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Diagnostic Accuracy of TB-LAMP for Diagnosis of Pulmonary Tuberculosis among Adult Presumptive TB in Nigeria

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ABSTRACT

Background: **Microscopy is still used in resource-limited countries for PTB diagnosis because of the challenges associated with the GeneXpert instrument. For these settings, the WHO recommended the replacement of microscopy with TB-LAMP for PTB diagnosis in adults. Evidence supporting this recommendation shows a wide variation in quality and TB-LAMP diagnostic accuracy; thus, the need to validate the assay before its deployment in Nigeria.**

Methods: **A cross-sectional study of 2636 consenting eligible adult presumptive TB from health facilities in two States of Nigeria. Sputum specimens were analyzed for PTB using TB-LAMP, Ziehl-Neelsen microscopy, Xpert, and solid culture (reference standard). Sensitivity and specificity of TB-LAMP, Xpert and smear microscopy for PTB diagnosis were determined.**

Results: **Sensitivity and specificity of TB-LAMP for PTB diagnosis among all participants were 76.7% and 99.3% respectively (Youden Index [*J*] = 0.76). TB-LAMP's PTB diagnostic accuracy was higher than microscopy (sensitivity = 54.3%, specificity = 99.8%, *J* = 0.54), but lower than Xpert (sensitivity = 84.5%, specificity = 99.1%). For HIV-seropositive participants, the diagnostic accuracy of TB-LAMP was similar to microscopy and Xpert (p > 0.05).**

Conclusion: **TB-LAMP had high accuracy for adult PTB diagnosis in Nigeria, and it can replace microscopy for PTB diagnosis in adults.**

INTRODUCTION

Tuberculosis (TB) is one of the top ten causes of mortality and a leading cause of death from an infectious agent globally.[1] Therefore, it is a public health concern that explains the inclusion of the 'end TB epidemic' by 2030 and 2035 as a target of the Sustainable Development Goal 3 (SDG-3) and End TB Strategy, respectively.[2,3] The disease is associated with poverty, thus its high prevalence in developing countries, including Nigeria. In 2018, about 429,000 new cases were estimated for Nigeria, which translated to 4.3% of the global TB incident cases; thus, Nigeria's burden of TB was the sixth globally and first in Africa.[1] Also, with an estimated National TB missing case rate of 76%, Nigeria accounted for about 12% of the 3 million unreported/undiagnosed cases.[1,4.]

To re-channel Nigeria to the tracks of achieving the future global TB targets,[2] the Nigeria Tuberculosis, Leprosy and Buluri Ulcer Control Programme (NTBLCP) embarked on finding the missing TB cases and enrolling them on treatment by expanding the number of health facilities involved in TB care and deployment of more GeneXpert instruments across the country.[4] Unfortunately, there are only 398 GeneXpert instruments distributed to 388 health facilities in the country as of 2019.[4] The limited number of GeneXpert instruments, frequent break down of the existing instruments, and unstable power supply, among other challenges,[5] resulted in the frequent use of Acid-fast bacilli (AFB) microscopy for pulmonary tuberculosis (PTB) diagnosis in Nigeria.[4] In 2019, Nigeria tested 22% of all presumptive TB using microscopy with AFB positivity rate of 12%,[4] implying that several PTB cases were missed among the microscopy-tested cohort because of the low sensitivity of AFB microscopy.[6,7]

Due to the prevailing GeneXpert related challenges in resource-limited settings and the low sensitivity of AFB microscopy, the World Health Organization (WHO) recommended the use of loop-mediated isothermal amplification (TB-LAMP) as a replacement for AFB microscopy for PTB diagnosis.[8] It is a simplified assay that processes 14 samples in less than 2 hours and produces a result that can be visually read.[8]

