

## THE DIAGNOSTIC VALUE OF CONVENTIONAL TUBERCULOSIS DIAGNOSTIC PROCEDURE COMPARED WITH GENE X-PERT MTB/RIF: A CROSS-SECTIONAL STUDY

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### ABSTRACT

**Objectives:** The objectives of the study were to evaluate the diagnostic value of conventional tuberculosis (TB) diagnostic procedure compared with Gene X-pert *Mycobacterium tuberculosis*/rifampicin (MTB/RIF).

**Methods:** A cross-sectional study conducted from January to December 2018. The accuracy of conventional TB diagnostic procedure: TB screening, chest X-ray, and sputum Ziehl-Neelsen (ZN) staining was compared to Gene X-pert MTB/RIF using 2 × 2 table.  $p < 0.05$  were taken as statistically significant. The collected data were processed using Statistical Package for the Social Science software version 26.0.

**Results:** A total of 117 participants suspected TB was found 44 (37.60%) confirmed TB. Among the suspected TB cases, 86 (73.50%) were male and 31 (26.50%) were female with the mean age of  $43.86 \pm 16.47$  years. The sensitivity and specificity of TB screening (prolonged cough) were 84.00% and 12.00%, respectively. Chest X-ray had the sensitivity and specificity (91.00%) and (10.00%). The sensitivity and specificity of sputum ZN were 57.00% and 99.00%.

**Conclusions:** Conventional TB diagnostic procedure has a high accuracy compared with Gene X-pert MTB/RIF. Therefore, it is still recommended as a TB diagnostic procedure routinely in era of Gene X-pert MTB/RIF, especially in Primary Health Care with limited settings.

**Keywords:** Pulmonary tuberculosis, Conventional tuberculosis diagnostic procedures, Gene X-pert *Mycobacterium tuberculosis*/rifampicin.

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### INTRODUCTION

Pulmonary tuberculosis (PTB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) and as a public health problem in the world including in Indonesia [1-4]. Early TB diagnosis followed by adequate treatment is a strategy to prevent morbidity and mortality [2,5]. The conventional TB diagnostic procedure including TB screening, Chest X-ray, and sputum Ziehl-Neelsen (ZN) staining. The World Health Organization (WHO) in the 2011 endorsed Gene X-pert MTB/rifampicin (RIF) assay, as an advanced diagnostic assay using real time polymerase chain reaction technology to simultaneously identify MTB and resistance of RIF. Gene X-pert MTB/RIF assay was compared with the sputum culture as a gold standard and it was reported as a rapid and promising technique with good sensitivity (93%) and specificity (98.3%) [2,6,7].

We evaluated the diagnostic value (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], positive likelihood ratio [LR], and negative LR) of conventional TB diagnostic procedure compared with Gene X-pert MTB/RIF whether conventional TB diagnostic procedure is still feasible. We wish this study results might give suggestion based on evidence especially in Primary Health Care, where there is not the facility for Gene X-pert MTB/RIF assay available.

### METHODS

#### Study design and population

A cross-sectional study enrolled adults ( $\geq 18$ -60 years) visited Merpati Clinic and Pulmonary Department, at Wangaya Hospital in Denpasar, Bali, Indonesia, who had TB signs and symptoms (TB screening). Following TB screening, chest X-ray, and direct smear examination with

ZN staining as a conventional TB diagnostic procedure was compared with Gene X-pert MTB/RIF.

#### Statistical analysis

The specificity, sensitivity, PPV, NPV, LR+, and LR- of conventional TB diagnostic procedure were compared to Gene X-pert MTB/RIF as a reference standard using contingency 2 × 2 tables with  $p < 0.05$  which were taken as statistically significant. The collected data were processed using the Statistical Package for the Social Science software package version 26.0.

The clinical implementation of sensitivity and specificity was important, although it had limitation. The prevalence of disease had a significant impact on the PPV and NPV. Furthermore, a high sensitivity and specificity of a given test, the PPV in a disease with low prevalence was very low.  $LR+ = \text{True positivity rate}/\text{false positivity rate}$ , which was the same as  $\text{sensitivity}/(1-\text{specificity})$  [8,9].

#### Ethical clearance

The study was conducted after approval by the research ethics committee of the Wangaya Hospital in Denpasar, Bali, Indonesia. Register number: 07/RSUDW/Litbang/2018). The participants who conducted in this study were explained and they signed a written informed consent.

