EVALUATION OF THE MOLECULAR RAPID TEST METHOD FOR TUBERCULOSIS CASE DETECTION IN SEVERAL HOSPITALS IN EAST INDONESIA DURING 2014-2018

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Abstract. Tuberculosis (TB) is a major public health issue that remains difficult to detect. Despite its low sensitivity and specificity, the most widely used TB examination method is sputum smear microscopy. The molecular rapid test method with expert microorganisms for tuberculosis/rifampicin (X-pert MTB/RIF) has better sensitivity and specificity than sputum smear microscopy. This study aimed to evaluate the utilization of molecular rapid test in several hospitals in East Indonesia. The design of this study was a cross sectional. Data on patients were collected by enumerator and the health facilities' TB team using the TB Forms 01, 04, 05, and 06. The data collected included patient characteristics, examination objectives, referral origin, specimen type, reference hospital, and molecular test results. This study included 16,186 patients, with 71% having molecular rapid testing method and the remaining 29% having a combination of molecular rapid test and microscopic method. Most of the patients were male (60%), aged 15-54 years (63.3%), and from internal health facilities (67.1%). The patient's status was mostly "new cases" (77.4%), and 99.9% of the specimens were sputum. For the past five years (2014-mid 2018), most patients sought an examination for drug-sensitive TB, then drug-resistant tuberculosis (DR-TB), and at least tuberculosis-human immunodeficiency virus (TB-HIV) and tuberculosis-diabetes mellitus (TB-DM). There was an increase in the number of patients tested using molecular rapid test during the 2014-2018 period in the East Indonesia region. The most significant increase in patients using the molecular rapid test detection method was in 2017. The high increase in the use molecular rapid

testing 2017 was related to its exclusion with the Ministry of Health Regulations number 67 in 2016 about tuberculosis control.

Keywords: molecular rapid test, X-pert MTB/RIF, tuberculosis

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INTRODUCTION

Tuberculosis (TB) is a major health problem worldwide, including in Indonesia. Tuberculosis is a deadly health threat and has quite a challenge in its detection methods. Based on the Global TB Report 2021 (WHO, 2021), Indonesia has the third highest TB burden in the world after India and China. The estimated number of TB cases in Indonesia is 824,000, with a notification rate of 393,232 cases. The number of TB deaths in Indonesia has reached 150,000 cases, with TB mortality rate of 55 per 100,000 population (KNCV Indonesia, 2022).

The most widely used TB examination method in TB-endemic countries, including Indonesia, is sputum smear microscopy, despite its low sensitivity and specificity and inability to determine drug sensitivity. Therefore, the molecular rapid test method was introduced in Indonesia to diagnose TB in 2012. The molecular rapid test, namely, the expert mycobacterium tuberculosis/rifampicin (X-pert MTB/RIF) method, is a developmental diagnostic tool that can be used to detect the presence of *Mycobacterium tuberculosis* germs automatically by molecular examination and can also be used to detect resistance to rifampin. Initially, the molecular rapid test was only used for testing for drug-resistant TB and human immunodeficiency virus - tuberculosis (HIV-TB). The molecular rapid test is used to diagnose new pulmonary TB in addition to drug-resistant TB and HIV-TB. The diagnosis of adult pulmonary TB is confirmed by bacteriological examination, including microscopic examination, molecular rapid test, and culture.

The molecular rapid test method with X-pert MTB/RIF has better sensitivity and specificity than microscopic examination. This method can detect 90.3% of confirmed cases of TB culture, compared to 67.1% of microscopic examinations (Boehme *et al*, 2010). Furthermore, a study in Tanzania reported that the accuracy of molecular rapid test with X-pert MTB/RIF for detecting MTB had a sensitivity and specificity of 88.4% and 99%, respectively (Ntinginya *et al*, 2012).

According to Ministry of Health, Research and Development Center of Public Health Efforts in research report on the Evaluation study of TB case detection by molecular rapid test in Indonesia, until the end of 2017, X-pert MTB/RIF machines had been distributed to 600 health facilities throughout Indonesia (MOH RI, 2018). The distribution of molecular rapid test is prioritized for hospitals that have passed the feasibility study. This study was conducted to further analyze the data from the Evaluation Study of TB Case Detection with Molecular Rapid Tests in Indonesia during 2014 to mid 2018. The aim of the study was to evaluate the utilization of molecular rapid test method for TB case detection in the East Indonesia Region.

