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Performance of Xpert® MTB/RIF in Detecting Multidrug-Resistance Tuberculosis in West Java, Indonesia

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Abstract

Indonesia is the 2nd country with the highest tuberculosis (TB) caseload in the world. Inappropriate TB treatment may lead to multidrug-resistance tuberculosis (MDR-TB) development. Tuberculosis rapid detection is important, and very much needed, to prevent transmission and deaths due to this disease. The Xpert® MTB/RIF is proposed to address this problem. This study aimed to assess the performance of the Xpert® MTB/RIF test in West Java, Indonesia. This was a cross-sectional study conducted on MDR-TB suspects referred to Dr. Hasan Sadikin General Hospital Bandung, West Java, Indonesia, using data from the eTB Manager. The performance of Xpert® MTB/RIF testing and its validity was tested against conventional drug susceptibility testing (DST). In total, data from 4,452 MDR-TB suspects were retrieved but only 578 data that had both DST and Xpert® MTB/RIF results were included in the study. The Xpert® MTB/RIF showed a sensitivity of 88% (95%CI: 85%-91%), specificity of 66% (95%CI: 60%-72%), positive predictive value of 79% (95%CI: 75%-83%), and negative predictive value of 80% (95%CI: 74%-85%), with a detection accuracy of 79%. Xpert® MTB/RIF test in this study shows a good performance for the diagnosis of MDR-TB when compared to the Mycobacterium tuberculosis culture as the gold standard. Therefore, rapid Xpert® MTB/RIF examination is recommended for MDR-TB screening for countries with a high TB burden as a complementary tool to the reference standard test.

Key words: MDR-TB, Sensitivity, Specificity, Xpert® MTB/RIF

Performa Xpert® MTB/RIF Dalam Mendeteksi Tuberculosis Resisten Obat di Jawa Barat, Indonesia

Abstrak

Indonesia adalah negara urutan ke-2 dengan jumlah kasus tuberkulosis (TB) tertinggi di dunia. Pengobatan TB yang tidak sesuai dapat mengakibatkan kuman TB menjadi resisten terhadap obat TB yang disebut TB *multidrug-resistances* (TB-MDR). Untuk itu diperlukan alat deteksi yang mumpuni sehingga kuman TB-DR dapat segera didiagnosis dan diberikan pengobatan yang tepat; dengan demikian pencegahan dan kematian akibat TB dapat ditekan. Penelitian ini bertujuan mengukur performa mesin Xpert® MTB/RIF dalam mendeteksi kuman TB-MDR di Jawa Barat, Indonesia. Studi potong lintang dilakukan dengan mengambil data dari 4452 pasien terduga TB-MDR yang terregistrasi di eTB Manager selama tahun 2012–2016 yang dikirim ke Rumah Sakit Dr. Hasan Sadikin Bandung. Walaupun demikian, hanya 578 yang memiliki hasil test kultur untuk mengetahui sensitivitas obat TB. Dari kedua test tersebut, didapatkan Xpert® MTB/RIF memiliki sensitivitas 88% (95% IK: 85%–91%), spesifisitas 66% (95% IK: 60%–72%), *positive predictive value* 79% (95% IK: 75%-83%), dan *negative predictive value* 80% (95% IK: 74%-85%), dengan akurasi 79%. Test TB-MDR menggunakan Xpert® MTB/RIF pada penelitian ini menunjukkan performa yang baik sehingga test ini sangat direkomendasikan untuk deteksi TB-MDR yang cepat, utamanya di daerah dengan prevalensi TB yang tinggi.

Kata kunci: MDR-TB, Sensitivitas, Spesifisitas, Xpert® MTB/RIF

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Introduction

Based on the Global Tuberculosis Report 2019, Indonesia is categorized as a country with the second-highest burden of tuberculosis (TB) in the world.[1] The National Health Research Data has reported that West Java is the province with the highest TB prevalence in Indonesia;[2] however, only 56.2% of TB patients have been treated with anti-TB drugs, including isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB), and streptomycin (STR) that are given as a directly observed treatment short-course (DOTS) program in two treatment phases.[3]

It is a well-known fact that inappropriate TB treatment may lead to multidrug-resistance tuberculosis (MDR-TB) due to the failure elimination of the bacteria, leading to resistant or mutant development.[4] The mutant bacteria acquire resistance that is transmitted into other hosts via air-droplet nuclei and further infect the new host with primary resistance.[5] MDR-TB is defined as resistance to at least two anti-TB drugs, especially INH and RIF. Around 12% of the new MDR-TB cases in Indonesia are caused by inappropriate TB treatment.[1] Because MDR-TB has a high mortality rate, rapid diagnosis is needed to reduce transmission and to increase the treatment success rate.[6]