The recommendation of TB-LAMP over smear microscopy was based on the evidence from a systematic review of 13 studies (n = 4760) from 11 countries, which showed that TB-LAMP had a sensitivity and specificity of 77.7 - 80.3% and 97.7% - 98.1%, respectively.[8,9] While TB-LAMP sensitivity was significantly higher than smear microscopy (sensitivity differences: 7.1 - 13.2%), their specificities were similar; however, it was unclear whether the TB-LAMP technology was superior to smear microscopy in adult presumptive TB living with human immunodeficiency virus (HIV).[8] A few other studies had supported the WHO recommendation,[10-13] except the study from Ethiopia, which showed that TB-LAMP had the same specificity with smear microscopy (98%) but a lower sensitivity than smear microscopy (75% versus 78.5%).[14]

Though these studies generally support the use of LAMP assay as an alternative for smear microscopy, there were wide variability in their quality and results, which justifies the need for more operational research on TB-LAMP in different epidemiological, and geographical settings.[8] The need for such research was critical in Nigeria - the most populous nation in Africa, ranked among the top 10 high TB burden countries, high TB/HIV burden countries, and high multidrug-resistant TB (MDR-TB) burden countries.[1]

It was important to confirm that TB-LAMP's PTB diagnostic accuracy is equivalent or better than AFB microscopy before its deployment to the field in Nigeria, to mitigate the possibility of magnifying the current low TB case notification. Therefore, this study was aimed to compare the PTB diagnostic accuracy of TB-LAMP with AFB microscopy and Xpert MTB/RIF among presumptive TB cases in Nigeria.

METHODS

Study design

A cross-sectional study of 2872consenting eligible presumptive TB recruited from two States of Nigeria.

Study setting

The study was conducted in Nasarawa and Anambra States, representing the Northern and Southern part of the country respectively.

Nasarawa State with a population of about 2.5 million,[16] has the third-highest TB burden in Nigeria .[4] Anambra State is in the South-East region of Nigeria,[16] reports the 9th highest HIV/TB rate.[4]

For this study, five health care facilities were selected: two (one private and one public) in Nasarawa and three (two public and one private) in Anambra state. The selection was based on their workload, location, supportive systems for testing optimization, and laboratory quality assurance records. KNCV Tuberculosis Foundation Nigeria in collaboration with NTBLCP and Mcpage company (the authorized service provider for TB-LAMP in Nigeria), installed the TB-LAMP platforms at the selected facilities and organized on-site training and sensitization meeting for health care workers on the operation and laboratory network.

Study Population

All consenting adult presumptive TB (≥15 years) at the study and spoke sites were eligible for the study. They include patients with cough of ≥2 weeks duration or persons living with HIV (PLHIV) with cough of any duration (with or without any other respiratory symptoms that define presumptive TB in Nigeria).[4] Exclusion criteria were adult presumptive TB with a history of TB treatment, including relapse cases, loss to follow-up, as well as those who could not produce an adequate volume of sputum.

Using the smear microscopy TB positivity rate in Nigeria of 12%,[4] the study was designed to detect a 25% difference in TB positivity at 95% confidence level, 80% power, and non-response of 20%, which gave a calculated sample size of 2442 participants. However, a sample population of 2500 participants (500 per study site) was proposed for the study. At the end of the six months study period (August 2020 – February 2021)

Diagnostic procedure

Each participant submitted two 'spot' sputa (≥1.5 ml each) produced by direct coughing. One sputum specimen was used for TB-LAMP, ZN smear microscopy, and Xpert MTB/RIF assay (Ultra cartridge) at the study site's laboratory; while the other specimen was maintained in a cold chain and transported within 48 hours to the TB reference laboratory for solid culture. A portion of every sputum specimen for culture was used for ZN smear microscopy at the reference laboratory before being processed for solid culture. Laboratory procedures for the TB-LAMP and other diagnostic methods were according to the respective standard operating protocols (SOP) and the instruments' manuals.[17,18] The participants' Xpert result was used for their prompt treatment where necessary, in line with the national guidelines.[17]

Ethical considerations

All participants gave written informed consent. The National Health Research Ethics Committee (NHREC) of Nigeria approved the study (NHREC/01/01/2007-03/09/2020).