MATERIALS AND METHODS

This study was conducted to further analyze the data from the Evaluation Study of TB Case Detection with Molecular Rapid Test in Indonesia in 2018. This was a descriptive study with a cross-sectional design. In this study, 22 district and city hospitals in Eastern Indonesia participated. The criteria for selecting the sample were hospitals that had operated the molecular rapid test device for six months. Sampling was carried out in eastern Indonesia due to more difficult geographical conditions with limited facilities and infrastructure. Therefore, this condition has an impact on community health.

A general description of the patient (age and gender), the type of examination (test for drug-sensitive tuberculosis (TB), tuberculosis drug resistance (TB DR), tuberculosis-HIV (TB-HIV), tuberculosis-diabetes mellitus

(TB-DM), and the origin of the referral (internal health services), facilities, public health centers, other hospitals, and doctor/private clinics), and data collected were obtained from tuberculosis forms (TB 01, 04, 05, and 06) from 2014 until mid-2018.

Data processing was performed after the cleaning and editing. Data were then analyzed with the Statistical Program for Social Science (SPSS) version 24, developed by IMB Corporation, Armonk, NY. The data were analyzed descriptively and displayed in tables and graphs.

Ethical approval for this study was obtained from the Ethics Committee of the Health Research and Development Agency, No. LB.02/2/KE 112/2018, signed on March 28, 2018.

RESULTS

A total of 16,186 patients were examined using the molecular rapid test method for five years in 22 hospitals in the study area in East Indonesia. During 2014-2018, using the molecular rapid test method to diagnose tuberculosis was the most in 2018 accounted for 8,602 patients (Table 1). The molecular rapid test method reported the highest number of TB patients diagnosed at the district hospitals of Kendari, Manado, and Sorong because the three districts have used molecular rapid test since 2014 until 2018 (Fig 1).

Most of the patients diagnosed with TB using the molecular rapid test method were male (60%), aged 15-54 years (63.3%), the origin of the referral was from an internal health facility (67.1%), the patient's treatment status was a new case (77.4%), and 99.9% of the specimens to be examined were sputum (Table 2). The molecular rapid test method is widely used for drug-sensitive TB testing, and only a small portion is used for TB-DM testing. From 2014 to mid-2018, most of the patients referred came from internal health facilities and were new TB cases. In addition, the number of positive TB cases diagnosed using the molecular rapid test method increased every year for both drug sensitive and resistant TB (Table 3).

