EVALUATION OF THE PERFORMANCE OF THREE DIAGNOSTIC TESTS FOR TUBERCULOSIS AMONG HIV PATIENTS PRESENTING TO KIBRA COMMUNITY HEALTH CENTER, NAIROBI COUNTY, KENYA.

EUNITA ATIENO BSc. MLS
H57/6928/2017

E- MAIL: atienoeunita2@gmail.com

A DISSERTATION SUBMITTED TO THE DEPARTMENT OF PUBLIC AND GLOBAL HEALTH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF PUBLIC HEALTH OF THE UNIVERSITY OF NAIROBI

UNIVERSITY OF NAIROBI

DECLARATION OF ORIGINALITY FORM

Name of student ..... Eunita Atieno Ochola

Registration number H57/6928/2017

Faculty ..... Health Sciences

Department ..... Public and Global Health

Course name ..... Master of Public Health

Title of the work ..... Evaluation of the performance of three diagnostic tests for Tuberculosis among HIV patients presenting to Kibra community health center, Nairobi county, Kenya.

DECLARATION

1. I understand what plagiarism is and I am aware of the University's policy in this regard
2. I declare that this proposal is my original work and has not been submitted elsewhere for examination, award of degree or publication. Where other people's work or my own work has been used, this has properly been acknowledged and referenced in accordance with the University of Nairobi's requirements.
3. I have not sought or used the services of any professional agencies to produce this work
4. I have not allowed, and shall not allow anyone to copy my work with the intention of passing it off as his/her own work
5. I understand that any false claim in respect of this work shall result in disciplinary action, in accordance with the University plagiarism policy.

Signature: _____ Date: 28/ul 2023.

SUPERVISORS APPROVAL

This dissertation has been submitted to the University with my approval as the supervisor

Dr. Marshal M. Mweu

BVetMed, PG Diploma, Msc, PhD

Senior Lecturer, Department of Public and Global Health, University of Nairobi

Signature: _____ Date: 28/11/2023

Approved by the chair, Department of Public and Global Health, University of Nairobi

Dr. Rose Okoyo Opiyo

B.Ed., M. Sc., Ph. D, Public Health Nutrition

Senior Lecturer, Department of Public and Global Health, University of Nairobi

Signature: _____ Date: 28/11/2023

DEDICATION

This work is dedicated to my loving parents, siblings and friends. I thank them all for their prayers and support throughout this journey.

ACKNOWLEDGEMENTS

First I am grateful to God for having seen me through this journey.

I am sincerely grateful to my supervisor Dr. Marshal Mweu for having provided great support as my supervisor during proposal development, data collection, data analysis and thesis writing. May God richly reward you

I would also like to thank the management of the County government of Nairobi, the Lang'ata sub county, and staff of Kibra Community Health Centre, and the study participants. God bless them all.

Last but not least I thank my parents for their love, support, prayers and encouragement. Alice Tarus my friend and classmate for her input and encouragement throughout my study. My pastor and his wife for their prayers and support.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS/ ACRONYMS

ART	Antiretroviral therapy
CFU	Colony Forming Units
DST	Drug Susceptibility Testing
ELISA	Enzyme Linked Immunosorbent Assay
FM	Fluorescence Microscopy
GFR	Glomerular Filtration Rate
HIV	Human Immunodeficiency Virus
LAM	Lipoarabinomannan
LCM	Latent Class Models
LJ	Lowenstein Jensen
LMIC	Low and Middle Income Countries
LPA	Line Probe Assay
MDR	Multi Drug Resistance
ML	Milliliter
MOH	Ministry of Health
MTB	*Mycobacterium tuberculosis*
MTB/RIF	Mycobacterium/ Rifampicin
NAAT's	Nucleic Acid Amplification Tests
NTM	Nontuberculous Mycobacteria
PLWHIV	People Living with Human Immunodeficiency Virus
PV -	Negative predictive value
PV +	Positive predictive value
SSM	Sputum Smear Microscopy
TAT	Turnaround Time
TB	Tuberculosis
WHO	World Health Organization
ZN	Ziehl- Neelsen stain

DEFINITION OF OPERATIONAL TERMS

Active tuberculosis case finding – Involves systematically looking or screening for TB among high-risk group individuals such as contacts of people diagnosed with TB or PLWHIV

Passive tuberculosis case finding – Persons with symptoms and evidence of active TB disease present themselves to the health facility for treatment

Paucibacillary disease- Presence of few bacilli

Sensitivity – The tests capability to ascertain diseased individuals correctly

Specificity – The tests capability to ascertain non- diseased individuals correctly

Sputum Smear Microscopy – TB diagnostic method employing the use of staining methods. The tests principle is based on the mycobacterium retaining the primary stain after decolorization with acid alcohol. The commonly used methods of staining are: ZN staining method and auramine staining method.

ABSTRACT

Background- The absence of an accurate reference test complicates the evaluation of tuberculosis (TB) diagnostic tests among people living with Human Immunodeficiency Virus (PLWHIV). Verifiable evidence on performance of the routinely used diagnostic tests is key to inform early TB detection and population-based surveillance among PLWHIV. The objective of this study was to estimate the sensitivity (Se), specificity (Sp) and negative and positive predictive values (NPV and PPV) of sputum smear microscopy (SSM), Xpert Ultra and lipoarabinomannan antigen (LAM) tests for TB among PLWHIV in Nairobi County, Kenya.

Methodology- This cross-sectional study enrolled a total of 190 patients aged ≥ 18 years with presumptive TB seeking treatment at the Kibra Community Health Center Comprehensive Care Centre (CCC) clinic between September 2022 and March 2023. The diagnostic data obtained from the three tests were analysed using a Bayesian latent class analysis framework to derive accuracy estimates of the three diagnostic tests.

Results- The Xpert Ultra assay registered a higher Se (85.0; 95% PCI [41.4 – 99.4]) compared to LAM (26.8; 95% PCI [4.7 – 67.6]) and SSM (56.7 [16.4 – 97.4]). However, SSM had the highest Sp (99.6; 95% PCI [97.7 – 100.0]). The Xpert Ultra assay yielded the highest overall combination of Se and Sp at 80.8% (95% PCI [37.0 – 96.5]). On predictive values, SSM recorded the highest PPV at 84.5% (95% PCI [38.4 – 99.4]). Nonetheless, all the tests exhibited noticeably high NPVs (>96%).

Conclusions- The Xpert Ultra assay recorded the highest Se of the three tests. However, SSM displayed the highest Sp and thus PPV estimate. Notwithstanding, the three tests registered similar NPV's. An optimal testing approach in this low-prevalence TB setting could entail an initial screening with the more sensitive Xpert Ultra test, with any resultant positives retested with the more specific SSM test - a two-test serial testing strategy.

1.0 INTRODUCTION

1.1 Background of the Study

Worldwide, Tuberculosis (TB) ranks among the main causes of mortality from a single pathogenic agent (Glaziou et al., 2018; WHO, 2020; World Health, 2018). Human Immunodeficiency Virus (HIV) infected patients have a 20 to 30 fold higher probability of contracting TB (WHO, 2017). As of 2017, approximately 9% of the 10 million new TB cases were individuals living with HIV (PLWHIV), with Africa accounting for a 72% disproportionate share (World Health, 2018). Kenya ranks amid the high-TB burden nations whose primary cause of death is TB (Enos et al., 2018).

In Kenya, pulmonary TB is the most prevalent type and 66% of TB cases occur among those of aged ≤44 years (MOH, 2016). In line with the national TB diagnosis and treatment guidelines, the commencement of TB treatment is informed by bacteriological confirmation of *Mycobacterium tuberculosis* (MTB). However, clinical diagnosis where bacteriological confirmation is not possible may suffice for initiation of treatment (MOH, 2013).

Sputum smear microscopy (SSM) has been the main diagnostic tool for TB especially in developing countries. It is extensively used because it is easy to run, rapid, inexpensive and has high specificity (Sp) for TB diagnosis (Akanbi et al., 2017; Gelaw et al., 2017). Nevertheless, it has a low limit of detection approximately 10,000 TB bacilli/ml of sputum. Notably, this poses a challenge for diagnosis of TB in PLWHIV since they have fewer bacilli in their sputum (Behr et al., 1999a).

Diagnostic tests with improved Se and rapid turnaround time (TAT) among PLWHIV could lead to improved patient outcomes, reduced mortality and lower progressive transmission of TB (Steingart et al., 2014). The real time polymerase chain reaction (PCR) assay utilizing the gene Xpert platform such as Xpert Ultra, offers better test Se and Sp with ability to discriminate between tuberculous and non-tuberculous mycobacteria (Chakravorty S et al., 2017). Moreover, the test may detect at least 15.6 Colony forming units (CFU) of MTB/ml in sputum samples in under two hours (Chakravorty S et al., 2017). Nonetheless, the technical and operational cost implications of the diagnostic test in resource-limited settings remain a challenge (Steingart KR et al., 2014; Stephen D. Lawn et al., 2011).

With sputum production among HIV infected individuals being limited (Peter et al., 2010), the need for alternative biological specimens for the diagnosis of TB arises. A rapid immunochromatographic test detecting the *Mycobacterium* cell wall antigen lipoarabinomannan (LAM) in urine samples, is available as a point-of-care test (POCT) for TB (Huerga et al., 2017). The test is easy to run, has no need for specialized equipment or laboratory facilities and results are obtainable within 25 minutes – rendering the test field applicable. Moreover, among PLWHIV, the test displays high Sp, with Se increasing with diminishing CD4 counts (Drain et al., 2014; Huerga et al., 2017; Peter et al., 2010; Shah et al., 2016)

1.2 Statement of the research problem

Kenya is largely dependent on passive case finding for TB detection (MOH, 2016). However, the implementation of active case finding by systematically screening and clinically evaluating individuals at risk such as those in close interaction with those diagnosed with TB and PLWHIV is expanding (MOH, 2016). Conventional laboratory tests implemented are likely to undermine large scale community based active surveillance efforts owing to their significant technical requirement and long turn- around times. POCTs would be an ideal complement in this situation. However, their field applicability needs to be evaluated.

The poor performance of the commonly used diagnostic tests further pose a challenge to the efforts made by the ministry in upscaling community active case detection. Smear-negative pulmonary TB, normal chest x- ray and increased instances of TB cases occurring apart from the lungs are commonly encountered among PLWHIV (CDC, 2012). This may in turn delay diagnosis leading to poor patient outcomes, increased mortality rate, increased healthcare-related costs, and silent transmission of the disease mainly among active working age groups who are mostly parents or guardians thus increasing exposure of children to the disease (Enos et al., 2018).

Previous TB diagnostic test evaluations have been conducted using mycobacterial culture as a reference test (Agrawal et al., 2016; Gelaw et al., 2017). A notable shortcoming of this method is that imperfect reference tests may introduce bias that undermines the accuracy estimates of the test(s) being evaluated. An alternative method involves the use of latent class models fit using Bayesian methods that allow for concurrent evaluation of Se and Sp of two or more tests with no prior knowledge of the unobserved disease status of individuals.

1.3 Justification

Diagnostic studies evaluating the performance of SSM, Xpert MTB/ RIF Ultra and TB LAM among PLWHIV have previously been conducted globally (Cattamanchi et al., 2009; Zifodya et al., 2021)). Several other studies have also been conducted in Kenya (Bonnet et al., 2008; Enos et al., 2018; Huerga et al., 2017). A major shortcoming of these evaluations is that the index tests were evaluated against imperfect reference tests. Hence introducing bias in the accuracy estimates of the evaluated tests.

Evidence on the performance of these diagnostic tools is critical to informing national guidelines for diagnosis and clinical management of TB. Furthermore, knowledge on the accuracy estimates of these tests is key to informing population-based surveillance of TB among PLWHIV with the aim of accurately quantifying its burden locally.

1.4 Research Questions

i. How accurate are SSM, Xpert Ultra and LAM antigen tests for the diagnosis of TB among HIV patients?

ii. What level of confidence is conferred by a positive or negative test result of SSM, Xpert Ultra and LAM in the diagnosis of TB among HIV infected individuals?

iii. What is the prevalence of MTB infection in this HIV population?