Various methods have been applied for MDR-TB detection including, among others, conventional culture methods, phenotype methods, and genotype molecular methods. The egg-based culture media (Lowenstein-Jensen media) with drug susceptibility test (DST) is used as a gold standard for TB detection, but this method needs 8–12 weeks for completing the diagnosis. To deal with the challenge of the slow detection time of the conventional method, a new method referred to as the Xpert® MTB/RIF (Cepheid, USA) has been introduced in 2004. This method applies the real-time polymerase chain reaction (RT-PCR) technics and is endorsed by the WHO in 2010.[7]

Indonesia has implemented the rapid Xpert® MTB/RIF detection by joining the TBXpert project. However, data on the Xpert® MTB/RIF detection validity as the new gold standard to complement the conventional method are limited. Therefore, this study aimed to describe the performance and validity of Xpert® MTB/RIF in detecting MDR-TB cases in Indonesia as one of the countries with a high TB burden.

Methods

This was a comparative cross-sectional study on TB diagnostic testing using the Xpert® MTB/RIF (Cepheid, USA) as the index test with the DST culture as the reference test result. This study was conducted in 2017 by reviewing the performance of Xpert® MTB/RIF compared to a conventional method for drug-sensitive test (DST). Data from suspected MDR-TB patients registered in the eTB Manager database from May 2012 until December 2016 were analyzed for their sensitivity, specificity, false-positive, false-negative, and accuracy values.

In brief, suspected MDR-TB patients from various districts and cities throughout West Java Province were referred to Dr. Hasan Sadikin General Hospital Bandung (Figure), in order to confirm the MDR-TB diagnosis, using Xpert® MTB/RIF. Of note, the year 2012 was the first time that Xpert® MTB/RIF was installed in this province. Data of suspected MDR-TB patients registered in eTB was collected, including age, *Ziehl-Neelsen* (ZN) smear result or otherwise fulfilled the definition of risk category of MDR-TB patients by National Guideline for Tuberculosis, Ministry of Health Republic of Indonesia as depicted in Table 1.[3] Only data of suspected MDR-TB patients with complete valid both DST culture and Xpert® MTB/RIF result was included in the analysis. The study protocol was permitted by the Ethical Committee of Dr. Hasan Sadikin General Hospital Bandung and the Faculty of Medicine, Universitas Padjadjaran under registration number of 0117030289 and 713/UN6.C.10/PN/2017, respectively.

Suspected MDR patients were defined according to the Definition of Risk Category of MDR-TB patients in the National Guideline for Tuberculosis, Ministry of Health Republic of Indonesia, as presented in Table 1.[3] Patients were asked to collect two consecutive expectorated morning sputum samples within the same day to be sent to the hospital. In brief, a minimum of 1mL sputum sample was collected in sterile tubes and stored at 2–8^{o}C for a maximum of 3 days. The sample was then divided for three purposes: ZN smear microscopic examination, culture using DST method, and Xpert® MTB/RIF examination.

Smear grading was performed according to the WHO/International Union Against Tuberculosis and Lung Disease. DST culture was performed at the Clinical Microbiology Laboratory of Balai Laboratorium Kesehatan, Bandung, whereas the

Xpert® MTB/RIF examination was conducted at the Clinical Pathology Laboratory, Dr. Hasan Sadikin General Hospital Bandung. Patients' sputum samples were taken to the Laboratory and the DST culture was carried out on Lowenstein-Jensen (LJ) media. The result was expected to be received after 8–12 weeks.

The patient's sputum sample was taken to the Xpert® MTB/RIF laboratory and then thawed and inactivated by adding a sterilizing agent containing NaOH and isopropanol at the ratio of 2:1, followed by incubation for 15 minutes at room temperature. Two milliliters of samples were then transferred into the Xpert® MTB/RIF cartridge. The cartridge was then loaded into the Xpert® MTB/RIF instrument and the result was generated after 2 hours. Results were reported as MTB positive or negative, with semi-quantified bacillary load categorized as high, medium, low, or very low. Results were also categorized into RIF-resistant MTB and RIF-susceptible MTB. The diagnostic tests were conducted by laboratory technicians supervised by a clinical pathologist with experiences in running TB diagnostic tests.

Patient data and the laboratory results were presented in frequency and tables. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of DST, and Xpert® MTB/RIF accuracy-test were then calculated statistically (SPSS version 22; IBM Inc.)

