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by Ayunda Imaniar

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Comparison between the PaxView TB/NTM MPCR-ULFA Kit and Xpert MTB/RIF for *Mycobacterium Tuberculosis* Detection in Indonesian Clinical Isolates

Ayunda Imaniar¹, Ucy Nadjmiyah¹, Munawaroh Fitriah², Soedarsono Soedarsono³, Aryati Aryati²

¹Resident, ²Lecturer, Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, ³Lecturer, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Abstract

The PaxView TB/NTM MPCR-ULFA Kit, which targets the IS6110 and mtp40 genes for *Mycobacterium tuberculosis* (MTB) detection, is a novel tool that substitutes gel electrophoresis for universal lateral flow assays. The sensitivity and specificity of this method were compared with those of established methodologies using Indonesian clinical isolates. In this study, 317 sputum specimens isolated from tuberculosis (TB) suspects were examined to evaluate the performance of the PaxView TB/NTM MPCR-ULFA Kit compared to that of smear microscopy and the Xpert MTB/RIF assay. Out of 317 cases, the rate of TB-positive samples evaluated by different methods was 33.4% (106/317; 95% CI 28.2-38.6) for smear microscopy, 37.9% (120/317; 95% CI 32.5-43.2) for the Xpert MTB/RIF, and 40.7% (129/317; 95% CI 35.3-46.1) for the PaxView TB/NTM MPCR-ULFA Kit. Compared to the Xpert MTB/RIF as a standard reference, the PaxView TB/NTM MPCR-ULFA Kit was found to possess a 92.5% sensitivity (111/120; 95% CI 87.8-97.2), a 90.8% specificity (179/197; 95% CI 86.8-94.8), 86.0% PPV (111/129; 95% CI 80.0-92.0), and a NPV 95.2% (179/188; 95% CI 92.2-98.3). The PaxView TB/NTM MPCR-ULFA Kit could be a useful molecular diagnostic tool to identify MTB in clinical samples in resource-limited countries, as this procedure is more cost-effective and sensitive than the Xpert MTB/RIF, and more convenient than conventional PCR gel electrophoresis approaches.

Keywords: *Mycobacterium tuberculosis*, multi-plex PCR, universal flow lateral assay, Xpert MTB/RIF, smear microscopy

Introduction

To this day, tuberculosis (TB) continues to be a major chronic infectious disease worldwide. According to the 2019 Global TB Report, the WHO estimated that 1.4 million people died due to TB and 10.0 million people developed TB worldwide in 2019. The current estimated tuberculosis incidence in Indonesia is 845,000, which ranks second globally, only surpassed by India. In Indonesia, notifications of people newly diagnosed with TB rose from 331,703 in 2015 to 562,049 in 2019.

However, there is still a large global gap between the estimated number of incident cases and the number of people newly diagnosed (7.1 million in 2019), due to underreporting of detected cases and underdiagnosis, and Indonesia accounted for 10% of the global gap. It has been estimated that 96,700 people died from tuberculosis in 2019 in Indonesia¹. Most deaths from TB could be prevented with early diagnosis and appropriate treatment^{2,3}, and therefore early TB diagnosis is essential to reduce its worldwide lethality.

There are many kinds of TB diagnostic tools, from the smear microscopy (SM) approach developed by Robert Koch in 1882 to modern sophisticated approaches including Xpert MTB/RIF (Cepheid, CA, USA). Smear microscopy has become the main method for diagnosing

Corresponding author:

Aryati

dr_aryati@yahoo.com

pulmonary TB in low- and middle-income countries. The procedure is simple, fast and inexpensive and very specific in areas with a very high prevalence of TB. The main drawback of SM is its limited sensitivity when the bacterial load is less than 10,000 organisms/mL^{4,5}.

Among the various existing TB diagnostic tools, molecular diagnostic tools are the fastest methods for the detection of *Mycobacterium tuberculosis* (MTB) in clinical specimens, and also possess satisfactory sensitivity and specificity⁶. The development of the Xpert[®] MTB/RIF assay (Cepheid, Sunnyvale, USA), which was endorsed by WHO in 2010, was a major step forward in improving the diagnosis of TB and rifampicin-resistant TB (RR-TB) globally. Compared with the reference standard of culture, however, it still had suboptimal sensitivity (particularly among people with smear-negative TB and people living with HIV) and specificity¹. And due to the expensive equipment, cartridges, and installation costs required by the Xpert MTB/RIF approach, this testing solution is not suitable for implementation in developing countries or in private sector unless international monetary aid is provided^{7,8}.

In house-PCR is the cheapest molecular diagnostic method, but requires cumbersome gel electrophoresis procedures. Therefore, PaxGenBio (Korea) developed the PaxView TB/NTM MPCR-ULFA Kit, which rapidly detects MTB without the need for gel electrophoresis after polymerase chain reactions (PCRs). Moreover, this procedure can be used with a conventional PCR instrument without the need for a specific expensive PCR device. Therefore, this study aims to evaluate the potential clinical applicability of the PaxView TB/NTM MPCR-ULFA Kit for the detection of MTB in clinical samples by comparing its performance with that of the Xpert MTB/RIF and SM, both of which have been extensively implemented worldwide.

