
Rifampicin-sensitive	Non-remote island borders areas-high fiscal	7	16.3	0.29	0.06	0.23–0.34	0.25
	Non-remote island borders areas-under intermediate fiscal	17	39.5	0.28	0.07	0.24–0.32	
	Remote island borders areas-high fiscal	3	7.0	0.32	0.08	0.12–0.51	
	Remote island borders areas-under intermediate fiscal	16	37.2	0.25	0.05	0.22–0.28	
Rifampicin-resistance	Non-remote island borders areas-high fiscal	7	16.3	0.04	0.03	0.01–0.07	0.23
	Non-remote island borders areas-under intermediate fiscal	17	39.5	0.03	0.02	0.02–0.04	
	Remote island borders areas-high fiscal	3	7.0	0.02	0.01	0.01–0.03	
	Remote island borders areas-under intermediate fiscal	16	37.2	0.02	0.02	0.01–0.03	

Notes: SD = Standard Deviation, CI = Confidence Interval

Table 3. Final Linear Regression of Rapid Molecular Test Results (Sensitive and Resistance of Rifampicin) Case Findings

Variable		B	SE	β	T	Sig.	95% CI
Rif-sensitive (constant)		-0.63	0.27		-2.35	0.02	-1.17– -0.09
	Male	0.59	0.15	0.49	3.83	0.00	0.28–0.90
	≥15 years old	0.56	0.28	0.26	2.00	0.05	-0.01–1.13
Rif-resistance (constant)		0.13	0.03		3.86	0.00	0.06–0.20
	2017	-0.10	0.04	-0.69	-2.41	0.02	-0.19– -0.02
	2018	-0.12	0.03	-1.00	-3.48	0.00	-0.18– -0.05

Notes: SD = Standard Deviation, CI = Confidence Interval

use of RTM/RIF for the case finding of rifampicin-resistant TB contributed the most to the results. A negative relationship was detected between the use of sensitive and rifampicin-resistant in 2018 and 2017.

According to Dougherty, a negative constant or intercept in Table 3 can be interpreted as 0, meaning that if the examination of a man suspected of having TB is 0, then rifampicin is sensitive (–0.63).[14] It can also be reversed, Y = 0.59 (X) – 0.63, meaning that if the RTM/RIF tool is used to detect TB in the male group, for example, the equation Y = 0.59(2) – 0.63 = 0.55 means that the rifampicin TB case finding is 55% sensitive.

Discussion

Using RTM/RIF in detecting suspected TB cases will help detect TB sensitivity and resistance to rifampicin. To treat TB resistance to other drugs, referrals must be made for culture propagation in hospitals with adequate equipment and human resources. The results of the R-squared analysis on the use of RTM/RIF for sensitive and resistant rifampin were 37% and 30%, while the remaining 63% and 70% can be explained by other vari-

ables.[15,16]

The group of male TB suspects detected using RTM/RIF had a high (59%) contribution to the case finding of rifampicin-sensitive TB. Meanwhile, the 15-year-old group contributed 56% to the case finding of rifampicin-sensitive TB. These results were consistent with several descriptions of TB cases in Indonesia reported in the Tuberculosis Prevalence Survey, TB inventories, and several TB studies conducted in Indonesia.[3-6,17]

The age group above 15 suspected of TB has a major contribution to the case finding of rifampicin-sensitive TB. These results also matched some findings in Indonesia, although this should be observed carefully because Indonesia's TB program prioritizes those over 15 years. Another problem with diagnosing TB in children is the limited number of human resources and equipment in all health facilities in Indonesia.

The use of devices in 2017 and 2018 significantly increased TB resistance to rifampicin. It shows an increase in the use of RMT from 0% to 60%, but it also shows a decrease in finding cases of resistance to rifampicin in 2017 and 2018. These results may be because many suspected TB cases were examined by RMT but not recorded. Several factors, including the possibility of changing or moving officers, may affect the health facilities in several study sample areas.[18-20]

Conclusion

This initial pilot study shows that in the distribution of years of use of RTM/RIF, there is an increase in the use of MTB/RIF in the detection of suspected TB cases. However, at the same time, there is a decrease in finding cases of resistance to rifampicin. Although the RMT will potentially facilitate and expedite the discovery, recording, reporting, and treatment of TB cases with rifampicin resistance and sensitivity to suppress such cases, further research is still needed. Some health facilities that use RMT must still be supported by the presence of reagents, the infrastructure, and the availability of TB drugs considering that RMT facilitates TB case finding.

Abbreviations

RMT: Rapid Molecular Test; TB: Tuberculosis; WHO: World Health Organization; DOTS: Directly Observed Treatment Short-Course.

Ethics Approval and Consent to Participate

The study was conducted following the Declaration of Helsinki, and approved by the Ethic Commission for Health Research, Indonesian Ministry of Health No. 880/KRKI/V/2018. Inform license obtained from institution and research subject.

Competing Interest

The authors declare that there are no significant competing financial, professional, or personal interests that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

Data and information used as study materials can be obtained publicly from the Center for Data Management, Indonesian Ministry of Health.

Authors' Contribution

MHH is the main contributor, responsible for the ideas created, analysis, and preparation of writings. MV and MHH performed formal analysis, investigation, interpretation, and writing-original draft preparation. MHH supervised the study and writing review and editing. D, DBL, MW, BR, RYP, R, FA, and HS were subsequently involved in conceptualization, methodology, software, validation, resources, data curation, writing review, and editing. All authors have made substantial contributions to the final manuscript for publication.

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