Results

Between May 2012 and December 2016, there were 4,452 suspected MDR-TB patients referred from various places in West Java Province to Dr. Hasan Sadikin General Hospital, which is located in Bandung, the capital city of West Java Province (Figure), consisting of 54.7% male and 45.3% female TB patients with a median age of 43 (range 1–94) and 39 (range 1–90) years old, respectively with most of them (80.1%) were in the productive years (Table 2). HIV examination was not performed in most TB patients. Only 448 patients (10%) were tested for HIV and 8 (1.8%) were positive.

After the dissemination of the Xpert® MTB/RIF examination program in West Java, the

Table 1 Definition of Risk Category of MDR-TB Patients According to the National Guideline for Tuberculosis, Ministry of Health of the Republic of Indonesia[3]

Risk Category	Definition
Chronic TB patient	Patients who are still sputum smear-positive at the end of the first-line TB re-treatment (Category 2)
TB patient with 2nd category treatment which not converted in 3 months of treatment	Patients on first-line TB re-treatment (Category 2) who are tested as smear-positive after 3 months of treatment
TB patient who have a non-standard TB treatment history using quinolone and 2nd line anti-tuberculosis drug injection for at least 1 month	Patients who received any type of TB treatment outside of the national program (example: non-DOTS, private clinic)
TB patients who failed 1st category treatment	Patients who are still sputum smear-positive at the end of the first-line TB treatment (Category 1)
TB patients with 1st category treatment who remain positive after 3 months of treatment	Patients on first-line TB treatment (Category 1) who are tested as smear-positive after 3 months of treatment
Relapse TB patient, categories 1 and 2	Patients whose most recent treatment outcome (Category 1 or 2) was 'cured' or 'treatment completed' and return with symptoms of TB
Returning TB patients after loss to follow-up (negligent treatment/default)	Patients who interrupted any type of TB treatment for 2 or more consecutive months and return with symptoms of TB
Suspected TB patients with a history of close contact with MDR-TB patients	People living in the same household or spending many hours a day in the same indoor living space with an MDR-TB patient and who show symptoms of TB
TB-HIV co-infection patients who do not respond to anti-tuberculosis drug administration	Patients who are tested positive for HIV and TB with diagnostic tests

Table 2 Age distribution among all MDR-TB patients referred for Xpert® MTB/RIF Examination in Dr. Hasan Sadikin General Hospital, Bandung, West Java – Indonesia, 2012–2016

	Male	Female	Total	
	n	n	n	(%)
Age				
≤10	27	43	70	(1.6%)
11–20	99	177	276	(6.2%)
*21–30	404	382	786	(17.7%)
*31–40	537	487	1024	(23%)
*41–50	497	410	907	(20.4%)
*51–60	534	313	847	(19%)
61–70	226	142	368	(8.3%)
>70	111	63	174	(3.9)
Total	2435	2017	4452	(100%)

Note: productive years were defined as between 21–60 years old

Table 3 Distribution of Xpert® MTB/RIF Examination and its Results in 2012–2016 for All MDR TB patients referred to Dr. Hasan Sadikin General Hospital, Bandung, West Java–Indonesia

	Xpert® MTB/RIF		Positive	Negative	Indeterminate
	n	(%)	n (%)	n (%)	n (%)
Total	4452	(100)	2085 (46.8)	2126 (47.8)	241 (5.4)
Year					
2012	55	(1.2)	37 (67.3)	3	15
2013	530	(11.9)	269 (50.7)	225	36
2014	910	(20.4)	387 (42.5)	476	47
2015	1544	(34.7)	745 48.2)	740	59
2016	1413	(31.7)	647 (45.7)	682	84
Suspected MDR-TB Criteria†					
1	303	(6.8)	195	91	17
2	213	(4.8)	152	51	10
3	45	(1.0)	30	11	4
4	547	(12.3)	297	215	35
5	563	(12.6)	399	140	24
*6	1994	(44.8)	653	1233	108
7	649	(14.6)	338	282	29
8	100	(2.2)	11	81	8
9	38	(0.9)	10	22	6

Note: * the most criterion of suspected MDR TB patients referred for Xpert® MTB/RIF examination. †Suspected MDR-TB Criteria according to the Ministry of Health of the Republic of Indonesia

Table 4 Distribution of Drug Sensitivity Test among MDR-TB patients referred to Dr. Hasan Sadikin General Hospital Bandung, West Java, Indonesia in 2012–2016

Result	n (%) n=578
Positive	
Monoresistance RIF	36 (6.2)
Monoresistance INH	46 (8.0)
MDR-TB	339 (58.7)
Negative	157 (27.2)

number of suspected MDR-TB patients referred to the hospital increased (Table 3); however, the result of Xpert® MTB/RIF examination revealed positive results in only 2,085 (46.8%) suspected MDR-TB patients (Table 3). Interestingly, most of the criteria used for referring patients to the hospital were in category 6, designated as relapsed TB patients (categories 1 and 2). These patients had been declared as being cured or had completed treatment; however, they returned to the primary health care with symptoms of TB. Interestingly, of those patients in category 6 (n=1,994), only (32.7%) (653 of 1,994) had a positive result on Xpert® MTB/RIF examination.