Methods

Specimens

In this study, we utilized sputum specimens from TB suspects, which were acquired from Karang Tembok Hospital and Ibnu Sina Gresik Hospital from July 2019 to March of 2020 in the Surabaya City, East Java, Indonesia.

Ziehl-Neelsen Smear Microscopy

Ziehl-Neelsen direct AFB smear and grading was performed by the technicians from each institute. Briefly, smears are fixed on heated surface (60 °C for at least 10 minutes) and then flooded with carbolfuchsin (primary stain). Smears then are heated to almost boiling and are after the smears were allowed to sit for 5 min, then the slides are washed in distilled water. The slides were then decolorized with 3% HCl in 95% ethanol for approximately 1 minute and washed with water. The methylene blue (counterstain) was then flooded to the slide and allowed to sit for 1 min before the slides being washed with distilled water and let dry upright. The slides were then examined microscopically according to the International Union Against Tuberculosis and Lung Disease (IUATLD) method⁹.

DNA extraction from specimens

After SM, the remaining sputum specimen was treated with Xpert MTB/RIF buffer. After proceeding Xpert MTB/RIF test, the remaining buffer treated sputum were stored in the refrigerator until maximum 20 days before DNA extraction from the TB bacilli for PaxView TB/NTM MPCR-ULFA test. DNA were extracted by the PaxView DNA Extraction Kit (PaxGenBio, Korea). Briefly, 1000 µl of the specimen pretreated with the Xpert MTB/RIF buffer was transferred into 1.5 ml screw capped tubes and then centrifuged at 13,000 rpm for 3 min. After the supernatant was discarded, 1000 µl of washing buffer were added (provided by the PaxView DNA Extraction Kit). This mixture was then centrifuged again at 13,000 rpm for 3 min, after that the supernatant was discarded. After washing the specimen once more, 100 µl of elution buffer were added into the tube, which was then transferred to a 95 °C heating block for 15 min. After centrifugation, 20 µl of supernatant were transferred into a new tube and used as a template.

Xpert MTB/RIF

Pretreated specimen was amplified with the GeneXpert kit following the manufacturer's instructions.

¹⁹ PaxView TB/NTM MPCR-ULFA Kit PCR and interpretation of the results

¹⁹ The PaxView TB/NTM MPCR-ULFA Kit includes multiple primer pairs, including two for MTB-specific

genes (IS6110 and mpt40), as well as for the mycobacteria rpoB gene. After multiplex PCR, the product identities were confirmed by universal lateral flow assay (ULFA), which is based on DNA-DNA hybridization with previously immobilized complementary DNA fragments on a nitrocellulose membrane. PCRs were performed with the following protocol: 50 °C for 4 min; 95 °C for 10 min; 25 cycles of denaturation (95 °C for 15 sec), annealing and extension (71 °C for 60 sec); 20 cycles of denaturation (95 °C for 15 sec), annealing (60 °C for 30 sec), and extension (72 °C for 30 sec).

After PCR amplification, 5 µl of PCR solution were added to the ULFA device inlet, after which 50 µl of running buffer (provided by the manufacturer) were added immediately. After 5 minutes, 50 µl of washing buffer were added into the inlet and the results were then read within 15 minutes.

Statistical Analysis

Demographic data were presented in mean±SD and percentages. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PaxView TB/NTM MPCR-ULFA Kit were compared to Xpert MTB/Rif as a reference standard using contingency tables 2×2.

Results

A total of 317 clinical specimens were compared the performances of the PaxView TB/NTM MPCR-ULFA Kit, SM, and the Xpert MTB/RIF. Demographic data was shown in Table 1. Out of 317 cases, the rate of TB-positive samples evaluated by different methods was 33.4% (106/317; 95% CI 28.2-38.6) for smear microscopy, 37.9% (120/317; 95% CI 32.5-43.2) for the Xpert MTB/RIF, and 40.7% (129/317; 95% CI 35.3-46.1) for the PaxView TB/NTM MPCR-ULFA Kit.

Table 1. Demographic Data of Study Participant.

Characteristic	Total (n=317)	%
Male	227	71.6%
Female	90	28.39%
Age (year)	Mean 48.19±14.59	

Compared to the Xpert MTB/RIF as a standard reference, the PaxView TB/NTM MPCR-ULFA Kit was found to possess a 92.5% sensitivity (111/120; 95% CI 87.8-97.2), a 90.8% specificity (179/197; 95% CI 86.8-94.8), 86.0% PPV (111/129; 95% CI 80.0-92.0), and a NPV 95.2% (179/188; 95% CI 92.2-98.3) (Table 2)

Table 2. Performance of Pax View MPCR ULFA Compared with Xpert MTB/Rif as Reference Standard.