### RESULTS

A total of 117 participants were enrolled in this study, 86 (73.50%) were males and 31 (26.50%) were female with mean age of the participants was found to be  $43.86 \pm 16.47$  (years). Various kinds of the TB screening (TB sign and symptoms) were found in this study; prolonged cough ( $\geq 2$  weeks) 104 (88.90%), fever  $> 4$  weeks 77

(65.80%), night sweat 56 (47.90%), weight loss 96 (82.10%), dyspnea 52 (44.40%), and lymphoid gland enlargement 5 (4.30%). A higher proportion of suggestive PTB by Chest X-ray was found 106 (90.60%). Direct smear examination with ZN staining positivity was found to be 26 (22.20%) and Gene X-pert MTB/RIF positivity for MTB remained 26 (22.20%) while 73 (62.48%) were negative on Gene X-pert MTB/RIF. All are describe in Table 1.

TB screening by identifying people at risk for TB infection based on ACHA guidelines (2016). Risks for exposure to and/or infection with MTB and should be tested and if positive, it is high priority for treatment [10].

The comparison between TB screening (a prolonged cough  $\geq 2$  weeks) with Gene X-pert MTB/RIF found that a prolonged cough  $\geq 2$  weeks had a high sensitivity: 84% (Table 2).

The comparison between chest X-ray with Gene X-pert MTB/RIF found that chest X-ray with positivity suggestive TB had a high sensitivity: 91% (Table 3).

**Table 1: Baseline characteristic data of the study participants (n=117)**

Variable	Mean $\pm$ SD/n (%)
Age (years)	
Sex	43.86 $\pm$ 16.47
Male	86 (73.50)
Female	31 (26.50)
Sign and symptoms (TB screening)	
Prolonged cough ( $\geq 2$ weeks)	
Yes	104 (88.90)
No	13(11.10)
Fever >4 weeks	
Yes	77 (65.80)
No	40 (34.20)
Night sweat	
Yes	56 (47.90)
No	61 (52.10)
Weight loss	
Yes	96 (82.10)
No	21 (17.90)
Dyspnea	
Yes	52 (44.40)
No	65 (55.60)
Lymphoid gland enlargement	
Yes	5 (4.30)
No	112 (95.70)
Chest X-ray	
Yes	106 (90.60)
No	11 (9.40)
Direct smear examination with ZN staining	
Positive	26 (22.20)
Negative	91 (77.80)
Gene X-pert MTB/RIF	
Positive	44 (37.60)
Negative	73 (62.48)

TB: Tuberculosis, MTB: *Mycobacterium tuberculosis*, RIF: Rifampicin.  
ZN: Ziehl-Neelsen

**Table 2: Comparison of TB screening (a prolonged cough  $\geq 2$  weeks) with Gene X-pert MTB/RIF (n=117)**

A prolonged cough ( $\geq 2$ weeks)	Gene X-pert MTB/RIF		Total (%)	p-value
	Positive (%)	Negative (%)		
Positive	37 (84.1)	64 (87.7)	101 (86.3)	0.389
Negative	7 (15.9)	9 (12.3)	16 (13.7)	
Total	44 (100.00)	73 (100.00)	117 (100.00)	

Sensitivity: 84%; Specificity: 12%; PPV: 37%; NPV: 56%; LR+: 0.96 (useless); LR-: 1.29 (useless). MTB: *Mycobacterium tuberculosis*, RIF: Rifampicin

The comparison between sputum smear examinations with ZN staining with Gene X-pert MTB/RIF found that sputum smear examination with ZN staining had a high specificity: 99% (Table 4).

The performance of conventional TB diagnostic procedure, a combination of TB screening (a prolonged cough  $\geq 2$  weeks), chest X-ray, and direct smear examination with ZN staining compared with Gene X-pert MTB/RIF (Table 5).

The conventional TB diagnostic procedure showed high sensitivity and high specificity compared with Gene X-pert (prolonged cough and chest X-ray showed high sensitivity and direct smear examination with ZN staining showed high specificity).

## DISCUSSION

TB screening does not need expensive equipment or a specialist. The TB screening consists of prolonged cough, fever, night sweat, weight loss, dyspnea, and lymphoid gland enlargement. The WHO recommends systemic TB screening as early case detection and continued by treatment that leads better outcome and decreased TB transmission [11,12].