After retrieving data on both DST and Xpert® MTB/RIF examination, only 578 patients data were analyzed and further assessed for its validity. As for the DST result, only a few had monoresistance to INH or RIF with a predominant double-resistance to RIF and INH (58.7%, n=339) as shown in Table 4. As for the Xpert® MTB/RIF results, 65.6% (n =379) were detected to have RIF-resistant MTB. The distribution of Xpert® MTB/RIF and DST results among MDR-TB patients are presented in Table 5. The sensitivity and specificity of Xpert® MTB/RIF to detect MDR-TB were 88% (95% CI, 85-91%) and 66% (95% CI, 60%-72%), respectively, with positive and negative predictive values of 79% (95% CI, 75%-83%) and 80% (95% CI, 74%-85%), respectively. The accuracy of Xpert® MTB/RIF to detect MDR-TB was 79% (Table 5).

Discussion

Rapid and accurate diagnosis of pulmonary TB remains a big challenge in a country with a high burden of TB, including in Indonesia as a country that experiences an increase of prevalence. In

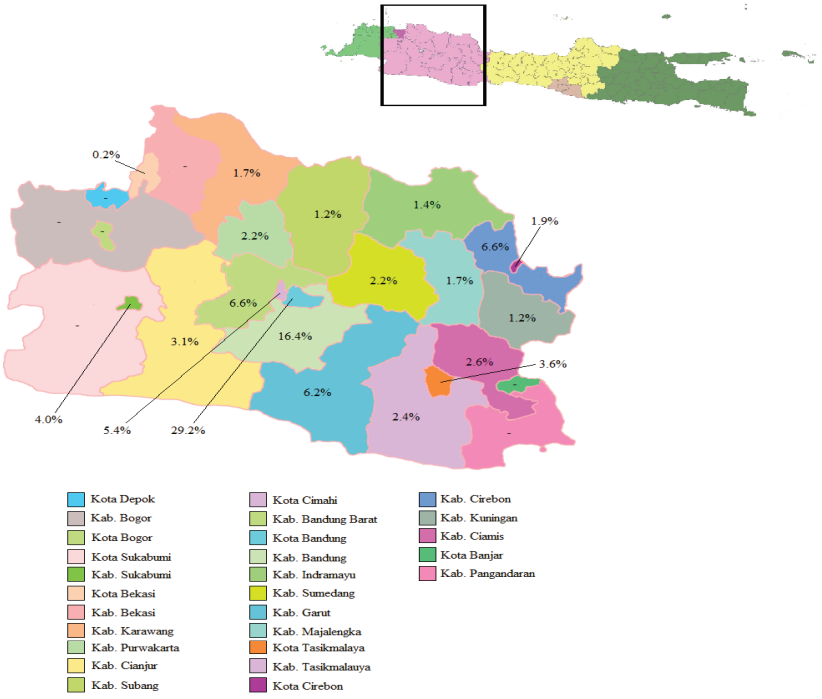

Figure Distribution of MDR TB Patients from Various Regions in West Java, Indonesia

Table 5 Distribution of Xpert® MTB/RIF and DST Results among MDR-TB Patients from Dr. Hasan Sadikin General Hospital Bandung, Indonesia, 2012–2016

MDR-TB (+)		DST		
		MDR-TB (-) (n=339)	Total (n=239)	(n=578)
Xpert® MTB/RIF	MDR-TB (+)	300	79	379
	MDR-TB (-)	39	160	199

Note: drug sensitivity test (DST)