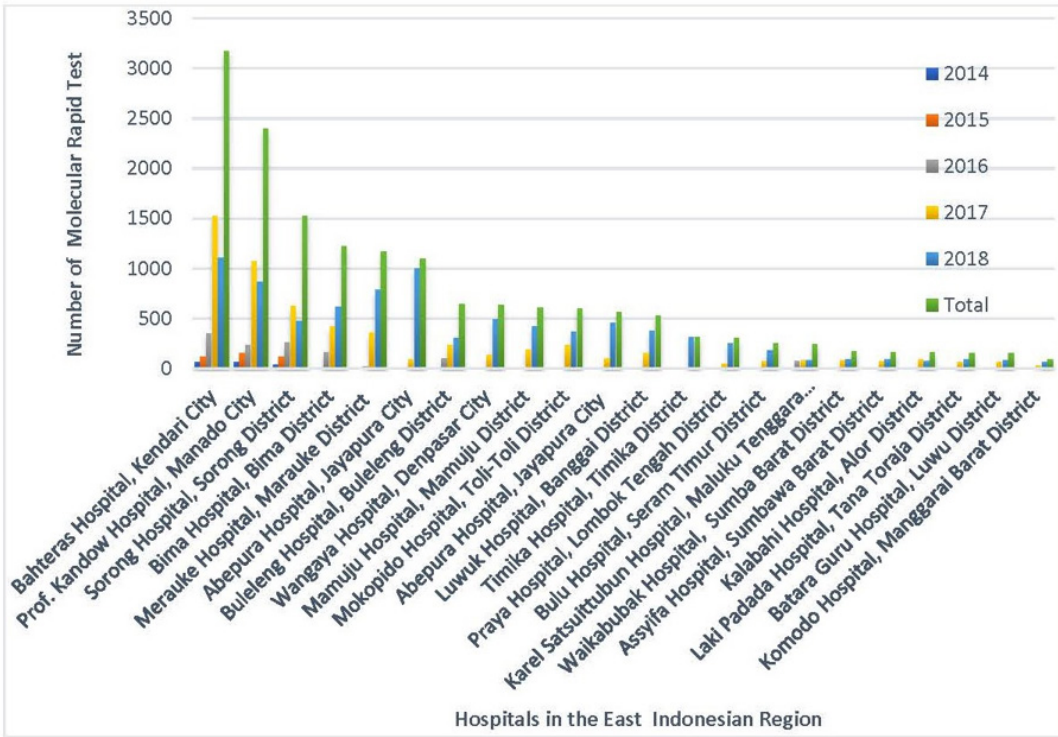

Fig 1 - Trend of hospitals that performed the molecular rapid test for tuberculosis diagnosis in the East Indonesia region (2014 to mid 2018)

DISCUSSION

The use of tuberculosis diagnosis technology with the molecular rapid test method in the East Indonesia Region study area has increased. This can be seen from the increasing number of patients who are examined using this method in hospitals every year. The highest number of patients diagnosed with the molecular rapid test method were in Kendari, Menado, and Sorong Hospitals. The high number of patients diagnosed using the molecular rapid test method in this area is due to the use of this method; the molecular rapid test has been carried out in each hospital since 2014. In several study

Table 1

Number of molecular rapid test method being utilized at health facilities in Eastern Indonesia in 2014-2018

Hospital	Number of molecular rapid tests being utilized at health facilities					Total
	2014	2015	2016	2017	2018	
Merauke District Hospital	0	0	26	360	783	1,169
Luwuk Banggai District Hospital	0	0	0	152	374	526
Mokopido Hospital, Toli-Toli District	0	0	0	235	369	604
Assyifa Hospital, Sumbawa Barat District	0	0	0	75	90	165
Bima Hospital, Bima District	0	17	168	421	619	1,225
Bulu Hospital, Seram Timur District	0	0	0	76	181	257
Abepura Hospital, Jayapura City	0	0	0	102	461	563
Praya Lombok Hospital, Tengah District	0	0	0	46	256	302
Waikabubak Hospital, Sumba Barat District	0	0	0	83	89	172
Kalabahi Hospital, Alor District	0	0	0	92	71	163
Komodo Hospital, Manggarai Barat District	0	0	0	27	63	90
Hospital Wangaya, Denpasar City	0	0	0	141	492	633
Prof. Kandow Hospital, Manado City	62	155	238	1,075	864	2,394

Table 1 (cont)

Hospital	Number of molecular rapid tests being utilized at health facilities					Total
	2014	2015	2016	2017	2018	
Timika Hospital, Kabupaten Timika	0	0	0	0	316	316
Buleleng Hospital, Buleleng District	0	0	100	232	310	642
Mamuju Hospital, Mamuju District	0	0	0	188	420	608
Laki Padada Hospital, Tana Toraja District	0	0	0	69	89	158
Sorong Hospital, Sorong District	43	122	263	629	471	1,528
Bahteras Hospital, Kendari City	66	118	352	1,529	1,110	3,175
Batara Guru Hospital, Luwu District	0	0	0	64	88	152
Karel Satsuittubun Hospital, Maluku Tenggara District	0	8	73	80	84	245
Abepura Hospital, Jayapura City	0	0	0	97	1,002	1,099
Total	171	420	1,220	5,773	8,602	16,186

Table 2
Characteristics of patients (N =16,186)

Characteristic	Frequency, *n* (%)
Sex	
Male	9,728 (60.1)
Female	6,458 (39.9)
Age group	
<15 years	345 (2.1)
15-54 years	10,248 (63.3)
≥55 years	5,593 (34.6)
Referral origin	
Internal health facility	10,860 (67.1)
Public health center	3,465 (21.4)
Other hospitals	1,191 (7.4))
General practitioner's clinics	416 (2.6)
Unknown	254 (1.6)
Treatment status	
New tuberculosis case suspect	12,532 (77.4)
Re-treatment of Tuberculosis-suspect	3,654 (22.6)
Type of specimens	
Sputum	16,165 (99.9)
Liquor Cerebrospinalis (LCS)/ Cerebrospinal fluid	2 (0.0)
Gastric lavage	7 (0.0)
Pleural fluid	11 (0.1)
Feces	1 (0.0)

