Advance Publication by J-STAGE

Japanese Journal of Infectious Diseases

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Received: November 10, 2020. Accepted: February 22, 2021.

Published online: March 31, 2021.

DOI:10.7883/yoken.JJID.2020.921

Advance Publication articles have been accepted by JJID but have not been copyedited
or formatted for publication.

Evaluation of Xpert MTB/RIF with microscopy and culture for the diagnosis of tuberculosis in a referral laboratory in Nepal

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Running title: Evaluation of Xpert MTB/RIF in Nepal

Keywords: Tuberculosis, Xpert MTB/RIF, Culture, Microscopy.

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Summary

Sputum microscopy and Xpert MTB/RIF are the primary rapid diagnostic methods for tuberculosis (TB) in Nepal. Disagreements among Xpert, microscopy, and culture, for example, cases with Xpert positive and microscopy negative, were frequently observed in Nepal including in our reference laboratory. The objective of this study was to compare the effectiveness of Xpert with culture and microscopy for TB diagnosis in Nepal. A total of 125 TB suspected sputum samples were processed for Xpert, microscopy, and culture. The Xpert results when compared with culture showed 100% sensitivity and 97.4% specificity with an excellent agreement ($\kappa = 0.96$), whereas microscopy showed the sensitivity and specificity of 43.2% and 98.7%, respectively, with a moderate agreement ($\kappa = 0.4$). The sensitivity and specificity of microscopy, when compared with Xpert, were 43.5% and 100%, respectively. The majority of Xpert positive samples of a medium MTB detection and all samples of low and very low MTB detection were missed by microscopy. Our study showed that Xpert MTB/RIF is a reliable tool for the diagnosis and management of TB in Nepal. Because of its high cost and sustainability, alternative simple and rapid diagnostic methods with a similar efficiency would be helpful for TB control in Nepal.

Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* complex (MTBC) is a global public health problem and remains a leading cause of death among infectious diseases worldwide. Despite all the global efforts to control TB, the World Health Organization (WHO) has estimated 10 million new TB cases and 1.4 million deaths globally in 2019 (1).

Despite the implementation of a nationwide TB control program with a 90% treatment success rate (2), notifications of new cases are not decreasing as expected. Nepal's National tuberculosis control program had estimated 42,000 new TB cases, 1,400 rifampicin-resistant/multidrug-resistant TB (RR/MDR-TB) cases, and 5,500 deaths in the fiscal year of 2018/2019 (3). However, in the same fiscal year, only 32,043 drug-susceptible (DS)-TB and 392 RR/MDR-TB cases were enrolled in the treatment system (3). Furthermore, the prevalence survey of 2018 estimated 69,000 TB cases, which was 1.6 times higher than the previous estimate (4), indicating that a large number of DS-TB and RR/MDR-TB cases have been missing from diagnosis.

The WHO ambitious goal of the End TB strategy which aims to achieve a 90% reduction in incidence and a 95% reduction in mortality by 2035 is not on track in most of the WHO regions and many high burden countries (1). The primary TB diagnostic tool in many developing countries and high burden countries including Nepal is still sputum microscopy, a 100 years old inexpensive and rapid test that misses nearly half of all TB cases (5). The World Health Organization (WHO) endorsed a molecular test, Xpert MTB/RIF as a rapid and accurate detection of *Mycobacterium tuberculosis* (MTB) and Rifampicin (RIF) resistance (6). Currently, it is widely used worldwide

due to its effectiveness. The Xpert system in Nepal is supported by the international community and the government of Nepal.

In Nepal, microscopy is used for the diagnosis of all TB suspects where Xpert is not available, and culture is limited to monitoring of drug-resistant treatment and selective retreatment cases. Xpert is used for all presumptive TB cases, symptomatic contacts of MDR-TB, previously treated cases, and vulnerable populations, so it is currently used as the main diagnostic tool in Nepal. However, it is not used for treatment monitoring (7). We frequently observed discrepant results among different diagnostic methods, such as a high rate of Xpert positive microscopy negative, Xpert negative culture positive, and Xpert positive culture negative. In addition, other decentralized TB centers also informed us about similar discrepancies between Xpert and microscopy. Similarly, most of the cases of low and very low MTB detection by Xpert were not detected by sputum microscopy in our setting. Although Xpert was found to be the accurate TB diagnostic methods in different countries, and a review of 25 previous studies on the evaluation of Xpert found the pooled sensitivity and specificity were 89% and 98% respectively (8), we initiated this study to assess its effectiveness in comparison to culture and microscopy in Nepal.

Materials and methods

Clinical sample collection

This cross-sectional study was done among the patient referred for Xpert MTB/RIF testing at Nepal Anti-TB Association/German Nepal TB Project (NATA/GENETU) National Reference Laboratory, Kalimati from 6th Feb 2020 to 18th Mar 2020. NATA/GENETUP is one of the two TB referral hospitals and WHO TB reference laboratories of Nepal. NATA/GENETUP offers culture, drug susceptibility testing, and other routine TB diagnostic tests including Xpert.