This study found that TB screening (TB signs and symptoms); 88.90% had a prolonged cough, 65.80% reported fever, 47.90% had night sweat, 82.10% reported weight loss, 44.40% experienced dyspnea, and 4.30% had lymphoid gland enlargement. A prolonged cough was reported as the most frequent with a high sensitivity (84%).

Loren *et al.* (2000), in Los Angeles County, found among participants with positive sputum smear confirmed TB, 52% experienced a cough for more than 2 weeks [12]. Bassett *et al.* (2010) found that the sensitivity of cough merely for the diagnosis of TB was 52% (95% confidence interval [CI] 64–79); the specificity of cough was 63% (95% CI 59–66) [13].

Similarly with the other studies, Shah *et al.* (2011) reported that in the TB screening found cough as a frequent symptom (96%) [14]. Rai *et al.* (2015) found that 89.18% had a cough [15] and Reechaipichitkul *et al.* (2017) also reported that cough as the most frequent symptom (68.0%) [16].

Chest X-ray is a part of conventional TB diagnosis procedure and screening of TB in many developing countries including Indonesia. Chest X-ray when was combined with symptoms, the value of chest

**Table 3: Comparison chest X-ray with Gene X-pert MTB/RIF (n=117)**

Chest X-ray	Gene X-pert MTB/RIF		Total (%)	p-value
	Positive (%)	Negative (%)		
Positive	40 (90.90)	66 (90.40)	106 (90.60)	0.602
Negative	4 (9.10)	7 (9.60)	11 (9.40)	
Total	44 (100.00)	73 (100.00)	117 (100.00)	

Sensitivity: 91%; Specificity: 10%. PPV: 38%. NPV: 64%. LR+: 1.01 (useless); LR-: 0.95 (useless). MTB: *Mycobacterium tuberculosis*, RIF: Rifampicin

**Table 4: Comparison sputum smear examination with ZN staining with Gene X-pert MTB/RIF (n=117)**

Sputum smear examination with ZN staining	Gene X-pert MTB/RIF		Total (%)	p-value
	Positive (%)	Negative (%)		
Positive	25 (56.80)	1 (1.40)	26 (22.20)	0.000*
Negative	19 (43.20)	72 (98.60)	91 (77.80)	
Total	44 (100.00)	73 (100.00)	117 (100.00)	

Sensitivity: 57 %; Specificity: 99%. PPV: 96%; NPV: 79%. LR+: 41.48 (excellent); LR-: 0.44 (Very Good). MTB: *Mycobacterium tuberculosis*, RIF: Rifampicin, ZN: Ziehl-Neelsen

**Table 5: Comparison a prolonged cough, chest X-ray, and sputum smear examination with ZN staining with Gene X-pert MTB/RIF (n=117)**

Diagnostic procedure	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
Prolonged cough	84	12	37	56	0.96	1.29
Chest X-ray	91	10	38	64	1.01	0.95
Direct smear examination with ZN staining	57	99	96	79	41.48	0.44

PPV: Positive predictive value, NPV: Negative predictive value, positive likelihood ratio (LR+); negative likelihood ratio (LR-). MTB: *Mycobacterium tuberculosis*, RIF: Rifampicin, ZN: Ziehl-Neelsen

X-ray for diagnosis increased [17]. The proportion of participants with chest X-ray findings suggestive of PTB was 3 times that using Gene X-pert, the diagnosis of smear negative TB using chest X-ray could be over diagnosis. It can be explained by the fact that other conditions with similar features of TB on chest X-ray [18].

This study found that chest X-ray compared with Gene X-pert showed a high sensitivity (91%) but low specificity (10%).

Cudahy and Sheno (2016) and Ryu (2015) reported that chest X-ray was performed for all of suspects TB whose a negative results of sputum smear ZN. The addition of chest X-ray to symptoms of TB increased sensitivity from 75.0% to 90.1% [19,20]. Vant Hoog *et al.* (2014) found that chest X-ray screening for abnormalities of TB added by Gene X-pert showed the highest case detection (87%). Chest X-ray is good for screening because of high sensitivity; it is not a good for diagnosis since a chest X-ray based clinical diagnosis has low specificity [21]. However, in the other hand, Swindells *et al.* (2013) found that the presence of one of the cardinal symptoms with chest X-ray compatible with TB increased specificity to 84% [22].