1.5. Objectives

1.5.1 Broad Objective

The broad objective of this study was to estimate the diagnostic accuracy of SSM, Xpert Ultra and LAM antigen examinations in detection of TB among HIV patients at Kibra Community Health Centre in Nairobi County, Kenya.

1.5.2 Specific Objectives

The specific objectives were as follows: -

i. To estimate the sensitivity and specificity of SSM, Xpert Ultra and urine LAM antigen tests for the diagnosis of TB among HIV patients.

ii. To estimate predictive values (positive and negative) of SSM, Xpert Ultra and urine LAM antigen tests for the diagnosis of TB among HIV patients.

iii. To estimate the true prevalence of TB infection among PLWHIV presenting at the Kibra Community Health Centre, Nairobi County.

2.0 LITERATURE REVIEW

2.1 The burden of TB among PLWHIV

TB remains to be the prime killer disease among PLWHIV with approximately 0.8 million cases and 250, 000 deaths having occurred in 2018. This is, in spite of the consistent improvements that have led in the enactment of extensive policies to lower the burden of HIV associated TB, hence resulting to a 60% and 68% reduction of deaths and mortality rates. From 620, 000 deaths experienced in 2000 to 250,000 deaths experienced in 2018 and mortality rate reduction from 10 per 100, 000 population experienced in 2000 to 3.3 per 100, 000 population in 2018. Kenya a high TB burden country, the HIV positive TB mortality rate is estimated to be at 26 per 100, 000 population (WHO, 2020; World Health, 2018).

A prevalence survey done in Kenya estimated TB/ HIV prevalence rate at 16.7%. This was considered to be lower in comparison to the TB/HIV notified cases which were estimated to be at 31 % in 2015 (MOH, 2017). This is attributable to successful execution of HIV interventions such as, expanding utilization of antiretroviral therapy (ART) coverage and regular screening done for HIV patients leading to early detection and treatment during the scheduled routine clinic visits (Onyango et al., 2017). Another possible explanation would be the high mortality rate associated with undiagnosed TB among PLWHIV in the community concealing the actual burden as reflected by the survey (Enos et al., 2018; Onyango et al., 2017).

Besides the mortality and morbidity burden, TB/ HIV disease poses a greater social and economic burden on individuals, families, communities and the health system as the most affected are the economically active age group. These infectious diseases are key contributors to poverty due to catastrophic health spending and high out of pocket expenditure due to their chronic nature (MOH, 2016).

Diagnostic challenges of HIV associated TB also further exacerbate the TB and HIV co- infection disease and death burden. Over the years the global surge in HIV has led to an increase in smear negative PTB hence making the bacteriological confirmation of TB a challenge (World Health, 2007). An estimated 45% of patients' enrollment for treatment has been guided by observing clinical features of TB and anomalies on chest radiography or histology results generally related with TB.

As a consequence a false positive outcome of TB diagnosis due to low Sp of the methods then leads to unnecessary enrollment in TB treatment (WHO, 2020).

2.2 Performance of TB diagnostic tests

2.2.1 SSM

Microscopy as a TB diagnostic tool is extensively used in underdeveloped nations as it is easy to use, its affordability, and high Sp of the test (Gelaw et al., 2017; Ngabonziza et al., 2016). The test Se has been variable depending on laboratory workload, user's expertise, capacity variation between laboratories, study setting, and sputum bacillary load (Park et al., 2014; Steingart et al., 2006).

A study conducted in Uganda evaluating the diagnostic accuracy of SSM among admitted HIV-infected patients found the test Se to be 52% and the Sp of 99% (Cattamanchi et al., 2009). A lower Se of 29% was obtained from a study conducted in India among HIV patients and the authors attributed this to the paucibacillary status of TB- HIV patients (Prasanthi and Kumari, 2005). A community-based study conducted in Kenya among HIV patients in an outpatient clinic reported a much lower test se ranging from 19%-22% (Bonnet et al., 2008). The test Se of SSM may vary depending on the colony-forming units (CFU) as was observed in a study conducted in Tanzania among HIV patients co infected with TB. In the study, samples with <20 CFU/ specimen had a Se of 22.6% whereas those with >100 CFU/ specimen the Se was shown to be 94.2 % (Matee et al., 2008).

2.2.2 Xpert Ultra

Molecular techniques have the advantage of having a fast TAT for identification of TB together with detection of drug resistance, standardized testing, and exhibiting the potential of being high throughput with reduction in biosafety requirements (Ramachandran and Muniyandi, 2018). Gene Xpert is one of such tests touted for its ability to rapidly identify TB and resistance to rifampicin drug which is important in enhancing patient care and reducing TB spread (Steingart et al., 2014). It is a molecular-based technique interfaced with single-use disposable cartridges and it is based on nucleic acid amplification. In comparison to other nucleic acid tests (NAATs), Gene xpert is distinct since it is mostly hands free as the sample processing, PCR amplification and diagnosis are incorporated in the gene xpert cartridge. Hence, the need for an expert staff or an advanced laboratory is not necessary (Pierre Le Palud and Bergot, 2014).

The widespread use of gene Xpert MTB/ RIF for the diagnosis of TB and rifampicin resistance was approved by WHO in 2010 for the following clinical indications (World Health, 2011) - Rapid TAT for TB detection and resistance to rifampicin antibiotic, improved tests Se and Sp and reduced to no production of aerosols as shown in a study, where neither the sample preparation step nor the automated processing led to the growth of culturable bioaerosols (Banada et al., 2010). The study findings on the average time for diagnosis of TB using gene Xpert was found to be 0 days (within 2hours) in comparison to microscopy which was 1 day, 30 and 16 days for solid and liquid culture respectively. Rifampicin resistance identification was found to be 0 days using gene Xpert in comparison to Line probe Assay and conventional DST which were found to be 20 days and 106 days respectively (Boehme et al., 2011). Xpert MTB/ RIF Ultra a successor technology to Xpert, using the same device after a software upgrade, was endorsed by the WHO in 2017 (WHO, 2017). Chiefly, Xpert Ultra has an additional semi- quantitative category for TB detection absent in Xpert MTB/ RIF that is reported as 'MTB trace detected' and this correlates to the lowest bacillary burden. Rifampacin results are however not available in this category and are reported as 'indeterminate'.

Studies have shown the test Se for Xpert Ultra (81%-91%) is less variable in comparison to Xpert MTB/ RIF (50% - 100%) (Boehme et al., 2011; Steingart et al., 2014; Zifodya et al., 2021) This is mainly because, Xpert MTB/ RIF Se varies with paucibacillary status. Among HIV-positive populations Se is improved among smear-positive HIV-positive individuals and it is sub-optimal among smear-negative HIV individuals (Boehme et al., 2011; Steingart et al., 2014). A study conducted in TB endemic countries such as Peru, South Africa, Philippines, and Uganda found the tests Se to be 71.8% % among smear-negative HIV individuals (Boehme et al., 2011). A lower Se of 53.3% was reported in a study conducted in a Prison setting in Malaysia as most of the participants had predominantly smear-negative samples (Al-Darraji et al., 2013). Xpert Ultra therefore has a higher incremental Se among paucibacillary status of TB. The test Sp is lower in Xpert Ultra (78%-96%) compared to Xpert MTB/RIF (92% - 100%) (Boehme et al., 2011; Steingart et al., 2014; Zifodya et al., 2021).

The operational feasibility of the test in resource-limited countries is however a challenge despite the tests' improved performance in diagnosing HIV associated TB. As of 2018, only 188 health facilities had the Gene Xpert equipment in Kenya (Enos et al., 2018). Some of the possible reasons attributed to the low uptake include: increased costliness of the assay, inability to satisfy operational

requirements such as continuous and steady power supply, temperature regulation, and annual standardization of the equipment components (Steingart et al., 2014; Stephen D Lawn and Nicol, 2011)

2.2.4 Lateral flow LAM Ag Test

The most promising antigen for Mycobacterial detection for TB diagnosis is LAM. It is a primary fragment of the mycobacterium cell wall that is filtered in urine from metabolically active and degrading bacterial cells from TB infected sites (Achkar et al., 2011; Minion et al., 2011). Urine as a diagnostic sample offers practicability clinically as it is easily obtainable from both adults and children and less hazardous as it is less contaminated (Achkar et al., 2011). A much easier lateral flow immunochromatographic point of care test detecting urinary LAM for diagnosis of TB among HIV infected individuals during routine screening has been in use from 2012 to date (Stephen D Lawn1, 2012).

This assay is ideally suitable for high burden TB- HIV resource limited countries with limited infrastructure. Initial sample processing of the urine sample is not necessary, the simplicity of the lateral flow test can be easily used for each patient at a non - laboratory based setting with non - laboratory staffs, it does not require special storage conditions or electricity and results are easily obtainable after 25 to 30 minutes making the possibility of the availability of results during one visit at the clinic. Its affordability enhances its accessibility as a diagnostic test for HIV associated TB among patients with increased mortality (Lawn et al., 2012).

The first evaluation study of the assay was conducted on a community-based ART clinic in South Africa and the tests overall Se was found to be 28%. Despite the low overall test Se, a negative correlation between improved tests Se with reducing CD4 cell counts was demonstrated. The tests Se was at its highest with reduced CD4 cell counts (66.7% at < 50 cells/ul, 51.7% at < 100 cells/ ul and 39% at 200 cells/ ul and Sp was > 98% for all strata. The tests PPV was found to improve with CD4 cell counts < 150 cells / ul but it reduced when the assay was applied among patients with increased CD4 cell counts. The NPV was however insufficiently high to exclude a TB diagnosis. These findings therefore reflect the restriction of the test's utility for screening of PTB in patients with progressive immunodeficiency caused by HIV. A test Se of 72.2% equivalent to a single gene xpert test se in this population group was obtained when LAM assay was combined with SSM (Lawn et al., 2012).

A study on performance of the assay conducted in South Africa with a different population group of HIV infected hospitalised patients, had the same findings of improved test Se with reduced number of CD4 counts. The LAM test was positive in roughly 50 percent of all patients with limited sputum production and smear negative HIV associated TB with < 200 cells/ ul CD4 cell counts and would have otherwise had the need for further investigations to be undertaken. A higher overall tests Se was observed i. e 45% possibly due to the advanced immunosuppression in this population group (Peter et al., 2012). Another study conducted in an outpatient clinic as opposed to a controlled laboratory setting, the overall tests Se was found to be lower (Se – 28.3%, Sp – 90.1%) slightly improving to (Se- 37.5%) among patients with CD4 counts < 100 cells/ ul. This were however higher than the SSM test Se which more cases were at (Se- 18.3%) with LAM having identified 10% of culture positive PTB than SSM. The reduced test se was attributed to, the patient group in this particular setting having generally less advanced disease (Paul K Drain and Rochelle P Walensky, 2014). These findings further confirm the tests effectiveness among TB patients co infected with TB and have greater mortality risk due to advanced immunodeficiency.

2.2.4 Other TB diagnostic tests

2.2.4.1 Culture based techniques

Solid and liquid media cultures are alternative diagnostic tests for TB (Dinnes et al., 2007). Culture is more sensitive in comparison to SSM as it has a detection limit of 10 to 100 viable bacteria/ ml of sputum (Parsons et al., 2011). Although not routinely used except for surveillance, treatment failure and or DST for TB diagnosis, solid culture media composed of Lowenstein Jensen (LJ) is more common than liquid culture media in resource limited countries (Diriba et al., 2017). The reason it is preferred over the liquid media is because: it is easily indigenously made, it has the ability to resist significant PH changes, it can be stored for a long length of time in cold storage, and it aids in the isolation of almost all Mycobacterium species and consists of Malachite green which hinders the growth of most contaminants. Liquid media on the other hand despite it having better Se, superior recovery rates and a shorter TAT than solid media, it is expensive as it requires a combination of expensive ingredients, it is more labor intensive and is more prone to contamination (Parsons et al., 2011).

Culture is increasingly gaining recognition as an important TB diagnostic tool especially among HIV patients as it is able to detect low bacillary load commonly experienced among this population (Getahun et al., 2010). The major challenge experienced with this method is that it is often slow, with the growth of the organism taking up to 6weeks especially with paucibacillary specimens and the need for infrastructure and high skilled labor which is a challenge in resource limited countries (Forbes et al., 2018).