A total of 125 samples from the TB suspected patients were included. Informed consent was taken from all enrolled patients. Age, sex, and history of TB treatment were recorded from all patients. We included only pulmonary TB suspected samples with ≥ 2 ml of sputum. The extra-pulmonary samples and the samples with a volume of ≤ 2 ml were not included in the study. Similarly, patients undergoing TB treatment were also excluded from the study. This study was ethically approved by NATA/GENETEU institutional review board.

Decontamination of sputum and inoculation to culture

The sputum samples included in this study were decontaminated with 4% NALC-NaOH for 15 mins in a 50 ml falcon tube, neutralized with phosphate buffer (pH 6.8) up to 50 ml, and centrifuged at 3000 g for 20 mins. After centrifugation, the supernatant was discarded, and the sediment was resuspended with 1 ml phosphate buffer. Resuspended samples (200 μ l) were inoculated into two slants of Löwenstein-Jensen (LJ) media (BBL™ Mycobactosel™ LJ Medium, BD). The resuspended sample was used for smear preparation. The inoculated LJ slants were incubated at 37°C and monitored for mycobacterial growth. For mycobacteria positive culture, MTBC was differentiated from NTM using TB Ag MPT64 Rapid assay (SD standard diagnostics Inc, Korea), as instructed.

Microscopy examination

Prepared 1 x 2 cm² standard smears were heat-fixed and stained with auramine (0.1%) for 20 mins. After decolorization with acid alcohol (0.5%) and staining with methylene blue (0.1%), the smears were examined by a LED microscope (Zeiss Primo Star).

GeneXpert MTB/RIF testing

The GenXpert MTB/RIF (Cepheid, Sunnyvale, CA) assay was performed as previously described (9, 10). Briefly, to 0.5 ml of the decontaminated sample, Xpert MTB/RIF sample reagent (SR) was mixed in the ratio of 1:3. The mixture was vigorously mixed twice during the 15 minutes incubation period at room temperature, and 2 ml of the mixture was transferred to the test cartridge. The cartridge was loaded into the Xpert machine, and the automatically generated results were read after 110 mins.

Statistical analysis

All the study data were entered into Microsoft excel. Pearson's chi-square test or Fisher's exact test as appropriate was used to compare the relationship between demographic and clinical characteristics of patients with different diagnostic methods by using the SPSS for Windows (version 26). A *p* value less than 0.05 was considered statistically significant. The sensitivity, specificity, and Cohen's Kappa coefficient were calculated.

Results

Evaluation of Xpert, culture, and microscopy with patient's characteristics and sputum sample quality

A total of 125 sputum samples were analyzed. The mean age of patients was 42.8 ± 19.5 years with a predominance of male patients (81, 64.8%) to female patients (44, 35.2%). Of these 125 samples tested, 17 (13.6%), 44 (35.7%), and 39 (31.4%) were detected positive by microscopy, culture, and Xpert, respectively. The results of microscopy, culture, and Xpert along with their association with patient's characteristics are summarized in Table 1. We found that except for an

association of microscopy with a history of TB treatment, patient's characteristics such as age group, sex, and history of TB treatment were not significantly associated with testing results from microscopy, culture, and Xpert. Furthermore, we found that sputum sample quality was significantly associated with the performance of microscopy, Xpert, and culture (Table 2).

Diagnostic performance parameters of microscopy, culture, and Xpert

When the Xpert result was compared with culture, all 37 culture positive samples that were correctly identified as MTB were accurately detected by Xpert with a sensitivity of 100% and specificity of 97.4%. The remaining 7 culture-positive samples that were identified as NTM were Xpert-negative. There was an excellent agreement between Xpert and culture (Kappa coefficient = 0.96). The sensitivity of microscopy in culture positive samples was 36.3% (16/44) and specificity in culture negative samples was 98.7% (78/79); and sensitivity and specificity of microscopy when compared with Xpert was 43.5% (17/39) and 100% (85/85) respectively indicating its limitation for accurately detecting TB. Among the 107 microscopy negative samples, an additional 22 samples were detected by Xpert (Table 3). Furthermore, we compared the quantitative result of Xpert with the microscopy smear gradings. While all Xpert negative samples were negative in microscopy, 1 (7.6%) sample that was positive with high MTB detection and 8 (61.5%) samples that were positive with medium MTB detection in Xpert were negative with microscopy (Table 4). The diagnostic performance parameters of microscopy, culture, and Xpert summarized in Tables 2 and 3 shows that Xpert is an accurate diagnostic method for TB in Nepal.