Outcome measures

The primary outcome measures were the AFB/MTB positivity rates of TB-LAMP, sputum microscopy, Xpert, sputum culture among presumptive TB; the sensitivity and specificity of TB-LAMP, sputum microscopy, and Xpert for PTB diagnosis among all participants (reference standard: sputum culture).

The secondary outcome measures were the sensitivity and specificity of TB-LAMP and Xpert for PTB diagnosis among smear-positive (+ve)/culture +ve and smear-negative (-ve)/culture +ve participants; the sensitivity and specificity of TB-LAMP for PTB diagnosis among PLHIV.

Data analysis

Data analysis was descriptive and inferential using IBM SPSS (version 20) and OpenEpi (Version 3.01).[19] Using sputum culture results as the reference standard, true positives (TP), true negatives (TN), false positive (FP), and false negative (FN) rates of TB-LAMP, smear microscopy, and Xpert for diagnosing PTB were determined for all participants and PLHIV. These rates were used to determine sensitivity and specificity for each of the diagnostic test among the participants' categories. The 95% Confidence intervals (CI) were determined by the Wilson score interval method. McNemar test for Binary matched-pair data and Youden's J statistic (where necessary) were used to compare the diagnostic performance of TB-LAMP with smear microscopy and Xpert MTB/RIF. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 2872 participants were recruited for the study, but only results of 2636 participants were analyzed. Data for 236 participants (8.2%) were excluded from analyses for various reasons. Details are shown in the study flow chart below (Figure 1).

The mean age of participants was 39.8 ± 15.5 years (range 15 – 93). As shown in table 1, the modal age group was 25 – 34 years (n = 717, 27.2%). Most of the participants were females (n = 1681, 63.8%), married (n = 1924, 73.0%), traders (n = 1032, 39.2%), and HIV-seronegative (n = 1280, 48.6%).

TB-LAMP was positive for MTB in 116 of all participants and 12 PLHIV giving a positivity rate of 4.4% (95%CI [3.7 – 5.3]) and 1.7 (1.0 – 2.9), respectively. The AFB/MTB positivity rates of other diagnostic tests are shown in table 2.

As shown in table 3, TB-LAMP had a sensitivity of 76.7% (95%CI: 68.8-83.2) and specificity of 99.3% (95%CI: 98.9-99.6). The specificity of smear microscopy and Xpert MTB/RIF were above 99%, while their sensitivities were 54.3% (95%CI: 45.7-62.6) and 84.5% (95%CI: 77.3-89.7), respectively.

The sensitivity of TB-LAMP was significantly higher than smear microscopy (X^2 = 27.1, p < 0.001) but the reverse was the case for the specificity (X^2 = 9.0, p = 0.003). Further analysis showed a J-Index of 0.76 and 0.54 for TB-LAMP and smear microscopy respectively. The sensitivity of TB-LAMP was slightly lower than Xpert MTB/RIF (X2 = 8.3, p = 0.004) but, their specificities were similar (X2 = 1.1, p = 0.297).

For smear+ve/culture+ve participants (n = 70), the sensitivity of TB-LAMP and Xpert MTB/RIF were 98.6% (95%CI: 92.3-99.8) and 97.1% (95%CI: 90.2 – 99.2) respectively, p = 0.480. For smear-ve/culture+ve participants (n = 59), TB-LAMP had a sensitivity of 50.8% (95%CI: 38.4-63.2) which was lower than Xpert MTB/RIF, 69.5% (95%CI: 56.9-79.8), p = 0.001.

Table 4 shows the sensitivity and specificity of TB-LAMP and other diagnostic tests among PLHIV (n = 715). The specificity values of all diagnostic tests were above 99%. The sensitivity of TB-LAMP was 60.0% (95%CI: 35.8-80.2) while that of smear microscopy and Xpert MTB/RIF were 53.3% (95%CI: 30.1-75.2) and 66.7% (95%CI: 41.7-84.8) respectively. The sensitivity and specificity of TB-LAMP for PTB diagnosis among HIV-seropositive participants were similar to that of smear microscopy and Xpert MTB/RIF (p > 0.05).