2.2.4.2 Loop mediated isothermal amplification (TB LAMP)

This is a manual molecular diagnostic test for TB that does not require specialized infrastructure for nucleic acid amplification. It is a rapid procedure as the outcome of the results are obtained within an hour and highly skilled labor is not required. Hence, rendering it more affordable and suitable for use in resource limited countries (Yan et al., 2016). The tests accuracy has been shown to be high in smear positive patients with a study conducted in Gambia reporting a Se of 99% and Sp of 94% (Bojang et al., 2016). Studies conducted in India and Ethiopia however reported lower test se of 75% and 79.5 % respectively. Among smear negative patients the test performed poorly with both studies reporting a test se of 33% (Gelaw et al., 2017; George et al., 2011). WHO, however recommends the use of gene xpert MTB/ RIF over TB LAMP especially among populations at risk of smear negative and multi drug resistance such as people living with HIV (World Health, 2016).

2.2.4.3 Serological tests

Immunochromatographic based tests are more favorable for use in primary health care clinics or basic health laboratories in low-income countries. They are more suitable, as they do not require sophisticated equipment, they take only a few minutes before obtaining a result and do not require highly skilled labor (WHO, 2008). Serological POCT for infectious diseases such as HIV and malaria have successfully been developed (Sturenburg and Junker, 2009). Efforts have been made for decades to develop sensitive and specific immune based tests for detection of TB without major success (Parsons et al., 2011). Following a systematic review study conducted to evaluate the accuracy of commercially available antibody detection tests for PTB detection, it was concluded that generally the tests have high variation in their performance with tests Se ranging from 10% to 90% and test Sp ranging from 47% to 100%. Increased test Se and increased test Sp were observed among smear positive samples and healthy volunteers respectively. Data on the performance of the tests in smear negative patients, children and among HIV patients was limited (Parsons et al., 2011; Steingart et al., 2006; WHO, 2008)

3.0 METHODOLOGY

3.1 Study area

The study was carried out at Kibra Community Health Centre. It is a level three hospital located in Laini Saba – Kibra, Nairobi County. A large proportion of households served within the health facility are from the neighboring slums of Kibra and Mukuru Kwa Njenga. It is a good study area due to the high dual burden of HIV/AIDS and TB. - leading causes of mortality in slums (Beguy et al., 2015) It registers about 150-200 outpatients daily, conducts approximately 50-60 deliveries monthly, and offers CCC services to over 1,500 patients per month.

At the CCC department, PLWHIV receive holistic care and management. Sub- sections within the CCC department include: HIV testing services, prevention of mother to child transmission, TB clinic, pharmacy, nutrition and records. The department is operational during the weekdays from 8 am to 5 pm. The cadres of health care workers within the department include: five clinicians, twenty-two nurses, three pharmacists, three laboratory technologist, six HIV testing services counsellors, two records officers, one screener, and two cough monitors

3.2 Study design

A facility- based cross-sectional study was used to evaluate the performance of the three diagnostic tests that is SSM, Xpert Ultra and LAM for TB among PLWHIV. The rationale for the choice of this design stems not only from the descriptive nature of the study but also the ease of recruitment of study participants presenting to the CCC clinic for care.

3.3 Study population

3.3.1 Target Population

This consisted of all PLWHIV seeking HIV care services within Kibra and its environs.

3.3.2 Source population

This comprised all PLWHIV seeking health services at Kibra Community Health Centre who met the eligibility criteria.

3.4 Eligibility criteria of study participants

3.4.1 Inclusion criteria

All PLWHIV (symptomatic and asymptomatic for TB) aged ≥18 years who visited the CCC at Kibra Community Health Centre for care and consented to be included in the study.

3.4.2 Exclusion criteria

All PLWHIV already under treatment for TB, and those not able to produce the required diagnostic specimen were excluded from the study.

3.5 Target condition

The underlying disease status (referred to here as presence of TB infection) intended for detection by the three tests (SSM, LAM assay and Xpert Ultra) was represented by a sputum and urine sample containing either live MTB or its antigens at any concentration level.

3.6 Sample size determination and sampling strategy

This was determined using the McNemar's sample size formula for paired proportions (Connor, 1987):

$$n_{per\ test} = \left(\frac{Z_{\alpha/2}\sqrt{p_{disc}} + Z_{\beta}\sqrt{p_{disc} - p_{diff}^2}}{p_{diff}} \right)^2$$

$$p_{disc} = (1 - Se_1) + (1 - Se_2)$$

$$p_{diff} = (1 - Se_1) - (1 - Se_2)$$

Where: $n_{per\ test}$= sample size required for each test, $Z_{\frac{\alpha}{2}}$ (1.96) is the value required for the two-sided 95% confidence level, and Z_{β} (-0.84) is the value specifying the desired power of 80%. Se_1 and Se_2 are estimates of Se of the Gene xpert MTB/RIF and SSM respectively from literature that is Se_1 is 90.3% and Se_2 is 67.1% (Boehme et al., 2011).

As per the above mentioned figures, a total sample size of 190 was generated, after upward adjustment by 5% to account for non- response.

3.7 Sampling strategy

Individuals visiting the hospital's CCC clinic were systematically randomly sampled following their order of arrival and every seventh person (after an initial random start) who met the eligibility criteria was selected. Recruitment was done on arrival at the clinic, right after triage by the nurse and examination by the clinician. The potential participant would then be taken through the study

instructions and the samples required before being requested to sign the consent form. Upon giving consent, the participant would then be sent to the laboratory to be instructed on the sample collection process and be given the tools for collection. Those not meeting the inclusion criteria were excluded without replacement. This was carried out up to the required sample size of 190.

3.8 Study flow chart

Figure 1: Flow chart displaying the process of evaluation of Se and Sp of TB LAM, Xpert Ultra and SSM

190 HIV positive presumptive TB patients screened for inclusion into the study and upon consenting assisted to fill questionnaire with clinician (n=190)

↓

190 participants referred to the lab for sample collection of sputum and urine.

2 unable to provide all samples hence excluded

↓

188 samples screened for TB. Sputum samples screened using the Xpert Ultra test and SSM. Urine samples screened using TB LAM.

5 MTB indeterminate Xpert Ultra results omitted

↓

Cross-tabulated counts of the three test outcomes at Kibra Community Health Centre n= 183

Stratum	Test outcomes combinations (LAM, Xpert Ultra & SSM)								Total (%)
	+ + +	+ + -	+ -+	- + +	+ - -	- + -	- - +	- - -	
Single Pop	a	b	c	d	e	f	g	h	n=183 (100%)

↓

Estimation of the accuracy of Se and Sp for LAM, Xpert Ultra and SSM using Bayesian latent class approach

Where: **a** = proportion of patients that tested positive to all the three tests,

b= proportion of patients that tested positive to both LAM and Xpert Ultra and negative to SSM,

c= proportion of patients that tested positive to LAM and SSM and negative to Xpert Ultra,

d= proportion of patients that tested negative to LAM and positive to both Xpert Ultra and SSM,

e= proportion of patients that tested positive to LAM and negative to Xpert Ultra and SSM,

f= proportion of patients that tested negative to both LAM and SSM and positive to Xpert Ultra,

g= proportion of patients that tested negative to both LAM and Xpert Ultra and positive to SSM,

h=proportion of patients that tested negative to all the three tests.

3.9 Study variables and their method of measurement

Taking into account the descriptive nature of the study, the variables of interest related to a positive or negative test outcome by the SSM, Xpert Ultra and LAM tests. Socio- demographic variables of the participants and their measurements were measured as outlined in the table below:

Table 1: Participants' socio- demographic characteristics and their method of measurement

Variable (type)	Measurement
Age (Continuous)	Was recorded in years
Sex (Binary)	Was captured as male or female
Residence (Binary)	Was captured as formal or informal
Employment status (Binary)	Was captured as either employed or unemployed
Level of education (Ordinal)	Was based on the highest level of education attainment categorised as either none, primary, secondary or tertiary
ART use (Binary)	Was reported as either experienced or naive
Marital status (nominal)	Was categorised as single, married, separated or divorced and widowed

3.9 Data management

3.9.1 Data collection plan

A clinical officer from the CCC department and a laboratory technologist from the laboratory department were recruited as research assistants. They were then trained on how to administer the questionnaires to the participants and instruct them on the collection of the required samples. The principal investigator together with the laboratory technologist carried out the test procedures.

3.10 Laboratory methods

3.10.1 SSM

This was performed as per standard guidelines (Fitz-gerald, 2013). Briefly, a sputum smear covering 2cm by 1 cm on the center of the slide was prepared immediately after receipt of the sample. The smears were then stained with the primary stain 1% Carbol fuchsin for a period not exceeding 10 minutes. Decolorization was then performed by flooding the slides with 25% sulphuric acid for 3 minutes and finally the counterstain 0.1% methylene blue was added for 1 minute. Slides were rinsed before every staining stage and excess water drained by gently tilting each slide. The slides were subsequently examined under a light microscope at 100x magnification. Mycobacterium quantification was achieved by counting the AFB and reported as per the International union against TB and lung disease recommended grading of sputum smear microscopy (Dawson, 2000). For analytical purposes, AFB counts above zero constituted a positive result; otherwise negative.

3.10.2 Xpert Ultra test

This was carried out as described elsewhere (Raja et al., 2005). Briefly, sample reagent (a constitution of sodium hydroxide and Isopropanol) was added into the sample in a ratio of 2:1 for liquefaction and inactivation of the sputum. The mixture was then vigorously shaken and incubated at room temperature for 15 minutes. The liquefied specimen was afterwards pipetted into the test cartridge. The pre-labelled test cartridge was then loaded into the MTB/RIF test platform where automated testing commenced. The semi- nested real time amplification and detection occurred in the integrated reaction tube and the results were printed. Results were interpreted as positive when MTB was detected.

3.10.3 LAM

Alere Determine™ TB LAM antigen kit was used to test for the presence of TB LAM antigen in the urine sample that had been collected. This was done as per the instructions in the Alere Determine™ TB LAM antigen manual (Abbott, 2010). A total of 60ul of urine was added into the strip sample well. In order to allow for the urine to flow towards both the test and control windows, the strip was incubated at room temperature for 25 minutes. A positive result was denoted by the appearance of two colour bands whereas one band appearing on the control line indicated a negative result.

3.11 Data processing and analysis

Bayesian latent class model fitted in Open BUGS v3.2.2 (Lunn et al., 2009) but called from R software through the 'BRugs' package (Thomas, 2006) was used to estimate the TB prevalence, Se and Sp of the three tests together with their predictive values. The guidelines for standards for reporting diagnostic accuracy studies that use BLCMs was used to inform the analysis and reporting of the results (Kostoulas et al., 2017).

Three assumptions are necessary when fitting a BLCM (Hui and Walter, 1980): Firstly, the tests should be conditionally independent given the TB infection status. This was met since microscopy targets the live bacterium, Xpert Ultra amplifies and detects the *Mycobacterium* DNA and TB LAM detects the *Mycobacterium* cell wall LAM antigen. Hence, the probability of testing either positive or negative on one diagnostic tool did not depend on the outcome of the other tests. Secondly, the Se and Sp of the tests being evaluated should be constant across the subpopulations studied. With a single target population, as was the case here, the tests' constancy premise was likely to be upheld. Thirdly, the target population should consist of two or more subpopulations with different

prevalences. In the situation where only a single population exists, at least three tests were necessary to provide sufficient degrees of freedom to achieve model identifiability (Toft et al., 2005).

A multinomial distribution was assumed for the counts (O) of the different test combinations (for example +, +, +) and took the form below:

$$O \mid Se_i\ Sp_i\ P \sim multinomial\ (Prob, n)$$

Where Sei and Spi reflect the specific test characteristics of the individual (i) tests ($i = 1, 2, 3$), P denotes the prevalence for the singular population, $Prob$ is a vector of probabilities of observing different test combinations and n denotes the sample size of the study population. As an illustration, the probability of an individual testing positive on all three tests is given by:

$$Prob = \Pr(T_1^+ T_2^+ T_3^+ | D^+) + \Pr(T_1^+ T_2^+ T_3^+ | D^-)$$

$$= Se_1\ Se_2\ Se_3 P + [1 - Sp_1][1 - Sp_2][1 - Sp_3][1 - P]$$

With three tests, a total of seven degrees of freedom was sufficient to estimate the required seven parameters (the Se and Sp of the three tests together with the single population prevalence). Since there was no reliable pre- existing information for any of the tests, uninformative priors ($beta\ (1,1)$) were used as initial parameters for the model.