2015, Indonesia was ranked 2nd among countries with the highest prevalence for TB, after previously ranked 5th among countries with the highest TB burden.[1] This study is a follow-up study assessing the performance of the Xpert® MTB/RIF examination with a larger sample size and a longer period. The first study was conducted for two years to explore the performance of the Xpert® MTB/RIF machines after the installation in West Java. The introduction of this machine has increased referral for patients who fail on second-line treatment, as well as to initiate earlier TB treatment because the conventional culture and DST require a longer time for diagnosis.[8] Furthermore, the performance of the Xpert® MTB/RIF examination has been proven to increase the diagnostic value in HIV patients.[9] Some T patients in this study experienced relapse due to possible ineffectiveness of Tb detection (n=173; 29.9%). This ineffectiveness may lead to TB therapy failure and resistant MTB development.[10] Furthermore, the false-negative result in the Xpert® MTB/RIF examination in this study (6%) is probably due to mutation in MTB that might occur in more than 5% of MTB outside the *rpoB* gene hotspot.[11] Further study is needed to confirm the possible mutations in resistant MTB. Interestingly, there are some false-positive results, which accounted for almost 15%, and this phenomenon might be due to delayed attachment of probes to the bacterial DNA site.[11] Another possibility is that this might be due to the detection of genotypic mutation of *rpoB* gene MTB strain as RIF resistant but phenotypically has not been detected. The mutation on *the rpoB* gene hotspot at a bacterial DNA site is detected using probes.[11] This *rpoB* gene, which generates RIF-resistant isolates, plays the role of a surrogate marker for MDR-TB because almost 90% of RIF-resistant isolates also exhibit resistance to INH.[12]

A metanalysis study has clearly shown that the Xpert® MTB/RIF has a relatively high sensitivity.[13] The machine may be a good diagnostic tool for ruling out TB disease in a large number of patients due to its high sensitivity (95.7%).[14] Moreover, 100% sensitivity has been shown in a study on both pulmonary and extra-pulmonary samples.[15] Such a rule-out sensitivity strategy enables primary care doctors to exclude a large proportion of patients suspected as suffering from MDR-TB, thereby reducing cost and patient burden, as well as speeding up treatment initiation.

In terms of the specificity of Xpert® MTB/RIF, this present study suggested a relatively low specificity compared to the specificity identified in a study in 5 countries, i.e. Peru, Azerbaijan, South Africa, and India, with a specificity that ranges from 97.1% to 100%. However, results from Tanzania presented a lower specificity than the one in this study for Xpert® MTB/RIF.[16] Therefore, the use of Xpert® MTB/RIF as a biomarker for monitoring TB treatment is crucial but should not replace the conventional method in ruling out TB or MDR-TB. For example, a study in Indonesia has shown a high sensitivity (89-93%) and specificity (81-92%), suggesting that the Xpert® MTB/RIF could be used as a diagnostic tool for ruling out TB or MDR-TB in Indonesia as one of the countries with a high TB burden.8 An effective TB treatment requires an accurate and early diagnosis as well as screening for drug resistance and HIV, which should be done with a low testing cost per sample.[17] Thus, new TB cases can directly benefit from the use of this Xpert® MTB/RIF examination.

Earlier diagnosis of pulmonary TB using Xpert MTB/RIF examination will lead to earlier and appropriate treatment. This examination can be used not only for sputum samples but also for urine and stool samples with high validity.[18,19] Thus, it provides opportunities to prevent TB transmission by providing some hospitals with Xpert® MTB/RIF to reach remote areas with high TB prevalence and dense population, making this a highly recommended approach. The Xpert® MTB/RIF examination

can serve as a new tool for rapid multi-drug resistance detection.[20]

The Xpert MTB/RIF examination is implemented to shorten the diagnosis time, which will enable early initiation of MDR-TB treatment. However, one should bear in mind that false positivity might be seen in Xpert MTB/RIF examinations. Since the Xpert MTB/RIF examination is a molecular test, unviable bacilli in sputum that might arise during sputum decontamination or delay in transportation and inoculation can be detected as positive as described in previous study.[8]

This study carries some limitations; not all patients have completed a standard test result in the database. Better integration of data management from different laboratories is highly needed, using a new technology in the digital era. Furthermore, as explained above, the Xpert MTB/RIF examination only detect rifampicin resistance while DST can detect other drug resistance also. Recently, several new molecular tests are introduced as diagnostic tools, including the *line probe assay* (LPA) that can detect more drug resistance such as isoniazid, rifampicin, fluoroquinolone, and any other second-line drug resistance. Further studies to compare the Xpert MTB/RIF examination with other molecular tests might be of great benefit as an effort to further explore drug resistance in a population. An accuracy of 79% is relatively high, considering that the Xpert MTB/RIF examination is a new tool at the time of the study. It is necessary to evaluate the Xpert MTB/RIF examination in a later period. In conclusion, Xpert® MTB/RIF examination has a satisfactory diagnostic performance for MDR-TB compared to culture as a gold standard due to its relatively high sensitivity and accuracy. Xpert® MTB/RIF examination is thus recommended for MDR-TB screening as a complement to the reference standard test, with confirmation using culture and DST. This could improve the affordability, rapidity, and precision of TB or MDR-TB detection for people in need, as well as adding to the data for further research.

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