SM	Xpert MTB/Rif Positive		Xpert MTB/Rif Negative		Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
	MPCR Positive	MPCR Negative	MPCR Positive	MPCR Negative				
Positive	96	3	7	0	92.5% (87.8 – 97.2)	90.8% (86.8 – 94.8)	86% (80.0 – 92.0)	95.2% (92.2 – 98.3)
Negative	15	6	11	179				
Total	111	9	18	179				

Nine samples (7.5%) of 120 Xpert MTB/RIF positive were PaxView TB/NTM MPCR-ULFA negative, and 3 (33.3%) of them were even SM positive. On the contrary, 18 samples (13.9%) of 129 PaxView MPCR-ULFA positive cases were Xpert MTB/RIF negative, and 7 (38.9%) of them were even SM positive. Compared to the Xpert MTB/RIF, the PaxView TB/NTM MPCR-ULFA Kit was found to possess a 92.5% sensitivity (111/120; 95% CI 88.4-97.4), a 94.2% specificity (179/197; 95% CI 90.9-97.5), a 91.5% PPV (111/129; 95% CI 86.6-96.3), and an NPV 95.2% (179/188; 95% CI 92.2-98.3) (Table 2).

Discussion

In this study, the TB detection rate of the Xpert MTB.RIF was 1.13 times (37.9%/33.4%) higher than that of SM, which is only a slight difference compared the 1.75-fold (84%/48%) in a study in Thailand¹⁰, and 1.8-fold (65.5%/36.2%) in Ethiopia¹¹. Generally, SM positive rates may vary depending on specimen quality, technician skill, and the number of samples treated in a day.

The PaxView TB/NTM MPCR-ULFA Kit showed a higher detection rate of MTB (40.7 percent) than that of the Xpert MTB/RIF (37.9 percent). In the study of another group on the detection of meningitis TB in India, the MPCR sensitivity was 1.7 times higher (87.2 percent /50.5 percent) than that of the Xpert MTB/RIF and 1.2 times higher (100 percent /82.9 percent) for pulmonary detection^{12,13}. This may have been due to target gene differences, as the former is IS6110-specific while the latter is rpoB-specific. Generally, IS6110 has higher copy numbers than the rpoB gene, which only has one copy.

The challenge of using PCR based method for mycobacteria detection in clinical samples (especially sputum) is the extraction of nucleic acids from the samples, since they contain a unique lipid rich cell wall and rather difficult to lyse¹⁴. Three samples (2,5%) of 120 Xpert MTB/RIF positive were PaxView TB/NTM MPCR-ULFA negative and smear microscopy positive. This may have been caused by DNA loss during the DNA extraction step, as several manual washing steps are required for DNA purification.

The PaxView TB/NTM MPCR-ULFA Kit incorporates multiplex PCR and universal lateral flow assay (ULFA) and uses the IS6110 and mtp40 genes for TB detection. The IS6110 gene was widely known for its better sensitivity in diagnosing both pulmonary and extra-pulmonary TB, due to its multiple copies in the genome of the MTB complex¹⁶. MTB was detected more often by IS6110 PCR method than by smear microscopy and culture techniques among clinically diagnosed child TB patients¹⁷. The MTP40 gene is exclusively present in MTB, i.e., not in *M. bovis*, *M. bovis* BCG, or NTM¹⁸. The addition of the use of the MTP40 gene together with IS6110 has been shown to increase sensitivity¹⁹. But we did not analyze the sensitivity of each gene in this study. There were 11 samples out of 197 Xpert MTB/Rif negative were PaxView TB/NTM MPCR-ULFA positive and smear microscopy negative. This indicated that the use of the IS6110 and MTP40 genes in PaxView results in better sensitivity than the use of single rpoB gene.

The newly-developed PaxView TB/NTM MPCR ULFA Kit incorporates multiple polymerase chain reactions and simplifies the result-reading process by implementing ULFA instead of a cumbersome electrophoresis procedure. Another advantage of the PaxView MPCR-ULFA Kit is that it only requires a standard PCR device. In contrast, the implementation of Xpert MTB/RIF requires specialized and expensive equipment.

Although in-house PCR or MPCR targeting IS6110 has satisfactory sensitivity and cost-effectiveness compared to the Xpert MTB/RIF targeting the rpoB gene, in-house PCR has the disadvantages of being time-consuming and requiring a cumbersome gel electrophoresis step. Therefore, the PaxView TB/NTM MPCR-ULFA Kit substitutes the gel electrophoresis step with ULFA for rapid PCR result detection.

Conclusion

In conclusion, the PaxView MPCR ULFA Kit has an excellent capacity for the detection of MTB in clinical specimens, and this kit could be implemented in laboratories with standard PCR equipment, bypassing the need to purchase expensive equipment. Moreover, the results of this kit can be obtained easily and quickly, without the need for unpractical electrophoresis

procedures. Therefore, this approach could be very useful to detect MTB in clinical samples in conventional molecular laboratories in resource-limited countries or private sector.

Conflict of Interest: The author declare that they have no conflict of interest.

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Ethical Approval: This study was approved by the Institutional Review Board of Airlangga University, under the project title "The evaluation of PaxView TB/NTM MPCR-ULFA compare to Xpert MTB/RIF for diagnosis of pulmonary tuberculosis" (Approval number: 164/EC/KEPK/FKUA/2019).

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