The positive predictive value (PPV) and negative predictive value (NPV) of the test (i) were estimated as follows:

$$ppv = PSe_i/(PSe_i + [1 - P][1 - Sp_i])$$

$$npv = [1 - P]Sp_i/(P[1 - Se_i] + [1 - P]Sp_i$$

Two Markov Chain Monte Carlo chains each having different values were used to initialize the Bayesian model. Convergence of the chains were then evaluated via the time series plots of selected variables and the Gelman-Rubin diagnostic plots. The posterior distribution of the test estimates (Se, Sp and the predictive values) and the population prevalence were reported as the median and the associated 95% posterior credible intervals (PCI). The Youden index which is a measure of a test's overall diagnostic ability was also computed as : $Se\ + Sp\ - 1$ (Schisterman et al., 2005)

3.12 Minimization of errors and biases

The participants were randomly selected so as to minimize selection bias and enhance generalizability of the study findings to the study population. Information bias was reduced by training the RAs on appropriate interviewing techniques as well as blinding the lab personnel screening the samples on the results of the other tests. Double entry of the data by two independent persons was done to ensure that data entry errors were minimized. A Bayesian model framework was employed to reduce bias in the index tests' estimates.

The tests being carried were done at Kibra Community Health Centre which is a facility regulated by the Kenya Medical Practitioners and dentists council. Qualified personnel ensured proper labelling of samples and instructed enrolled participants on the correct way of sample collection to avoid pre-analytical errors. The laboratory technologists within the facility would conduct the tests as per the laid down standard operating laboratory procedures and at the same time observing the specified quality control measures. Manufacturer's instructions for kits, use of equipment, reagents preparation and testing was also adhered to.

3.13 Ethical Considerations

Approval for carrying out of the study was sought and obtained from the Kenyatta National Hospital (KNH)-University of Nairobi (UoN) Ethics and Research Committee (ERC)- Reference number (KNH/ERC/R/ 145 and KNH/ ERC/ Mod & SAE/ 347), Nairobi metropolitan services-Reference number (EOP/NMS/HS/ 222), the lang'ata sub-county offices and the Kibra Community health center administration for data collection. Additionally, a research license was obtained from the National Commission for Technology and Innovation (NACOSTI)- License number (NACOSTI/ P/ 21/ 14098). The study type and test investigations that were to be executed were explained to the participants and informed consent sought from them before enrollment into the study. The patients were also informed due to the voluntary nature of the study, those who declined to enroll in the study would still get treatment without interruption of the usual care and where facilitation was required it was done. Patient confidentiality was assured by ensuring entry of data into a password-protected database.

4.0 RESULTS

4.1 Descriptive statistics

In total, 190 patients seeking care at the Kibra Community Health Center CCC clinic were enrolled in the study between September 2022 and March 2023. Two of the participants were unable to

provide all the required samples and were thus excluded from the analysis. Five were also excluded from the analysis because their Xpert Ultra results were invalid.

The sociodemographic characteristics and information on HAART status is as shown in **Table 2.** The median age of the participants was 43 years (Range: 19 – 82 yrs). The majority of participants were female (64.0%, n=117), married (60.7%, n=111); with only 2.2% (n=4) lacking a formal education. A substantial percentage of the participants were on HAART (97.5%, n=178).

Table 2: Summary statistics on the sociodemographic characteristics and information on HAART status for HIV patients presenting to the Kibra Community Health Center, Nairobi County, Kenya. (n=183)

Variable	Values	Median	Range	Frequency n (%)
Age (years)				
	-	43	19-82	-
Weight (kg)				
	-	60	40-101	-
Sex				
	Male	-	-	66(36.1)
	Female	-	-	117(64.0)
Marital status				
	Married	-	-	111(60.7)
	Single	-	-	50(27.3)
	Separated/ divorced	-	-	18(9.8)
	Widowed	-	-	4(2.2)
Level of education				
	None	-	-	4(2.2)
	Primary	-	-	91(49.7)
	Secondary	-	-	69(37.7)
	Tertiary	-	-	19(10.4)
Area of residence				
	Formal	-	-	60(32.8)
	Informal	-	-	123(67.2)
Occupation				
	Employed	-	-	67(36.6)
	Unemployed	-	-	116(63.4)
HAART				
	Naïve	-	-	5(2.7)
	Experienced	-	-	178(97.3)

The cross-tabulated counts of the tests' outcomes are displayed in **Table 3.**

Table 3: Cross- classified results for rapid diagnostic test LAM, XPERT ULTRA and Sputum smear microscopy (SSM) tests for diagnosis of TB among people living with HIV (PLWHIV) in the study population in Kibra Community Health Centre CCC clinic, Nairobi County, Kenya. (n=183)

Cross-tabulated counts of the three test outcomes									
Stratum	Test outcomes combinations (LAM, XPERT ULTRA & SSM)								Total (%)
	+ + +	+ + -	+ -+	- + +	+ - -	- + -	- - +	- - -	
Single Pop	1	1	0	3	21	8	0	149	183 (100%)

4.3 Sensitivity, Specificity, predictive values and true prevalence

The estimates of the Se, Sp of the three tests, along with their respective predictive values and the prevalence of *Mycobacterium tuberculosis* infection are shown in **Table 4.** The Xpert Ultra assay registered a higher Se (85.0; 95% PCI [41.4 – 99.4]) compared to LAM (26.8; 95% PCI [4.7 – 67.6]) and SSM (56.7 [16.4 – 97.4]). However, SSM had the highest Sp (99.6; 95% PCI [97.7 – 100.0]). As per the Youden indices, Xpert Ultra yielded the highest overall combination of Se and Sp at 80.8% (95% PCI [37.0 – 96.5]). On predictive values, SSM recorded the highest PPV at 84.5% (95% PCI [38.4 – 99.4]). Nonetheless, all the tests exhibited noticeably high NPVs (>96%). The true prevalence of MTB infection was low (4.1; 95% PCI [1.2 – 11.2])

Table 4. Estimates of prevalence, sensitivity, and specificity of TB lipoarabinomannan (LAM), Gene Xpert *Mycobacterium/Rifampicin* (MTB/RIF) Ultra, and Sputum smear microscopy (SSM) tests for *Mycobacterium tuberculosis* infection among HIV patients, their corresponding predictive values and Youden indices.

Parameter	Estimate (95% PCI)
Se_{LAM}	26.8 (4.7 – 67.6)
Se_{Xpert}	85.0 (41.4 – 99.4)
Se_{SSM}	56.7 (16.4 – 97.4)
Sp_{LAM}	87.6 (82.1 – 92.0)
Sp_{Xpert}	96.0 (91.6 – 99.6)
Sp_{SSM}	99.6 (97.7 – 100)
P	4.1 (1.2 – 11.2)
NPV_{LAM}	96.7 (89.7 – 99.3)
NPV_{Xpert}	99.4 (95.1 – 100)
NPV_{SSM}	98.3 (91.5 – 100)
PPV_{LAM}	8.3 (1.1 – 26.8)
PPV_{Xpert}	45.3 (13.5 – 94.8)
PPV_{SSM}	84.5 (38.4 – 99.4)
$Y.index_{LAM}$	14.3 (-8.9 – 55.6)
$Y.index_{Xpert}$	80.8 (37.0 – 96.5)
$Y.index_{SSM}$	56.2 (15.7 – 96.8)

5.0 DISCUSSION

This study has utilized Bayesian latent class analysis for the estimation of the accuracy of SSM, Xpert Ultra and LAM tests (together with their corresponding predictive values) for the diagnosis of TB infection among PLWHIV. This is a key strength in this study, since BLCM allows for the estimation of index tests' characteristics devoid of classification errors typically inherent in traditional evaluation studies employing the use of imperfect reference standards (Claes Enøe et al., 2000). Accordingly, the estimates obtained from this study can be considered generalizable to settings with similar MTB burden among PLWHIV.

On Se, Xpert Ultra assay recorded the highest Se of the three tests. This result is in agreement with previous reports that demonstrated the superiority of Xpert Ultra Se over other tests in TB screening and diagnosis among PLWHIV in outpatient settings. In particular, in a systematic review involving studies conducted in high TB prevalence settings among PLWHIV, the Xpert Ultra test Se ranged between 81% - 90% (Zifodya et al., 2021). The superiority of the test Se owes to its low limit of detection of tubercle bacilli (16 CFU/ ml of sputum) (Helb et al., 2010) compared to SSM whose threshold is 5,000- 10,000 CFU/ ml of sputum (Behr et al., 1999b) and LAM at ~ 2000 CFU / ml (Kawasaki et al., 2019; Nakiyingi et al., 2014).

The LAM test exhibited the lowest Se in the diagnosis of TB in the present study. This performance is comparable with findings from studies carried out in other outpatient settings. For instance, among existing, ART-naïve and newly diagnosed HIV patients presenting to outpatient facilities in LMICs, LAM's Se was found to range between 25% - 30% (Balcha et al., 2014; Drain et al., 2014; Nakiyingi et al., 2014; Stephen D Lawn, 2012). Notably, an inverse relationship has been demonstrated, with LAM's test Se increasing with reducing CD4 counts (Aliasgar Esmail and Michele Tomasicchio, 2020; Drain et al., 2014). This is especially so among critically ill patients. LAM Se was observed to be at its highest (≥65%) among patients with CD4 counts <50 cells/ul and Se of ≤35% and ≤55% for patients with CD4 counts < 100 and < 200 cells/ul respectively (Aliasgar Esmail and Michele Tomasicchio, 2020; Drain et al., 2014). Increased uptake of ART in the present study setting may have contributed to improved CD4 counts in the patient population and consequently a low Se of the LAM test - underscoring its limited utility in this setting. SSM registered a test Se of (56.7%) which falls within the 18% - 94.2% range observed in other studies (Jean Claude Semuto Ngabonziza et al., 2016; Mecky Matee et al., 2008). This variability in performance is attributable to the number of CFUs available in a sample, with Se increasing with

higher CFUs. Moreover, the test Se is also highly dependent on user expertise and other technical and operational factors (Mecky Matee et al., 2008).

As regards Sp, SSM recorded the highest which is consistent with findings from studies carried out in outpatient settings among PLWHIV (Balcells et al., 2012; Catharina C. Boehme et al., 2010). The low Sp displayed by LAM is also corroborated by findings from other studies carried out in similar low-resource settings where specificities ranging between >90%-100% were registered (Balcha et al., 2014; Nakiyingi et al., 2014; Paul K. Drain, 2015; Peter et al., 2015). Xpert Ultra Sp is in agreement with specificities found in other similar settings where the test Sp was reported to range between 78%- 96% (Berhanu et al., 2018; Zifodya et al., 2021).

False negative and false positive results compromise the Se and Sp test's estimates respectively. As for LAM and SSM, false negative results are more likely to occur in patients with bacterial load below the tests detection limits (Saeed et al., 2018). Additionally, LAM is more likely to give false negative results in patients who have already received anti-TB treatment (Nel et al., 2017). False positive results by LAM have been demonstrated in samples contaminated with non- Mycobacterial pathogens such as Nocardia and Candida spp. that similarly exhibit LAM-like glycoprotein antigens. (Peter et al., 2015) . SSM is also unable to distinguish MTB from other smear positive mycobacteria spp. (Maxwell Oluwole Akanbi et al., 2017). False positives by Xpert Ultra could be attributable to detection of MTB DNA in patients previously treated for TB (Balcells et al., 2012).

Notably, in this population, the three tests' sensitivities displayed wide credible intervals (signifying low precision of the estimates) since there were few diseased individuals. In contrast, the tests' Sps demonstrated high precision owing to the significant number of truly non-diseased individuals. Overall, in this low-prevalence TB setting, Xpert Ultra affords good promise for informing treatment and surveillance for TB among PLWHIV.