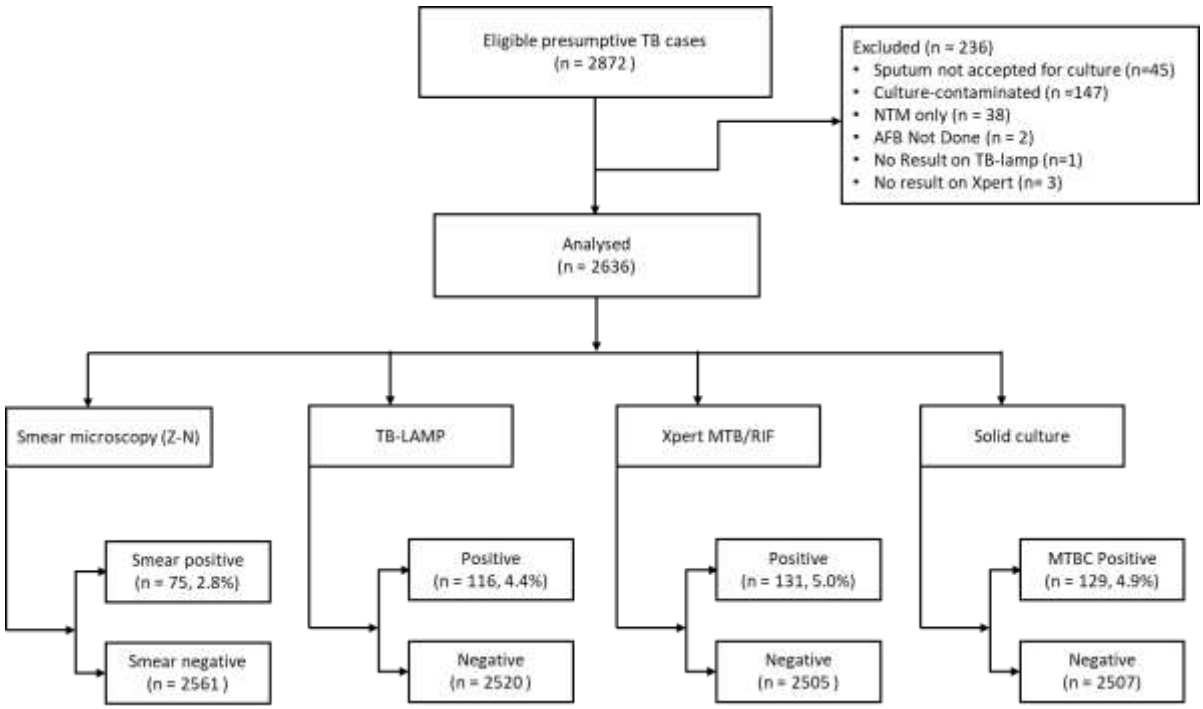

Figure 1: Study Flow Chart

Table 1: Basic Characteristics of Study Participants

Characteristic	Sub-group	Frequency (n = 2636)	Percentage (%)
State of Residence	Anambra	1410	53.5
	Nasarawa	1226	46.5
Sex	Male	955	36.2
	Female	1681	63.8
Age group (years)	15-24	391	14.8
	25-34	717	27.2
	35-44	627	23.8
	45-54	396	15.0
	55-64	272	10.3
	>=65	233	8.8
Marital Status	Married	1924	73.0
	Single	704	26.7
	Widowed	6	0.2
	Others	2	0.1
Occupation	Trading	1032	39.2
	Civil servant/Public servant	296	11.2
	Skilled worker	264	10.0
	Student/Corper	362	13.7
	House wife	228	8.6
	Farming	295	11.2
	Others	105	4.0
	Unemployed	25	0.9
	No response	29	1.1
HIV Status	Sero-negative	1280	48.6
	Sero-positive	715	27.1
	Unknown	641	24.3