Discussion

The government of Nepal's national TB management guidelines 2019 (7) has prioritized the Xpert for diagnosis and treatment algorithm because of its simplicity and ability to rapidly diagnose TB and MDR-TB. Along with smear microscopy, it is used for diagnosis and management of new and retreatment cases in two TB reference laboratories and some decentralized TB centers, whereas culture is limited to two reference laboratories and exclusively used to monitor treatment of MDR-TB and epidemiologically important retreatment cases. Frequent observation of discrepancy among Xpert, microscopy, and culture in our reference laboratory and other facilities prompted us to evaluate the efficacy of Xpert with standard culture and microscopy.

Our study reiterates the effectiveness of Xpert because it correctly identified all 37 culture confirmed cases with a sensitivity of 100%. There were 2 cases where Xpert was positive and the culture was negative, indicating effectiveness of Xpert as previously described (11). Although Xpert detected higher number of MTB cases than culture, further study with higher number of samples is necessary to compare its effectiveness over culture.

The sensitivity of Xpert in our study was higher than the sensitivity of 76.7% from a previous Nepalese study of 2016 (12), indicating that the Xpert diagnostic system has now been systematically established in Nepalese settings because of the improvement of the TB control program under the direct supervision of WHO. Similarly, our sensitivity was similar (100%) to that from India and Saudi Arabia (13, 14). A review and meta-analysis of 37 different studies found that sensitivity and specificity of Xpert range from 50% to 100% and 55% to 100%, respectively (15). These wide variations may depend upon the quality of samples and laboratory protocols. In our study, the Rifampicin resistance detected by the Xpert was 7.7% (3/39), similar to the global report (16). Furthermore, the 7 NTM samples from 44 culture positive samples were not detected

by Xpert. Reliable identification of MTB from NTM in all TB suspected cases is important to avoid unnecessary treatment.

We used the Primo Star LED microscope at a lower magnification (400X) with the examination of at least 55 fields that has 10 % more sensitivity in contrast to Ziehl-Neelsen staining. However, the sensitivity and specificity of our microscopy in comparison to culture was only 43.2% and 98.7%, and when compared to Xpert was 43.5% and 100%, respectively. The low sensitivity of microscopy is similar to studies from India (48%) (13) and Saudi Arabia (45%) (14) but lower than Thailand (60.5%) (17). Upon comparison of Xpert result with microscopy smear gradings, we found that Xpert could successfully detect an additional 22 microscopy negative samples, indicating its effectiveness in detecting MTB in samples. The lower sensitivity of microscopy is further illustrated by its inability to detect 1 (7.6%) sample that was positive with high MTB detection and 8 (61.5%) samples that were positive with medium MTB detection in Xpert. Furthermore, an additional 13 samples that had low (11, 100%) and very low MTB (2, 100%) detection in Xpert were not detected by microscopy, confirming the superiority of Xpert over microscopy.

The effectiveness of microscopy, Xpert, and culture was found to be significantly associated with the sputum sample quality. Of the three sputum types, microscopy could only detect TB bacilli in mucoid samples, whereas Xpert and culture could also additionally detect TB bacilli in saliva and blood-stained sputum samples. Thus, sample quality is critical for accurate and sensitive detection of TB.

In this study, we did not find a close association of patient's characteristics such as age group, sex, and history of TB treatment with the performance of different diagnostic methods, except with that of history of TB treatment with the microscopy, so the accuracy of Xpert is

irrespective of these patient's characteristics. The significant association between treatment history with microscopy was found to be related to the patient's history of previous treatment with positive cases in microscopy, and the reason may be that these patients may have a relatively high number of TB bacilli in their sputum which had a higher possibility of being detected by the low sensitive microscopy. However, relatively higher sensitive detection methods like culture and Xpert did not have a significant association with the patient's history of treatment. In this study, the patient's characteristics were limited and did not include broad-scale epidemiological features.

This study contains several limitations. The number of study samples was low, and the study period was short. Therefore, a long-term comprehensive study with an increased sample size may provide an accurate picture of the effectiveness of different diagnostic methods. We do not have phenotypic DST results to compare with Xpert rifampicin resistance.

Although Xpert has advantages for accurate diagnosis of TB and detection of drug resistance, its sustainability is questioned in the long run because of its commercial nature and high cost. Importantly, developing countries like Nepal are implementing the Xpert system with substantial international support. In addition, the Xpert system is not available in all decentralized TB centers, so all the TB suspected patients of Nepal do not have access to it. So, the development of an alternative diagnostic point of care method that combines the simplicity of microscopy and accuracy of Xpert would be helpful for TB control in high burden TB countries like Nepal (5, 18, 19)

In conclusion, our study showed that Xpert MTB/RIF is an excellent tool for the diagnosis and management of TB in Nepal. Our study also underscores the importance of rapid diagnostic methods with the sensitivity of Xpert and the simplicity of microscopy for the TB control program in Nepal.