In this HIV population with low MTB prevalence (4.1%), generally low PPV's but high estimates of NPV's (> 96%) were obtained for all the three tests. These estimates signify a stronger confidence in a negative than a positive test result. Consequently, in this low-prevalence setting where the probability of false positives is highly expected, a multiple testing strategy with serial interpretation of the test results may be necessary in order to raise the confidence in a positive test result. This could entail an initial screening with the more sensitive Xpert Ultra test, with any

resulting positives followed up with the more specific SSM test. This approach should diminish the likelihood of subjecting false positive individuals to unnecessary protracted therapy for TB.

6.0. CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

The study findings revealed that Xpert Ultra registered the highest Se compared to SSM and LAM. However, SSM registered the highest Sp and thus PPV estimate. Nonetheless, the three tests recorded similar NPVs.

6.2 Recommendations

- Owing to the low prevalence of TB in the study setting, an optimal testing approach could entail an initial screening with the more sensitive Xpert Ultra assay, with the resultant positives re-tested with the more specific SSM test – a serial testing strategy - to bolster the overall PPV of a treatment or surveillance program.
- Future studies could focus on validating these findings in similar low-prevalence TB settings.

7.0 LIMITATIONS

- In this single population, it afforded seven degrees of freedom only sufficient to estimate seven parameters. The available degrees of freedom precluded an assessment of the BLCM assumptions. Particularly the constancy of the Se and Sp of the three tests and the conditional independence of the test given the MTB infection status.

7.0 REFERENCES

Abbott, 2010. Determine™ TB LAM Ag SAVING LIVES with early TB diagnosis in people with HIV.

Achkar, J.M., Lawn, S.D., Moosa, M.Y., Wright, C.A., Kasprowicz, V.O., 2011. Adjunctive tests for diagnosis of tuberculosis: serology, ELISPOT for site-specific lymphocytes, urinary lipoarabinomannan, string test, and fine needle aspiration. J Infect Dis 204 Suppl 4:S1130-41.

Agrawal, M., Bajaj, A., Bhatia, V., Dutt, S., 2016. Comparative Study of GeneXpert with ZN Stain and Culture in Samples of Suspected Pulmonary Tuberculosis. J Clin Diagn Res 10:DC09-12.

Akanbi, M.O., Achenbach, C., Taiwo, B., Idoko, J., Ani, A., Isa, Y., Agbaji, O., Ukoli, C., Akande, P., et al., 2017. Evaluation of gene xpert for routine diagnosis of HIV-associated tuberculosis in Nigeria: A prospective cohort study. BMC Pulm Med 17:87.

Al-Darraji, H.A., Abd Razak, H., Ng, K.P., Altice, F.L., Kamarulzaman, A., 2013. The diagnostic performance of a single GeneXpert MTB/RIF assay in an intensified tuberculosis case finding survey among HIV-infected prisoners in Malaysia. PLoS One 8:e73717.

Aliasgar Esmail, a., b Anil Pooran,a,b Natasha F. Sabur,a,c Mohammed Fadul,a,b Mantaj S. Brar,d Suzette Oelofse,a,b, Michele Tomasicchio, a., b Keertan Dhedaa,b,e,f, 2020. An Optimal Diagnostic Strategy for Tuberculosis in Hospitalized HIV-Infected Patients Using GeneXpert MTB/RIF and Alere Determine TB LAM Ag. Journal of clinical microbiology.

Balcells, M.E., García, P., Chanqueo, L., Bahamondes, L., Lasso, M., Gallardo, A.M., Cifuentes, L., 2012. Rapid molecular detection of pulmonary tuberculosis in HIV-infected patients in Santiago, Chile. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 16:1349-53.

Balcha, T.T.W., N. Sturegard, E. Skogmar, S. Reepalu, A., Jemal, Z.H., Tibesso, G., Schon, T., Bjorkman, P., 2014. Detection of lipoarabinomannan in urine for identification of active tuberculosis among HIV-positive adults in Ethiopian health centres. Tropical medicine & international health : TM & IH 19:734-42.

Banada, P.P., Sivasubramani, S.K., Blakemore, R., Boehme, C., Perkins, M.D., Fennelly, K., Alland, D., 2010. Containment of bioaerosol infection risk by the Xpert MTB/RIF assay and its applicability to point-of-care settings. J Clin Microbiol 48:3551-7.

Beguy, D., Elung'ata, P., Mberu, B., Oduor, C., Wamukoya, M., Nganyi, B., Ezeh, A., 2015. Health & Demographic Surveillance System Profile: The Nairobi Urban Health and Demographic Surveillance System (NUHDSS). International journal of epidemiology 44:462-71.

Behr, M.A., Warren, S.A., Salamon, H., Hopewell, P.C., de Leon, A.P., Daley, C.L., Small, P.M., 1999a. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. The Lancet 353:444-49.

Behr, M.A., Warren, S.A., Salamon, H., Hopewell, P.C., Ponce de Leon, A., Daley, C.L., Small, P.M., 1999b. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. Lancet 353:444-9.

Berhanu, R.H., David, A., da Silva, P., Shearer, K., Sanne, I., Stevens, W., Scott, L., Forbes, B.A., 2018. Performance of Xpert MTB/RIF, Xpert Ultra, and Abbott RealTime MTB for Diagnosis of Pulmonary Tuberculosis in a High-HIV-Burden Setting. Journal of clinical microbiology 56.

Boehme, C.C., Nicol, M.P., Nabeta, P., Michael, J.S., Gotuzzo, E., Tahirli, R., Gler, M.T., Blakemore, R., Worodria, W., et al., 2011. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. The Lancet 377:1495-505.

Bojang, A.L., Mendy, F.S., Tientcheu, L.D., Otu, J., Antonio, M., Kampmann, B., Agbla, S., Sutherland, J.S., 2016. Comparison of TB-LAMP, GeneXpert MTB/RIF and culture for diagnosis of pulmonary tuberculosis in The Gambia. Journal of Infection 72:332-37.

Bonnet, M., Ramsay, A., Githui, W., Gagnidze, L., Varaine, F., Guerin, P.J., 2008. Bleach sedimentation: an opportunity to optimize smear microscopy for tuberculosis diagnosis in settings of high prevalence of HIV. Clin Infect Dis 46:1710-6.

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D.,, Shubhada Shenai, P.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S.,, Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D.,, David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D.,, David Alland, M.D., and Mark D. Perkins, M.D., 2010. Rapid Molecular Detection of Tuberculosis and Rifampin Resistance. The New England Journal of Medicine 363.

Cattamanchi, A., Dowdy, D.W., Davis, J.L., Worodria, W., Yoo, S., Joloba, M., Matovu, J., Hopewell, P.C., Huang, L., 2009. Sensitivity of direct versus concentrated sputum smear microscopy in HIV-infected patients suspected of having pulmonary tuberculosis. BMC Infect Dis 9:53.

CDC, 2012. CDC Grand Rounds: the TB/HIV Syndemic, Geneva, Switzerland.

Chakravorty S, S.A., Rowneki, M, P.H., Cao Y, Ryan J, Banada PP,, Deshpande S, S.S., Gall A, Glass J,, Krieswirth B, S.S., Nabeta P,, Tukvadze N, R.C., Skrahina A, Tagliani E,, Cirillo DM, D.A., Denkinger CM, Persing, D, K.R., Jones M, Alland D. , 2017. The new Xpert MTB/RIF Ultra: improving detection of Mycobacterium tuberculosis and resistance to rifampin in an assay suitable for point-of-care testing. American Society for Microbiology Volume 8.

Claes Enøe, Marios P Georgiadis, Johnson, W.O., 2000. Estimation of sensitivity and specificity of diagnostic tests and disease prevalence when the true disease state is unknown, Preventive Veterinary Medicine. 45:61-81.

Connor, R.J., 1987. Sample size for testing differences in proportions for the paired-sample design. Biometrics 43:207-11.

Dinnes, J., Deeks, J., Kunst, H., Gibson, A., Cummins, E., Waugh, N., Drobniewski, F., Lalvani, A., 2007. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health technology assessment (Winchester, England) 11:1-196.

Diriba, G., Kebede, A., Yaregal, Z., Getahun, M., Tadesse, M., Meaza, A., Dagne, Z., Moga, S., Dilebo, J., et al., 2017. Performance of Mycobacterium Growth Indicator Tube BACTEC 960 with Lowenstein-Jensen method for diagnosis of Mycobacterium tuberculosis at Ethiopian National Tuberculosis Reference Laboratory, Addis Ababa, Ethiopia. BMC Res Notes 10:181.

Drain, P.K., Losina, E., Coleman, S.M., Giddy, J., Ross, D., Katz, J.N., Walensky, R.P., Freedberg, K.A., Bassett, I.V., 2014. Diagnostic accuracy of a point-of-care urine test for tuberculosis screening among newly-diagnosed HIV-infected adults: a prospective, clinic-based study. BMC infectious diseases 14:110.

Enos, M., Sitienei, J., Ong'ang'o, J., Mungai, B., Kamene, M., Wambugu, J., Kipruto, H., Manduku, V., Mburu, J., et al., 2018. Kenya tuberculosis prevalence survey 2016: Challenges and opportunities of ending TB in Kenya. PLoS One 13:e0209098.

Forbes, B.A., Hall, G.S., Miller, M.B., Novak, S.M., Rowlinson, M.C., Salfinger, M., Somoskövi, A., Warshauer, D.M., Wilson, M.L., 2018. Practical Guidance for Clinical Microbiology Laboratories: Mycobacteria. Clinical microbiology reviews 31.

Gelaw, B., Shiferaw, Y., Alemayehu, M., Bashaw, A.A., 2017. Comparison of loop-mediated isothermal amplification assay and smear microscopy with culture for the diagnostic accuracy of tuberculosis. BMC Infect Dis 17:79.

George, G., Mony, P., Kenneth, J., 2011. Comparison of the efficacies of loop-mediated isothermal amplification, fluorescence smear microscopy and culture for the diagnosis of tuberculosis. PLoS One 6:e21007.

Getahun, H., Gunneberg, C., Granich, R., Nunn, P., 2010. HIV infection-associated tuberculosis: the epidemiology and the response. Clin Infect Dis 50 Suppl 3:S201-7.

Glaziou, P., Floyd, K., Raviglione, M.C., 2018. Global Epidemiology of Tuberculosis. Semin Respir Crit Care Med 39:271-85.

Helb, D., Jones, M., Story, E., Boehme, C., Wallace, E., Ho, K., Kop, J., Owens, M.R., Rodgers, R., et al., 2010. Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. Journal of clinical microbiology 48:229-37.

Huerga, H., Ferlazzo, G., Bevilacqua, P., Kirubi, B., Ardizzoni, E., Wanjala, S., Sitienei, J., Bonnet, M., 2017. Incremental Yield of Including Determine-TB LAM Assay in Diagnostic Algorithms for Hospitalized and Ambulatory HIV-Positive Patients in Kenya. PLoS One 12:e0170976.

Hui, S.L., Walter, S.D., 1980. Estimating the Error Rates of Diagnostic Tests. Biometrics 36:167-71.

Jean Claude Semuto Ngabonziza, W.S., Florence Mutua, Gabriela Torrea, Augustin Dushime,, Michel Gasana, E.A., Schifra Uwamungu, Alaine Umubyeyi Nyaruhirira, Dufton Mwaengo and, Muvunyi, C.M., 2016. Diagnostic performance of smear microscopy and incremental yield of Xpert in detection of pulmonary tuberculosis in Rwanda. BMC infectious diseases.

Kawasaki, M., Echiverri, C., Raymond, L., Cadena, E., Reside, E., Gler, M.T., Oda, T., Ito, R., Higashiyama, R., et al., 2019. Lipoarabinomannan in sputum to detect bacterial load and treatment response in patients with pulmonary tuberculosis: Analytic validation and evaluation in two cohorts. PLoS Med 16:e1002780.

Kostoulas, P., Nielsen, S.S., Branscum, A.J., Johnson, W.O., Dendukuri, N., Dhand, N.K., Toft, N., Gardner, I.A., 2017. STARD-BLCM: Standards for the Reporting of Diagnostic accuracy studies that use Bayesian Latent Class Models. Prev Vet Med 138:37-47.

Lawn, S.D., Kerkhoff, A.D., Vogt, M., Wood, R., 2012. Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. The Lancet Infectious Diseases 12:201-09.