Table 2: MTB Positivity Rates of TB-LAMP and other Diagnostic Modalities

Participants' category	Diagnostic modality	MTB Detected/Positive		MTB positivity rate (95%CI)
		Yes	No	
		Freq. (%)	Freq. (%)	
All Participants (n = 2636)	TB-LAMP	116 (4.4)	2520 (95.6)	4.4 (3.7 – 5.3)
	Smear microscopy	75 (2.8)	2561 (97.2)	2.8 (2.3 – 3.6)
	XPert MTB/RIF	131 (5.0)	2505 (95.0)	5.0 (4.2 – 5.9)
	Sputum culture	129 (4.9)	2507 (95.1)	4.9 (4.1 – 5.8)
HIV-seropositive (n = 715)	TB-LAMP	12 (1.7)	703 (98.3)	1.7 (1.0 – 2.9)
	Sputum microscopy	10 (1.4)	705 (98.6)	1.4 (0.8 – 2.6)
	XPert MTB/RIF	13 (1.8)	702 (98.2)	1.8 (1.0 – 3.1)
	Sputum culture	15 (2.1)	700 (97.9)	2.1 (1.3 – 3.4)

Table 3: Sensitivity and Specificity of TB-LAMP, microscopy, and Xpert for all participants

Modality	Test outcome Vs Standard		Sensitivity (95%CI) %	Specificity (95%CI) %	Kappa score (κ) (95%CI)	p-value
TB-LAMP (n = 2636)	True Positive	99	76.7 (68.8-83.2)	99.3 (98.9-99.6)	0.80 (0.76-0.84)	<0.001
	False Negative	30				
	True Negative	2490				
	False Positive	17				
Sputum microscopy (n = 2636)	True Positive	70	54.3 (45.7-62.6)	99.8 (99.5-99.9)	0.67 (0.64-0.71)	<0.001
	False Negative	59				
	True Negative	2502				
	False Positive	5				
Xpert MTB/RIF (n = 2636)	True Positive	109	84.5 (77.3-89.7)	99.1% (98.7-99.4)	0.83 (0.79-0.87)	<0.001
	False Negative	20				
	True Negative	2485				
	False Positive	22				

Table 4: Sensitivity and Specificity of TB-LAMP and other Test Modalities for PLHIV

Modality	Test outcome Vs Standard		Sensitivity (95%CI) %	Specificity (95%CI) %	Kappa score (95%CI)	p-value
TB-LAMP (n = 715)	True Positive	9	60.0 (35.8-80.2)	99.6 (98.8-99.9)	0.66 (0.59-0.73)	<0.001
	False Negative	6				
	True Negative	697				
	False Positive	3				
Smear microscopy (n = 715)	True Positive	8	53.3 (30.1-75.2)	99.7 (99.0-99.9)	0.63 (0.56-0.71)	<0.001
	False Negative	7				
	True Negative	698				
	False Positive	2				
Xpert MTB/RIF (n = 715)	True Positive	10	66.7 (41.7-84.8)	99.6 (98.8-99.9)	0.71 (0.64-0.78)	<0.001
	False Negative	5				
	True Negative	697				
	False Positive	3				

DISCUSSION

The study's goal was to investigate the diagnostic accuracy of TB-LAMP for PTB among presumptive TB in Nigeria. The participants' age groups and occupations represent the current demographics of Nigeria.[20] Tuberculosis is associated with HIV infection, which explains the higher HIV prevalence among PTB patients and vice versa. The high HIV-seroprevalence rate of 27% among participants in this study was due to health facility screening of hospital attendees at different service delivery point including the HIV treatment centers. In 2019, the national TB/HIV prevalence was 10.4%;[4] however, a TB/HIV prevalence of up to 36.2% was reported at State levels.[21]