Table 3

Distribution of hospital patients having molecular rapid test based on testing purpose, treatment status, referral origins, and molecular rapid test results in 22 Districts/Cities in East Indonesia region (2014- 2018)

Patients underwent molecular rapid test	Frequency, *n* (%)				
	2014 (N = 171)	2015 (N = 420)	2016 (N = 1,220)	2017 (N = 5,773)	2018 (N = 8,602)
Purpose of molecular rapid test examination					
Tuberculosis-drug sensitive	118 (69.0)	275 (65.5)	588 (48.2)	4,098 (71.0)	6,762 (78.6)
Tuberculosis drug resistance	39 (22.8)	126 (30.0)	495 (40.6)	1,348 (23.4)	1,385 (16.1)
Human Immunodeficiency Virus - Tuberculosis (HIV-TB)	14 (8.2)	19 (4.5)	132 (10.8)	295 (5.1)	375(4.4)
Diabetes Mellitus Tuberculosis (DM-TB)	0 (0.0)	0 (0.0)	5 (0.4)	32 (0.6)	80 (0.9)
Treatment status					
New case	121 (70.8)	280 (66.7)	655 (53.7)	4,328 (75.0)	7,148 (83.1)
Recurrent case	50 (59.2)	140 (33.3)	565 (46.3)	1,445 (39.5)	1,454 (39.8)
Origin of reference					
Internal health facility	89 (52.0)	179 (42.6)	722 (59.2)	3,673 (59.2)	6,197 (72.0)
Public health center	20 (11.7)	92 (24.2)	295 (22.4)	1,291 (22.4)	1,767 (20.5)
Other hospitals	10 (5.8)	82 (19.5)	98 (8.0)	677 (11.7)	324 (3.8)
General practitioner's clinic	6 (3.5)	64 (15.2)	105 (8.6)	105 (1.8)	136 (1.6)
Unknown	46 (26.9)	3 (0.7)	0 (0.0)	27 (0.5)	178 (2.1)

Table 3 (cont)

Patients underwent molecular rapid test	Frequency, *n* (%)				
	2014 (N = 171)	2015 (N = 420)	2016 (N = 1,220)	2017 (N = 5,773)	2018 (N = 8,602)
Molecular rapid test results					
Negative	94 (55.0)	213 (50.7)	707 (58.0)	3,859 (66.8)	6,150 (71.5)
Rifampicin sensitive	32 (18.7)	129 (30.7)	368 (30.2)	1,615 (28.0)	2,187 (25.4)
Rifampicin resistant	40 (23.4)	61 (14.5)	110 (9.0)	170 (2.9)	163 (1.9)
Rifampicin indeterminate	1 (0.6)	3 (0.7)	2 (0.2)	20 (0.3)	29 (0.3)
Invalid	2 (2.1)	7 (1.7)	22 (1.8)	39 (0.7)	19 (0.2)
Error	2 (1.2)	7 (1.7)	10 (0.8)	57 (1.0)	47 (0.5)
No result	0 (0.0)	0 (0.0)	1 (0.1)	13 (0.2)	7 (0.1)

areas, an increase in molecular rapid test use was identified from 2014 to mid 2018. This increase in the molecular rapid test use is estimated to be related to the better and more equitable distribution of the molecular rapid test in eastern Indonesia. In 2014, only three (13.6%) out of 22 hospitals in eastern Indonesia used the molecular rapid test. Then in 2015 the number of hospitals using molecular rapid test to diagnose TB has increased to five times (22.7%), and in 2016, it reached seven times (31.8%). The coverage of bacteriologically confirmed TB cases with molecular rapid test is targeted to reach 75% in 2024 (MOH RI, 2020b). In 2017-2018, all the hospitals in the study area have used the molecular rapid test to diagnose TB. The number of patients using the molecular rapid test method to diagnose TB is increasing every year in eastern Indonesia. The highest increase occurred in 2017, about 4 times when compared to 2016. However, the highest number of patients using molecular rapid test to diagnose tuberculosis in 2018. The increase in the use of molecular rapid test method in health facilities in Eastern Indonesia is one of the efforts towards eliminating TB in 2030 (MOH RI, 2020b). However, there was no significant increase in the utilization of the molecular rapid test for diagnosing TB from 2017 to 2018 because the data were collected only until July 2018. The significant increase in the use of the molecular rapid test in 2017 was related to the issuance of Ministry of Health Regulation No. 67 of 2016, concerning tuberculosis prevention (MOH RI, 2016). In addition, the molecular rapid test method with X-pert MTB/RIF is superior to microscopic examination due to its higher sensitivity in diagnosing sensitive and resistant rifampicin and can also examine non-sputum specimens (Simarmata and Lolong 2020).