Acknowledgments

Authors wish to thank Mr. Bijendra Bhakta Raya, Mira Shrestha, and Priya Khadka who contributed to sample collection, patient history taking, and laboratory works.

Conflict of interest

None to declare.

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Table 1. Demographic and clinical characteristics of patients by different detection methods.

	Microscopy			culture [§]			Xpert [#]		
	Positive	Negative	<i>p</i> value	Positive	Negative n (%)	<i>p</i> value	Positive	Negative	<i>p</i> value
Gender									
Male	12 (9.6)	69 (69)	0.59	29 (23.5)	50 (40.6)	0.08	26 (20.9)	55 (44.3)	0.83
Female	5 (4)	39 (31.2)		15 (12.1)	29 (23.5)		13 (10.4)	30 (24.1)	
Age group									
0-25	5 (4)	28 (22.4)	0.32	12 (9.7)	21 (17)	0.93	13 (10.4)	19 (15.3)	0.13
26-42	5 (4)	25 (20)		12 (9.7)	18 (14.6)		11 (8.8)	19 (15.3)	
43-60	6 (4.8)	27 (21.6)		11 (8.9)	21 (17)		10 (8)	23 (18.5)	
>60	1 (0.008)	28 (22.4)		9 (7.3)	19 (15.4)		4 (3.2)	24 (19.3)	
Cases									
New	10 (8)	88 (70.4)	0.03*	32 (26)	64 (52)	0.28	28 (22.5)	69 (55.6)	0.24
Re-treatment	7 (5.6)	20 (16)		12 (9.7)	15 (12.1)		11 (8.8)	16 (12.9)	
Prevalence	17 (13.6)	108 (86.4)		44 [‡] (35.7)	79 (64.2)		39 (31.4)	85 (68.5)	

[§]2 culture samples that were contaminated are not included.

[#]1 Xpert sample that showed an error is not included.

*Significant association between TB treatment history and microscopy ($p < 0.05$)

7 samples that were culture positive were confirmed to be NTM.

Table 2. Evaluation of Xpert, culture, and microscopy with sputum sample quality

	Microscopy			culture [§]			Xpert [#]		
	Positive	Negative	<i>p</i> value	Positive	Negative n (%)	<i>p</i> value	Positive	Negative	<i>p</i> value
Sample quality									
Mucoid	17 (13.6)	48 (38.4)	<0.001*	30 (24.3)	35 (28.4)	0.03*	28 (22.5)	37 (29.8)	0.01*
Saliva	0	57 (45.6)		13 (10.5)	42 (34.1)		10 (8)	46 (37)	
Blood stained	0	3 (2.4)		1 (0.8)	2 (1.6)		1 (0.8)	2 (1.6)	

§2 culture samples that were contaminated are not included

#1 Xpert sample showed error is not included

*Significant association between sputum sample quality and diagnostic methods ($p < 0.05$)

7 samples that were culture positive were confirmed to be NTM

Table 3. Sensitivity, specificity, and Kappa coefficient results of Xpert, culture, and microscopy

		Culture		Sensitivity (%, 95%CI)	Specificity (%, 95%CI)	Cohen's kappa coefficient	Strength of agreement
		Positive	Negative				
Xpert	Positive	37	2	100, 90.5 - 100	97.4, 91 - 99.6	0.96	Excellent
	Negative	0	76				
Microscopy	Positive	16	1	43.2, 27.1 – 60.5	98.7, 93.1 - 99.9	0.49	Moderate
	Negative	21	78				
		Xpert		43.5, 27.8 - 60.3	100, 95.7 - 100	0.51	Moderate
		Positive	Negative				
Microscopy	Positive	17	0				
	Negative	22	85				

7 samples that were culture positive but Xpert negative were confirmed to be NTM

2 samples were contaminated in culture.

1 sample showed an error result twice in Xpert.

Kappa < 0: “No agreement”; Kappa 0-0.2: “Slight agreement”; Kappa 0.21-0.4: “Fair agreement”; Kappa 0.41-0.6: “Moderate agreement”; Kappa 0.6-0.8: Good agreement; Kappa 0.81-1: “Excellent”.

Table 4. Comparison of Xpert results with microscopy smear gradings

Xpert	Microscopy smear gradings [§]				Total
	3+	2+	1+	Negative	
	n (%)				
MTB detected (High)	4 (30.7)	5 (38.4)	3 (23)	1 (7.6)	13
MTB detected (Medium)	1 (7.6)	2 (15.3)	2 (15.3)	8 (61.5)	13
MTB detected (Low)				11 (100)	11
MTB detected (Very low)				2 (100)	2
MTB not detected				78 (100)	78

[§]Smear grading according to WHO-IUTLD guidelines.

Seven NTM samples are not included in this table.