Acid fast bacilli is a once tool for diagnosis of TB. The lower load of sputum bacillary often leads to the lower sensitivity. It can also be false negative when the sputum mycobacterium concentration is <10.000 organisms/ml [23]. The simple not expensive and the power prediction of the ZN staining sputum smear microscopy makes it to be practical laboratory diagnostic procedure for TB in facilities limited settings [24]. A TB suspect was confirmed when at least one of the three sputum smears result by ZN staining was positive [25-28].

Ngozika *et al.* (2018), in their study, had identified among 561 patients, 98.2% with smear positive TB [29]. Orina *et al.* (2017) found that smear microscopy revealed low sensitivity (26.4%) and a higher specificity (98.2%) [30]. Agrawal *et al.* (2016) reported that Gene X-pert assay had a sensitivity of 86.8% for PTB, which was superior to that of smear microscopy 36.8% and specificities of Gene X-pert and smear microscopy were 93.1% and 100% [27]. Munir *et al.* (2015) found that ZN smear positivity for acid fast bacilli was 67.5%. Gene X-pert positivity for TB remained 77.4%. Sensitivity (90.1%), specificity (98.3%), NPV (62.6%), and accuracy of Gene X-pert (91.3%) were significantly higher as compared to smear which was sensitivity (77.7%), specificity (91.4%), NPV (40.8%), and accuracy of Gene X-pert (79.7%). PPV were 99.7%, 98.2% for two techniques and there was no significant difference [31]. Bajrami *et al.* (2016) reported that sensitivity, specificity, PPV, and NPV of direct smear sputum microscopy compared with Gene X-pert showed which were 94.1% (95% CI 71.3-99.8); 85.7% (95% CI 77.4-92.1); 53.3% (95% CI 34.3-71.6); 98.8% (95% CI 93.7-99.9) versus 82.3% (95% CI 65.5-93.2); 97.6% (95% CI 91.5-99.7); 93.3% (95% CI 77.9-99.1); and 93.0% (95% CI 85.4-97.4) [32].

Liu *et al.* (2020) found that sensitivity, specificity, PPV, and NPV of direct smear sputum microscopy compared with Gene x-pert showed which were 5.2% (95% CI 1.2-9.3); 85.7% (95% CI 77.4-92.1); 53.3% (95% CI 34.3-71.6); 98.8% (95% CI 93.7-99.9) versus 82.3% (95% CI 65.5-93.2); 97.6% (95% CI 91.5-99.7); 93.3% (95% CI 77.9-99.1); and 93.0% (95% CI 85.4-97.4) [33].

This study found that 22.20% of the participants were with smear positive TB. Direct smear examination with ZN staining compared

with Gene X-pert was showed a high specificity: 99% (the probability of participants with a negative test result in a subjects without disease was 99%); high PPV: 96% (the proportion of participants with cough who had TB was 96%), and positive LR: 41.40 (excellent).

The conventional TB diagnostic procedure compared with Gene X-pert assay showed; prolonged cough (TB screening) was confirm for screening because of high sensitivity (84%), but it is not good for diagnosis because of low specificity (12%). Furthermore, chest X-ray is a good for screening (sensitivity 91%) but is not for diagnosis (low specificity 10%). In the other hand, sputum smear examination with ZN staining is a good for diagnosis because of high specificity (99%), high PPV (96%), and an excellent of positive LR: 41.48.

## CONCLUSIONS

The diagnostic value of conventional TB diagnosis procedure, a prolonged cough  $\geq 2$  weeks, Chest X-ray shows a good screening (had a high sensitivity) and a direct smear examination with ZN staining showed a good diagnosis because has a high specificity compared with Gene X-pert. Therefore, conventional TB diagnostic procedure is still reasonable to perform routinely in era of Gene X-pert MTB/RIF especially in Primary Health Care with limited settings.

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## AUTHORS' CONTRIBUTIONS

Ketut Suryana is responsible in concepts and design, data acquisition, data analysis, manuscript preparation, and editing. Hamong Suharsono and Ida Bagus Rai are responsible in preparation, drafting, review, and approval of this manuscript.

## CONFLICTS OF INTEREST

The author declared that there are no conflicts of interest related to this study.

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