Lunn, D., Spiegelhalter, D., Thomas, A., Best, N., 2009. The BUGS project: Evolution, critique and future directions. Stat Med 28:3049-67.

Matee, M., Mtei, L., Lounasvaara, T., Wieland-Alter, W., Waddell, R., Lyimo, J., Bakari, M., Pallangyo, K., von Reyn, C.F., 2008. Sputum microscopy for the diagnosis of HIV-associated pulmonary tuberculosis in Tanzania. BMC Public Health 8:68.

Maxwell Oluwole Akanbi, Chad Achenbach, Babafemi Taiwo, John Idoko, Agatha Ani, Yetunde Isa, Agbaji, O., , C.U., Patrick Akande, et al., 2017. Evaluation of gene xpert for routine diagnosis of HIV-associated tuberculosis in Nigeria: A prospective cohort study. BMC Pulmonary medicine.

Mecky Matee, L.M., Tarja Lounasvaara, Wendy Wieland-Alter,, Richard Waddell, J.L., Muhammad Bakari,, Reyn, K.P.a.C.F.v., 2008. Sputum microscopy for the diagnosis of HIV-associated pulmonary tuberculosis in Tanzania.

Minion, J., Leung, E., Talbot, E., Dheda, K., Pai, M., Menzies, D., 2011. Diagnosing tuberculosis with urine lipoarabinomannan: systematic review and meta-analysis. Eur Respir J 38:1398-405.

MOH, 2013. Guidelines for management of Tuberculosis and Leprosy in Kenya, Nairobi, Kenya.

MOH, 2016. Kenya Tuberculosis Prevalence Survey: Final Survey Report, Nairobi, Kenya.

MOH, 2017. National Tuberculosis, Leprosy and Lung Disease Program (NTLD- P), Nairobi, Kenya.

Nakiyingi, L., Moodley, V.M., Manabe, Y.C., Nicol, M.P., Holshouser, M., Armstrong, D.T., Zemanay, W., Sikhondze, W., Mbabazi, O., et al., 2014. Diagnostic accuracy of a rapid urine lipoarabinomannan test for tuberculosis in HIV-infected adults. Journal of acquired immune deficiency syndromes 66:270-9.

Nel, J.S., Lippincott, C.K., Berhanu, R., Spencer, D.C., Sanne, I.M., Ive, P., 2017. Does Disseminated Nontuberculous Mycobacterial Disease Cause False-Positive Determine TB-LAM Lateral Flow Assay Results? A Retrospective Review. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 65:1226-28.

Ngabonziza, J.C., Ssengooba, W., Mutua, F., Torrea, G., Dushime, A., Gasana, M., Andre, E., Uwamungu, S., Nyaruhirira, A.U., et al., 2016. Diagnostic performance of smear microscopy and

incremental yield of Xpert in detection of pulmonary tuberculosis in Rwanda. BMC Infect Dis 16:660.

Onyango, D.O., Yuen, C.M., Cain, K.P., Ngari, F., Masini, E.O., Borgdorff, M.W., 2017. Reduction of HIV-associated excess mortality by antiretroviral treatment among tuberculosis patients in Kenya. PLoS One 12:e0188235.

Park, S.H., Kim, C.K., Jeong, H.R., Son, H., Kim, S.H., Park, M.S., 2014. Evaluation and comparison of molecular and conventional diagnostic tests for detecting tuberculosis in Korea, 2013. Osong Public Health Res Perspect 5:S3-7.

Parsons, L.M., Somoskovi, A., Gutierrez, C., Lee, E., Paramasivan, C.N., Abimiku, A., Spector, S., Roscigno, G., Nkengasong, J., 2011. Laboratory diagnosis of tuberculosis in resource-poor countries: challenges and opportunities. Clin Microbiol Rev 24:314-50.

Paul K Drain, E.L., Sharon M Coleman, Janet Giddy, Douglas Ross, Jeffrey N Katz,, Rochelle P Walensky, K.A.F.a.I.V.B., 2014. Diagnostic accuracy of a point-of-care urine test for tuberculosis screening among newly-diagnosed hiv-infected adults: a prospective, clinic-based study.

Paul K. Drain, M., MPH1,2, Elena Losina, PhD1,3,4, Sharon M. Coleman, MS6, Janet Giddy, MBBCh7, Douglas Ross, MBBCh, MBA8, Jeffrey N. Katz, MD4, and Ingrid V. Bassett, MD, MPH, 2015. Value of Urine Lipoarabinomannan Grade and Second Test for Optimizing Clinic-based Screening for HIV-associated Pulmonary Tuberculosis.

Peter, J., Green, C., Hoelscher, M., Mwaba, P., Zumla, A., Dheda, K., 2010. Urine for the diagnosis of tuberculosis: current approaches, clinical applicability, and new developments. Curr Opin Pulm Med 16:262-70.

Peter, J., Theron, G., Chanda, D., Clowes, P., Rachow, A., Lesosky, M., Hoelscher, M., Mwaba, P., Pym, A., et al., 2015. Test characteristics and potential impact of the urine LAM lateral flow assay in HIV-infected outpatients under investigation for TB and able to self-expectorate sputum for diagnostic testing. BMC infectious diseases 15:262.

Peter, J.G., Theron, G., van Zyl-Smit, R., Haripersad, A., Mottay, L., Kraus, S., Binder, A., Meldau, R., Hardy, A., et al., 2012. Diagnostic accuracy of a urine lipoarabinomannan strip-test for TB detection in HIV-infected hospitalised patients. Eur Respir J 40:1211-20.

Pierre Le Palud, V.C., Brigitte Malbruny, Romain Magnier, Karine Campbell, Youssef Oulkhouir,, Bergot, G.Z.a.E., 2014. Retrospective observational study of diagnostic accuracy of the Xpert® MTB/RIF assay on fiberoptic bronchoscopy sampling for early diagnosis of smear-negative or sputum-scarce patients with suspected tuberculosis. BMC pulmonary medicine.

Prasanthi, K., Kumari, A.R., 2005. Efficacy of fluorochrome stain in the diagnosis of pulmonary tuberculosis co-infected with HIV. Indian J Med Microbiol 23:179-81.

Raja, S., Ching, J., Xi, L., Hughes, S.J., Chang, R., Wong, W., McMillan, W., Gooding, W.E., McCarty, K.S., Jr., et al., 2005. Technology for automated, rapid, and quantitative PCR or reverse transcription-PCR clinical testing. Clin Chem 51:882-90.

Ramachandran, R., Muniyandi, M., 2018. Rapid molecular diagnostics for multi-drug resistant tuberculosis in India. Expert Review of Anti-infective Therapy 16:197-204.

Saeed, M., Rasheed, F., Iram, S., Hussain, S., Ahmad, A., Riaz, S., Ahmad, M., 2018. False Negativity of Ziehl-Neelsen Smear Microscopy: Is the Scale-up the Worth It in Developing Countries? Journal of the College of Physicians and Surgeons--Pakistan : JCPSP 28:201-05.

Schisterman, E.F., Perkins, N.J., Liu, A., Bondell, H., 2005. Optimal Cut-Point and Its Corresponding Youden Index to Discriminate Individuals Using Pooled Blood Samples. Epidemiology 16:73-81.

Shah, M., Hanrahan, C., Wang, Z.Y., Dendukuri, N., Lawn, S.D., Denkinger, C.M., Steingart, K.R., 2016. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in HIV-positive adults. Cochrane Database Syst Rev:CD011420.

Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, N, D., 2014. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Review). JohnWiley & Sons, Ltd.

Steingart, K.R., Henry, M., Ng, V., Hopewell, P.C., Ramsay, A., Cunningham, J., Urbanczik, R., Perkins, M., Aziz, M.A., et al., 2006. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. The Lancet Infectious Diseases 6:570-81.

Steingart, K.R., Schiller, I., Horne, D.J., Pai, M., Boehme, C.C., Dendukuri, N., 2014. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev:CD009593.

Stephen D Lawn1, 2012. Point-of-care detection of lipoarabinomannan (LAM) in urine for diagnosis of HIV-associated tuberculosis: a state of the art review. BMC Infectious Diseases.
Stephen D Lawn, Nicol, M.P., 2011. Xpert® MTB/RIF assay:development, evaluationand implementation of anew rapid moleculardiagnostic for tuberculosisand rifampicin resistance.

Stephen D Lawn, A.D.K., Monica Vogt, Robin Wood, 2012. Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study.

Stephen D. Lawn, Sophie V. Brooks, Kranzer, K., , M.P.N., Andrew Whitelaw, Monica Vogt, Linda-Gail Bekker, Robin Wood, 2011. Screening for HIV-Associated Tuberculosis and Rifampicin Resistance before Antiretroviral Therapy Using the Xpert MTB/RIF Assay: A Prospective Study. PLOS MEDICINE 8.

Sturenburg, E., Junker, R., 2009. Point-of-care testing in microbiology: the advantages and disadvantages of immunochromatographic test strips. Dtsch Arztebl Int 106:48-54.

Thomas, A., O'Hara, R, Ligges, U & Sturtz,, 2006. 'Making BUGS open', R News.,.

WHO, 2008. Laboratory- based evaluation of 19 commercially available rapid diagnostic tests for Tuberculosis, Switzerland.

WHO, 2017. WHO meeting report of a technical expert consultation: non-inferiority analysis of Xpert MTF/RIF Ultra compared to Xpert MTB/RIF. Geneva: World Health Organization, Geneva.

WHO, 2020. World Health Organization annual report 2019 WHO Country Office Lebanon: health for all. World Health Organization. Regional Office for the Eastern Mediterranean, Cairo.

World Health, O., 2007. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents : recommendations for HIV-prevalent and resource-constrained settings / Stop TB Department ; Department of HIV/AIDS. World Health Organization, Geneva.

World Health, O., 2011. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system: policy statement. World Health Organization, Geneva.

World Health, O., 2016. The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis: policy guidance. World Health Organization, Geneva.

World Health, O., 2018. Global tuberculosis report 2018. World Health Organization, Geneva.
Yan, L., Xiao, H., Zhang, Q., 2016. Systematic review: Comparison of Xpert MTB/RIF, LAMP and SAT methods for the diagnosis of pulmonary tuberculosis. Tuberculosis (Edinb) 96:75-86.

Zifodya, J.S., Kreniske, J.S., Schiller, I., Kohli, M., Dendukuri, N., Schumacher, S.G., Ochodo, E.A., Haraka, F., Zwerling, A.A., et al., 2021. Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis. The Cochrane database of systematic reviews 2:CD009593.

8.0 APPENDICES

Appendix 1: Research participants' consent form

Title of the study: Assessment of the performance of three diagnostic tests for pulmonary Tuberculosis among HIV patients presenting to Kibra Community Health Centre, Nairobi County, Kenya.

Kichwa cha utafiti: *Tathmini ya utendaji wa vipimo vitatu vya uchunguzi wa Kifua kikuu cha mapafu kati ya wagonjwa wa VVU wanaowasilisha katika kituo cha afya ya Jumuia ya Kibra Nairobi, Kenya.*

Principle Investigator and institutional affiliation: Eunita Atieno Ochola, University of Nairobi, School of Public Health

Kanuni ya Kichunguzi na ushirika wa taasisi: Eunita Atieno Ochola, Chuo Kikuu cha Nairobi, Shule ya Afya ya Umma

Supervisor (*Msimamizi*):

Dr. Marshall Mweu,

University of Nairobi, School of Public Health (*Chuo kikuu cha University of Nairobi, shule wa afya ya umma)*

Introduction: My name is Eunita Atieno, a student pursuing a master's degree in Public Health. Among the requirements for the award of the degree is to conduct a research. This study aims to estimate the diagnostic accuracy of sputum smear microscopy, Xpert Ultra and LAM antigen tests in the diagnosis of TB among people living with HIV presenting to Kibra Community Health Centre, Nairobi County, Kenya. This form provides the necessary information to guide you in deciding whether or not you would like to participate in the study.