In Nigeria, smear microscopy is used for PTB diagnosis in areas where Xpert MTB/RIF assay is not accessible.[17] In 2019, 22% of the presumptive TB in the country were tested with microscopy. With the high diagnostic performance of the genotypic test modalities from this study, the low comparative MTB positivity rate of smear microscopy suggests that many PTB cases were missed, with obvious public health implications. For all participants in this study, both the diagnosis of PTB with TB-LAMP and Xpert MTB/RIF showed kappa statistics scores of ≥0.8, which indicate a strong degree of agreement with the standard test (sputum culture).[28] On the other hand, smear microscopy showed a moderate degree of agreement with the standard test results (κ = 0.67), and a lower J-index compared to TB-LAMP, which suggests a lower PTB diagnostic performance.[22,23] The significantly higher sensitivity of TB-LAMP over smear microscopy in this study agrees with the findings of two systematic reviews,[9,10] and other related studies,[11,12] but differed from a small sample, single-center study from Ethiopia.[14]

Furthermore, in agreement with previous studies, this study result demonstrates a high diagnostic performance of Xpert MTB/RIF's over smear microscopy for PTB diagnosis, supporting the reason for its use as the primary TB diagnostic method in Nigeria.[17] It also suggests that Xpert MTB/RIF is better than TB-LAMP for PTB diagnosis in the general population because the sensitivity was significantly higher than TB-LAMP while their specificities were similar (table 5).[23]

Though the TB-LAMP had high and comparable sensitivities with Xpert MTB/RIF for the PTB diagnoses among smear+ve/culture+ve patients in this study, its sensitivity was significantly lower than Xpert MTB/RIF for the smear-ve/culture+ve PTB cases. The higher sensitivity of Xpert MTB/RIF over TB-LAMP for smear-

ve/culture +ve PTB cases in this study supports Xpert's endorsement as the most sensitive rapid assay for PTB diagnosis in smear-ve respiratory samples.[24] The sensitivity of TB-LAMP for smear-ve/culture+ve PTB participants, in this study, seems closer to the pooled values of 40–42% reported in a systematic review,[9] when compared to the sensitivity of 90% reported by the Gambian study.[12]

For the HIV-seropositive participants, the TB-LAMP sensitivity of 60% and specificity of 99.6% may be comparable to the sensitivity and specificity results (63.8% - 73.4% versus 95.0% - 98.8%) of the systematic review that guided the WHO's TB-LAMP recommendation.[8,9] Furthermore, this study shows that among PLHIV, TB-LAMP, smear microscopy, and Xpert MTB/RIF had a moderate degree of agreement with the standard test (i.e., $\kappa = 0.60–0.79$),[22] which suggests a comparable diagnostic performance of the three tests. Likewise, the specificity and sensitivity of TB-LAMP for PTB diagnosis in PLHIV did not differ from smear microscopy and Xpert MTB/RIF, thus suggesting a comparable diagnostic performance for the three diagnostic tests.[23] Nevertheless, considering the low culture-based PTB rate in the HIV-seropositive cohort of this study (Table 2), larger sample studies among PLHIV may be required to confirm this study's findings.

This study was limited by use of solid TB culture technique, which is associated with lower MTB yield and longer time to positive culture.[25] However, the culture processing period of up to eight weeks and adherence to the laboratory SOP, ensured optimal mycobacterial growth and reduced contamination rate.

CONCLUSION

In Nigeria, the TB-LAMP's diagnostic accuracy for PTB among adult presumptive TB was more sensitive to ZN smear microscopy but slightly lower than Xpert MTB/RIF sensitivity rate. However, for the PLHIV, the study suggests that PTB diagnostic accuracy of TB-LAMP was comparable to Xpert MTB/RIF and smear microscopy. Therefore, TB-LAMP can replace smear microscopy for PTB diagnosis among adults in Nigeria, particularly in locations where GeneXpert service is not accessible.

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Conflict of interest

Authors declare no conflict of interest.

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