Patients who received the molecular rapid test in several hospitals in east Indonesia were mostly male, with a mean age ranging from 15 to 54 years. This condition is similar to a study conducted in Cipto Mangunkusumo Hospital and Persahabatan Hospital in Jakarta, where there were more male than female patients receiving the molecular rapid test (Afriliyantina *et al*, 2015). Most TB cases affect more male than female patients. The result of

Rukmini and Chatarina (2011) showed that the risk of getting TB is 1.6 times higher for male than female. The results of the Tuberculosis Prevalence Survey in Indonesia showed that the prevalence of TB in males was three times higher than in females (Lolong *et al*, 2015). The higher prevalence of TB in males is because males are more exposed to TB risk factors such as smoking and lack of drug adherence.

In this study, the molecular rapid test to diagnose TB is mostly used in patients aged 15-54 years (63.3%) while Pangaribuan *et al* (2020) reported that approximately 75% of patients with pulmonary TB were at the most economically productive age 15-49 years. Pulmonary tuberculosis affects almost all age groups in Indonesia and can be harmful to the community, especially in the productive age (15-49 years), because sufferers can become a burden on the family and have an impact on the family economy (Nurjana, 2015).

According to study results, most of the patients having the molecular rapid test came from internal health facilities referrals from 2014 to 2018. The remaining cases came from public health centers, other hospitals, and general practitioner clinics. Internal health facilities are parts of the hospital which include a pulmonary polyclinic, internal medicine, children's, and emergency departments. Therefore, most cases came from pulmonary polyclinics compared to others. The flow of patients referred for the molecular rapid test examination to a hospital that comes from a public health center or other hospital or clinic or general practitioner clinics usually has to go through the registration section before going to the pulmonary polyclinic. Then, the doctors assigned at the pulmonary polyclinic have the decision to recommend whether the patient should have the molecular rapid test or not. According to study results, hospital TB patients referred for the molecular rapid test who originally come from the public health center were only above 20%, except in 2014 (11%). The percentage of patients in respective hospitals who had the molecular rapid test and were referred from other hospitals has fluctuated. On the other hand, the number of patients referred from public health center

has decreased from 2014 to 2018 due to the TB treatment policy with the directly observed treatment short course (DOTS) program, which is mostly located at public health center. The DOTS strategy focuses on five main points of action. These include government commitment to control TB, diagnosis based on sputum-smear microscopy tests done on patients who actively report TB symptoms, direct observation short-course chemotherapy treatments, a definite supply of drugs, and standardized reporting and recording of cases and treatment outcomes (Gabriel and Mercedo, 2011). Usually, when a TB suspect or patient is found in general practitioner clinics, they are directly referred to a public health center or regional general hospital. According to result of another study, most of the patients referred to have molecular rapid test at the Sorong Hospital came from internal health facilities/hospitals (Kristina *et al*, 2020). Some patients' identities are unknown; this shows the lack of neat recording and reporting in hospitals. Recording and reporting can make it easier for officers to monitor TB cases or treatment (Setyowati and Prasetya, 2020).

Our study has several limitations, including the fact that some of the data in the medical records is incomplete, so there are patients whose identities are unknown because of the source of the referral.

Most TB patients were new cases, and only 22.6% were recurrent cases. Every year (2014-2018), an average of almost 70% of those having the molecular rapid test were new treatment cases. Specifically, in 2016, the number of patients with recurrent cases who had the molecular rapid test examinations was quite high (46.3%); this was due to a steep increase in TB drug resistance examinations that year (40.6%). Drug-resistant TB patients are people who have TB symptoms with one or more treatment histories or who meet the nine criteria in the technical guidelines for the management of drug-resistant tuberculosis in Indonesia (MOH RI, 2020a). The molecular rapid test method can detect *Mycobacterium tuberculosis* and rifampicin resistance in two hours (MOH RI, 2017).