Utangulizi:*Jina langu ni Eunita Atieno, mwanafunzi anayefuata digrii ya uzamili katika Afya ya Umma. Miongoni mwa mahitaji ya tuzo ya shahada hiyo ni kufanya utafiti. Utafiti huu unakusudia kukadiria usahihi wa utambuzi wa microscopy ya sputum smear, Xpert Ultra na vipimo vya antijeni vya LAM katika utambuzi wa TB kati ya watu wanaoishi na VVU wanaowasilisha kituo cha afya ya jumuiya ya Kibra, Kaunti ya Nairobi, Kenya. habari ya kukuongoza katika kuamua ikiwa ungependa kushiriki katika utafiti au la.*

Procedure:

Once you have agreed to take part in the study, you will be asked to sign this consent form and questions relating to your demographic and clinical information will also be obtained. You shall then be requested to provide sputum and urine samples for analysis. Instructions on the collection of the following samples will be provided.

Utaratibu:

Mara tu utakapokubali kushiriki katika utafiti, utaulizwa kusaini fomu hii ya idhini na maswali yanayohusiana na habari yako ya idadi ya watu na kliniki pia yatapatikana. Kisha utaombwa kutoa sampuli za makohozi na mkojo kwa uchambuzi. Maagizo juu ya ukusanyaji wa sampuli zifuatazo yatatolewa.

Benefits:

There are no monetary benefits, but the laboratory tests will be done free of charge. The information obtained will also be relayed to your primary physician to facilitate your treatment.

Faida:

Hakuna faida ya kifedha, lakini vipimo vya maabara vitafanywa bila malipo. Habari iliyopatikana pia itapelekwa kwa daktari wako wa msingi kuwezesha matibabu yako.

Risks:

No risk is anticipated in the provision of a sputum sample except for mild chest discomfort from the coughing process while attempting to expectorate sputum for testing. You might also experience some slight discomfort at the sight of venipuncture when blood is being drawn.

Hatari:

Hakuna hatari inayotarajiwa katika utoaji wa sampuli ya makohozi isipokuwa usumbufu mdogo wa kifua kutoka kwa mchakato wa kukohoa wakati wa kujaribu kutazamia makohozi kwa upimaji. Unaweza pia kupata usumbufu kidogo machoni pa kupeana damu wakati damu inachorwa.

Confidentiality:

Strict confidentiality will be maintained and all data obtained will be securely stored with password protected computers and used for purposes of this study only.

Usiri:

Usiri mkali utadumishwa na data zote zilizopatikana zitahifadhiwa salama na kompyuta zilizolindwa na nywila na kutumika kwa madhumuni ya utafiti huu tu.

Withdrawal from the study:

Should you want to opt out of the study at any point you are free to do so without compromise to your care as participation in this study is voluntary. You are free to ask any questions now or later, before and after signing the consent form. The principal investigator, Eunita Atieno on mobile number: 0719246186 or the KNH-UoN Ethics Review Committee (ERC), Kenya through email at uonknh_erc@uonbi.ac.ke.

Kujiondoa kwenye utafiti:

Ikiwa unataka kuchagua kutoka kwa utafiti wakati wowote uko huru kufanya hivyo bila kuathiri utunzaji wako kwani kushiriki katika utafiti huu ni kwa hiari. Uko huru kuuliza maswali yoyote sasa au baadaye, kabla na baada ya kusaini fomu ya idhini. Mchunguzi mkuu, Eunita Atieno kwa simu ya runununu: 0719246186 au Kamati ya Kupitia Maadili ya KNH-UoN (ERC), Kenya kupitia barua pepe kwauonknh_erc@uonbi.ac.ke.

Consent form

The study has been explained to me together with the answers to my questions. I have understood all what this study is about. I willingly accept to participate in this study

I give informed consent to participate in this study and for the collection of required samples

YES ☐ **NO** ☐

Participant's signature: _____ **Date** _____

Participant's name: _____ **Time** _____

Where subject is illiterate :(Witness to observe and sign below)

I verify the study has been explained to the participant together with the answers to the questions. The participant fully understands and freely agrees to participate in the study

Witness' signature: _____ **Date**_____

Investigator's statement

I have clearly communicated to the study participant and s/he understands and has freely accepted to give consent to participate in the study

Researcher's signature: _____**Date** _____

Researcher's name : _____ Time_____

Fomu ya idhini

Utafiti umeelezwa kwangu pamoja na majibu ya maswali yangu. Nimeelewa yote utafiti huu unahusu nini. Ninakubali kushiriki katika utafiti huu

Ninatoa idhini kamili ya kushiriki katika utafiti huu na ukusanyaji wa sampuli zinazohitajika

NDIO LA ☐ ☐

Saini ya mshiriki: _____ Tarehe _____

Jina la mshiriki: _____ Wakati _____

Pale ambapo somo halijui kusoma na kuandika: (Shahidi wa kuchunguza na kusaini hapa chini)

Ninathibitisha kuwa utafiti umeelezewa kwa mshiriki pamoja na majibu ya maswali. Mshiriki anaelewa kikamilifu na anakubali kwa uhuru kushiriki katika utafiti

Saini ya Shahidi: _____ **Tarehe**_____

Kauli ya mchunguzi

Nimewasiliana wazi na mshiriki wa utafiti na anaelewa na amekubali kwa hiari kutoa idhini ya kushiriki katika utafiti

Saini ya mtafiti: _____Tarehe _____

Mtafiti jina: _____ Wakati_____

Appendix 2: Questionnaire & Data collection tool

Interviewee code (*Kitambulisho cha mhojiwa*): _____

Interview date (DD/M/year) (*Tarehe la kuhojiwa*): _____

Point of recruitment (*Pahali pa ajira*): _____

Part 1: Background information

1. Date of birth (DD/M/Year) (*Tarehe ya kuzaliwa*) _____
2. Sex of the respondent (*Jinsia ya mhojiwa*)

- ❑ Male (Mwanamme)
- ❑ Female (Mwanammke)

3. Weight in Kg (*Uzito wa kilo*) _____
4. Highest level of education of respondent (*Je, mhojiwa amekamilisha kiwango gani cha juu kabisa cha elimu*?)
    - ❑ None (*Hajasoma*)
    - ❑ Primary (*Elimu ya msingi*)
    - ❑ Secondary (*Elimu ya sekondari*)
    - ❑ Tertiary/ University (*Elimu ya Juu*)
5. Occupation of the respondent (*Kazi ya mhojiwa*)
    - ❑ Unemployed (*Wasio na ajira*)
    - ❑ Employed (Kuajiriwa)
    - ❑ Business man/ woman (*Mfanyabiashara*)
6. Type of residence of the respondent (*Aina ya makao ya mhojiwa*)_____
    - ❑ Urban informal (*Mjini isiyo rasmi*)
    - ❑ Urban formal (*Rasmi ya mjini*)
    - ❑ Rural (*Vijijini*)

Part 2: Signs and symptoms (*Dalili*):

- ❑ Fever (*Homa*)
- ❑ Chills (*Baridi*)
- ❑ Chest pain (*Maumivu ya kifua*)
- ❑ Dyspnea (*Kupumua kwa pumzi*)
- ❑ Night sweats (*Jasho la usiku*)
- ❑ Weight loss (*Kupungua uzito*)
- ❑ Fatigue (*Uchovu*)
- ❑ Malaise (*Unyonge*)
- ❑ Productive cough (*Kikohozi cha uzalishaji*)
- ❑ Haemoptysis (*Kikohozi cha damu*)
- ❑ Lack of appetite (*Ukosefu wa hamu ya kula*)

Part 3: Chest x-ray results suggestive of PTB (*X-ray ya kifua inayopendekeza PTB*)

- ❑ Positive (*Chanya*)
- ❑ Negative (*Hasi*)
- ❑ Unknown (*Haijulikani*)
- ❑ Not done (*Haijafanywa*)

Part 4: Patient clinical information *(Sehemu ya 4: Habari ya kliniki ya mgonjwa)*

1. Known CD 4 count (*Hesabu ya CD4 inayojulikana*) _____
2. Known viral load (*Kiwango cha virusi kinachojulikana*) _____
3. ART status (Hali ya SANAA):
   - ❑ Naïve (*Naïve*)
   - ❑ Experienced (*Uzoefu*)
4. ART regimen(*Regimen ya SANAA*):
   - ❑ 1st line (*Mstari wa 1*)
   - ❑ 2nd line (*Mstari wa 2)*
5. Pre- existing lung disease (*Ugonjwa wa mapafu uliopo*)
   - ❑ COPD
   - ❑ Asthma (*Pumu)*
   - ❑ Bronchitis (*Mkamba)*
   - ❑ Others (*Wengine*)
6. Cigarette smoking (*Uvutaji sigara)*
   - ❑ Yes (*Ndio*)
   - ❑ No (*Hapana*)
7. Co- morbidities (*Magonjwa*)
   - ❑ Hypertension (*Shinikizo la damu*)
   - ❑ Diabetes(*Ugonjwa wa kisukari)*
   - ❑ Viral hepatitis (*Hepatitis ya virusi)*
   - ❑ Kidney disease (*Ugonjwa wa figo)*

Part 5: TB diagnostic Laboratory test results *(Sehemu ya 5: Matokeo ya uchunguzi wa Maabara ya uchunguzi wa TB)*

1. Sputum analysis results (*Matokeo ya uchambuzi wa makohozi*)
    - ❑ None (Hakuna)
    - ❑ +
    - ❑ ++
    - ❑ +++
2. TB LAM results (*Matokeo ya TB LAM*)
    - ❑ Grade 1 (*Daraja la 1*)
    - ❑ Grade 2 (*Daraja la 2*)
    - ❑ Grade 3 (*Daraja la 3*)
    - ❑ Grade 4 (*Daraja la 4*)
3. Xpert results and RIF resistance (*Matokeo ya Xpert na upinzani wa RIF)*
    - ❑ Negative (*Hasi*)
    - ❑ Positive (*Chanya*)
    - ❑ Invalid (*Si sahihi)*
    - ❑ RIF resistance detected (*Upinzani wa RIF umegunduliwa)*
    - ❑ RIF resistance **not** detected (*Upinzani wa RIF haujagunduliwa)*

Appendix 3: Laboratory tests procedures

3.1 SSM using the Ziehl Nelseen Method

The procedure will be carried out as below:

3.1.1 Sputum smears covering 2cm by 1cm on the center of the slide will be prepared immediately after receipt of the sample

3.1.2 The smears will then be allowed to air dry

3.1.3 Heat fixing will then be done by passing the smear 3 times through the flame of a spirit lamp

3.1.4 The slides will then be placed on a staining rack over the sink with the smears facing upwards about a finger width apart

3.1.5 The slides will then be completely flooded with 1% carbol fuchsin stain

3.1.6 Each slide will then be heated from below until steam rises. The heat will be kept constantly moving and when steam rises heating will be stopped.

3.1.7 The heated stain will then be left on the slides for a minimum of 10 minutes.

3.1.8 Rinsing of the slides will then be gently done and draining of excess water will be done by tilting each slide.

3.1.9 25% sulphuric acid will then be added as a decolorizing solution on the slides and left for 3 minutes

3.1.10 The decolorizing solution will then be gently rinsed and excess water drained by tilting each slide

3.1.11 0.1% Methylene blue will then be added as the counterstain solution for 1 minute and gently rinsed off and excess water drained by tilting each slide

3.1.12 The smears will then be allowed to air dry away from direct sunlight and examined under oil immersion lens

(Fitz-gerald, 2013)

Results:

Acid Fast Bacilli appear as red slender rods, sometimes with one or more granules.