The types of specimens examined by the molecular rapid test method in the study area of the east Indonesia region were mainly sputum (99.87%); the others were pleural fluid, gastric lavage, cerebrospinal fluid (CSF), and feces. This is according to the technical guidelines for using the molecular rapid test. In addition to sputum, other specimens that can be examined with the molecular rapid test consist of cerebrospinal fluid (CSF), biopsy tissue, gastric lavage, and gastric aspirate. Moreover, another study stated that the molecular rapid test specimens were bronchial or bronchoalveolar lavages (BAL) used to diagnose TB; the sensitivity was 81.6% and the specificity was 100% (Lee *et al*, 2013)

During 2014 to mid 2018, the average goal of the molecular rapid test patients was to diagnose drug-sensitive TB, with the remainder being to examine drug-resistant TB (DR-TB), HIV-TB, and DM-TB. The number of TB-positive patients increases every year, both for rifampicin-sensitive and rifampicin-resistant TB. The utilization of molecular rapid test for DM-TB examination began in 2017, and the number was very small at around 0.75%.

The results of other studies at the Wangaya Hospital reveal that the molecular rapid test was mostly used for the examination of new pulmonary TB cases and drug-sensitive cases (Novianti *et al*, 2020). The other study found the molecular rapid test was used for HIV and TB drug resistance testing (Zheng *et al*, 2017) the molecular rapid test with gene X-pert in health facilities was initially aimed at diagnosing drug-resistant TB. However, since the issuance of Ministry of Health Regulation Number 67 in 2016, the molecular rapid test can be used to diagnose new pulmonary TB, TB-HIV, and TB-DM (MOH RI, 2016).

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published by Ministry of Health Republic of Indonesia (MOH RI, 2017). In addition to sputum, other specimens that can be examined with the molecular rapid test consist of cerebrospinal fluid (CSF), biopsy tissue, gastric lavage, and gastric aspirate. Moreover, another study stated that the molecular rapid test specimens were bronchial or bronchoalveolar lavages (BAL) used to diagnose TB; the sensitivity was 81.6% and the specificity was 100% (Lee *et al*, 2013).

The percentage of rifampicin-sensitive molecular rapid test increased year after year. This is inversely proportional to the results of rifampicin-resistant the molecular rapid test where the percentage decreases every year. This means that there should be an adjustment made to the World Health Organization's (WHO) and the government's policies. MOH RI (2017) referred to WHO's recommendation (WHO, 2014) in using the molecular rapid test as an initial examination for the diagnosis of drug-resistant TB and HIV patients. Furthermore, the use of the molecular rapid test for TB is regulated through the Minister of Health Regulations No. 67 of 2016 (MOH RI, 2016) concerning TB control and the national action plan for TB control through strengthening TB laboratories. The molecular rapid test can be used in healthcare facilities to diagnose drug-sensitive TB rather than resistant TB.

The molecular rapid test results were still 0.6% invalid and 0.75% incorrect from 2014 to 2018. If the molecular rapid test result is invalid, it means that *Mycobacterium tuberculosis* DNA is not detected and the presence of *Mycobacterium tuberculosis*. *Mycobacterium tuberculosis* DNA cannot be determined because of several factors; among them, statistical process control (SPC) curve does not show an increase in the number of the amplicons, the sampling process is not correct, and polymerase chain reaction (PCR) reaction is hampered. The molecular rapid test error results indicate the presence of *Mycobacterium tuberculosis* DNA cannot be determined, the internal quality control fails, or a system failure occurs. If the results of the molecular rapid test are incorrect and invalid, a repeat inspection must be carried out, and this requires the addition of a new cartridge. An increase in the use of cartridges

can lead to an increased the molecular rapid test check fee (MOH RI, 2017).

In summary, there has been an increase in the use of the molecular rapid test to diagnose tuberculosis in 22 hospitals in the East Indonesia Region every year from 2014 to mid 2018. Most of the patients having the molecular rapid test were referred from internal health facilities, with the smallest number coming from general practitioner clinics. The molecular rapid test method is mostly to be diagnosed drug-sensitive TB.

ACKNOWLEDGMENTS

This study was supported by the Ministry of Health, Research and Development Center of Public Health Efforts.

CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

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