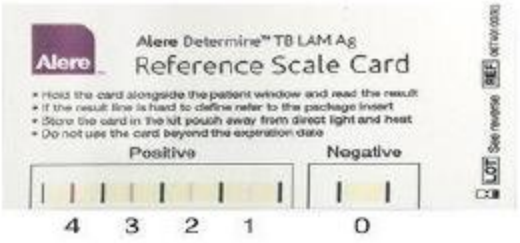
Table 5: IUATLD recommended grading of sputum smear microscopy results (Dawson, 2000)

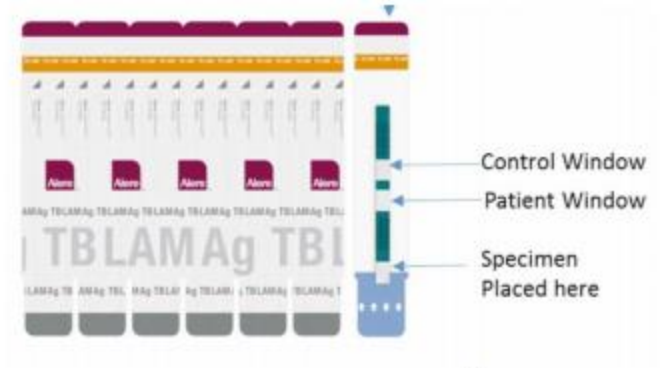
AFB counts	Recording/reporting
No AFB in at least 100 fields	0/negative
1 to 9 AFB in 100 fields*	Actual AFB counts†
10 to 99 AFB in 100 fields‡	+
1 to 10 AFB per fields in at least 50 fields†	++
> 10 AFB per field in at least 20 fields‡	+++

3.2 TB LAM lateral flow assay

The test procedure is as follows:

3.2.1 60 ul of urine sample will be pipetted onto the test strip followed by 25 minutes incubation at room temperature (World Health, 2016)





Individual LF-LAM strip: Courtesy of Alere™

Results:

Appearance of two color bands will be interpreted as positive with comparison done between any appearing visible band on the patient window with the one on the reference scale card. One color band on the control window will be interpreted as a negative result.

3.3 Xpert Ultra assay

The test will be carried out as follows:

3.3.1 Sample reagent will be added in to the sample in a ratio of 2:1 for liquefaction and inactivation of the sputum, the two will be vigorously shaken and followed by 15 minutes room temperature incubation

3.3.2 Using the provided pipette, the liquefied specimen will be pipetted until above the minimum mark into the test cartridge

3.3.3 The pre labelled test cartridge will then be loaded into the MTB-RIF test platform where automated testing will commence

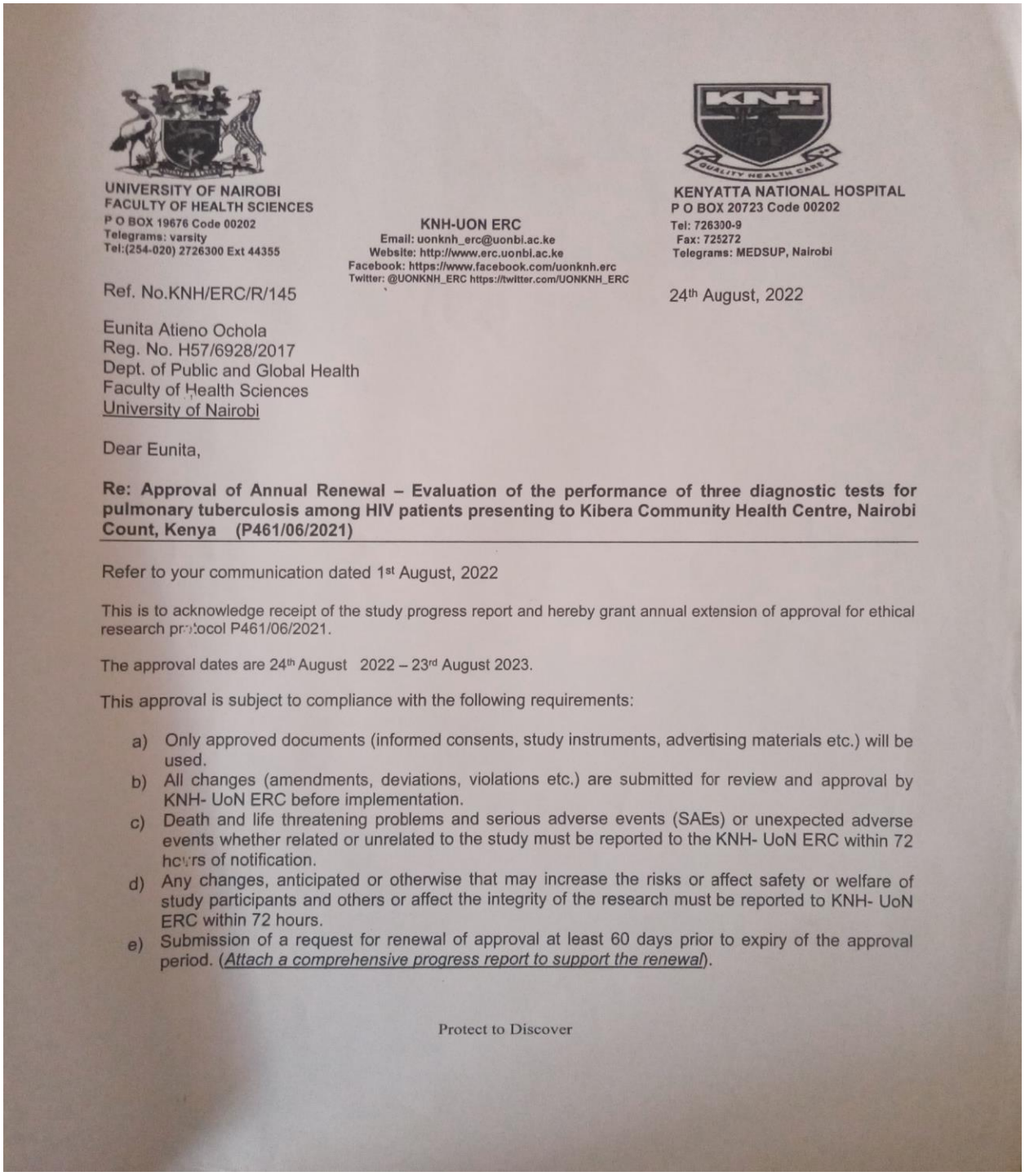
3.3.4 At the end of the automated process a print out of the test outcome will be obtained

Results Interpretation:

MTB is reported as either "MTB detected" or "MTB not detected"

Rifampacin resistance is reported as: "RIF resistance detected" or "RIF resistance not detected" or "RIF resistance indeterminate"

Appendix 4: KNH- UoN ERC Approval Letter



UNIVERSITY OF NAIROBI
FACULTY OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref. No.KNH/ERC/R/145

24th August, 2022

Eunita Atieno Ochola
Reg. No. H57/6928/2017
Dept. of Public and Global Health
Faculty of Health Sciences
University of Nairobi

Dear Eunita,

Re: Approval of Annual Renewal – Evaluation of the performance of three diagnostic tests for pulmonary tuberculosis among HIV patients presenting to Kibera Community Health Centre, Nairobi Count, Kenya (P461/06/2021)

Refer to your communication dated 1st August, 2022

This is to acknowledge receipt of the study progress report and hereby grant annual extension of approval for ethical research protocol P461/06/2021.

The approval dates are 24th August 2022 – 23rd August 2023.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc.) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH- UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH- UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).

Protect to Discover

UNIVERSITY OF NAIROBI
FACULTY OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref.No.KNH/ERC/Mod&SAE/347

24th August, 2022

Eunita Atieno Ochola
Reg. No. H57/6928/2017
Dept. of Public and Global Health
Faculty of Health Sciences
University of Nairobi

Dear Eunita,

Re: Approval of Modifications - study titled, "Evaluation of the performance of three diagnostic tests for pulmonary tuberculosis among HIV patients presenting to Kibera Community Health Centre, Nairobi County, Kenya" (P461/06/2021)

Your communication dated 1st August, 2022 refers.

The KNH- UoN ERC has reviewed and **approved** the following modifications made to the study:

1. Change of study site from St. Mary's Mission Hospital, Nairobi to ***Kibera Community Health Centre, Nairobi County, Kenya***.
2. Change of study title from 'Evaluation of the performance of three diagnostic tests for pulmonary tuberculosis among HIV patients presenting to St. Mary's Mission Hospital, Nairobi County, Kenya' to "***Evaluation of the performance of three diagnostic tests for pulmonary tuberculosis among HIV patients presenting to Kibera Community Health Centre, Nairobi County, Kenya***".

The requested modifications to the study are adequately justified and are incorporated in the revised research proposal. No further risk is anticipated on the participants.

The revised study consent document and tools are hereby endorsed and stamped for use.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH- UoN ERC

cc. The Dean, Faculty of Health Sciences, UoN
The Senior Director, Clinical Services, KNH
The Chairperson, KNH- UoN ERC
The Chair, Dept. of Public and Global Health, UoN
Supervisor: Dr. Marshal M. Mweu, Dept. of Public and Global Health, UoN

Protect to Discover

Appendix 5: Authorization to collect data in Nairobi County

REPUBLIC OF KENYA

EXECUTIVE OFFICE OF THE PRESIDENT
NAIROBI METROPOLITAN SERVICES

Telegraphic Address
Telephone +3313002/4
When replying please quote

Kenyatta International Convention Centre
P. O. Box 49130-00100
NAIROBI

REF: EOP/NMS/HS/222

DATE: 19th September, 2022

EUNITA ATIENO OCHOLA
UNIVERSITY OF NAIROBI

Dear Ms. Eunita,

RE: RESEARCH AUTHORIZATION

This is to inform you that the Nairobi Metropolitan Services - Health Directorate's Research Ethics Committee (REC) reviewed the documents on the study titled "Evaluation of the performance of three diagnostic tests for pulmonary tuberculosis among HIV patients presenting to St. Mary's Mission Hospital, Nairobi County, Kenya."

I am pleased to inform you that you have been authorized to carry out the study at Kibera Community Health Centre in Nairobi County. The researcher will be required to adhere to the ethical code of conduct for health research in accordance to the Science Technology and Innovation Act, 2013 and the approval procedure and protocol for research for Nairobi.

On completion of the study, you will submit one hard copy and one copy in PDF of the research findings to the REC. In addition, you will disseminate recommendations of the research at a virtual meeting organized by the REC. By copy of this letter, the Sub County Medical Officer of Health – Langata/Kibra is to accord you the necessary assistance to carry out this research study.

Yours sincerely,

DR. ANDREW TORO
CHAIR – RESEARCH ETHICS COMMITTEE

Cc: Director Health Services,
the Sub County Medical Officer of Health – Langata/Kibra

Appvd & forwarded
DR. ASMG AWADH

SUB COUNTY
27/9/2022
DATE
OF HEALTH

REPUBLIC OF KENYA

EXECUTIVE OFFICE OF THE PRESIDENT
NAIROBI METROPOLITAN SERVICES

Telegraphic Address
Telephone +3313002/4
When replying please quote

Kenyatta International Convention Centre
P. O. Box 49130-00100
NAIROBI

REF: EOP/NMS/HS/222

DATE: 19th September, 2022

EUNITA ATIENO OCHOLA
UNIVERSITY OF NAIROBI

Dear Ms. Eunita,

RE: RESEARCH AUTHORIZATION

This is to inform you that the Nairobi Metropolitan Services - Health Directorate's Research Ethics Committee (REC) reviewed the documents on the study titled "Evaluation of the performance of three diagnostic tests for pulmonary tuberculosis among HIV patients presenting to St. Mary's Mission Hospital, Nairobi County, Kenya."

I am pleased to inform you that you have been authorized to carry out the study at Kibera Community Health Centre in Nairobi County. The researcher will be required to adhere to the ethical code of conduct for health research in accordance to the Science Technology and Innovation Act, 2013 and the approval procedure and protocol for research for Nairobi.

On completion of the study, you will submit one hard copy and one copy in PDF of the research findings to the REC. In addition, you will disseminate recommendations of the research at a virtual meeting organized by the REC. By copy of this letter, the Sub County Medical Officer of Health – Langata/Kibra is to accord you the necessary assistance to carry out this research study.

Yours sincerely,

DR. ANDREW TORO
CHAIR – RESEARCH ETHICS COMMITTEE

Cc: Director Health Services,
the Sub County Medical Officer of Health – Langata/Kibra

RECEIVED
Name
Signature
Date 23/9/22

Appendix 6: NACOSTI Research License

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Ref No: 710297

Date of Issue: 18/November/2021

RESEARCH LICENSE

This is to Certify that Miss.. Eunita Atieno Ochola of University of Nairobi, has been licensed to conduct research in Nairobi on the topic: Evaluation of the performance of three diagnostic tests for pulmonary tuberculosis among HIV patients presenting to St. Mary's Mission Hospital, Nairobi County, Kenya. for the period ending : 18/November/2022.

License No: NACOSTI/P/21/14098

710297

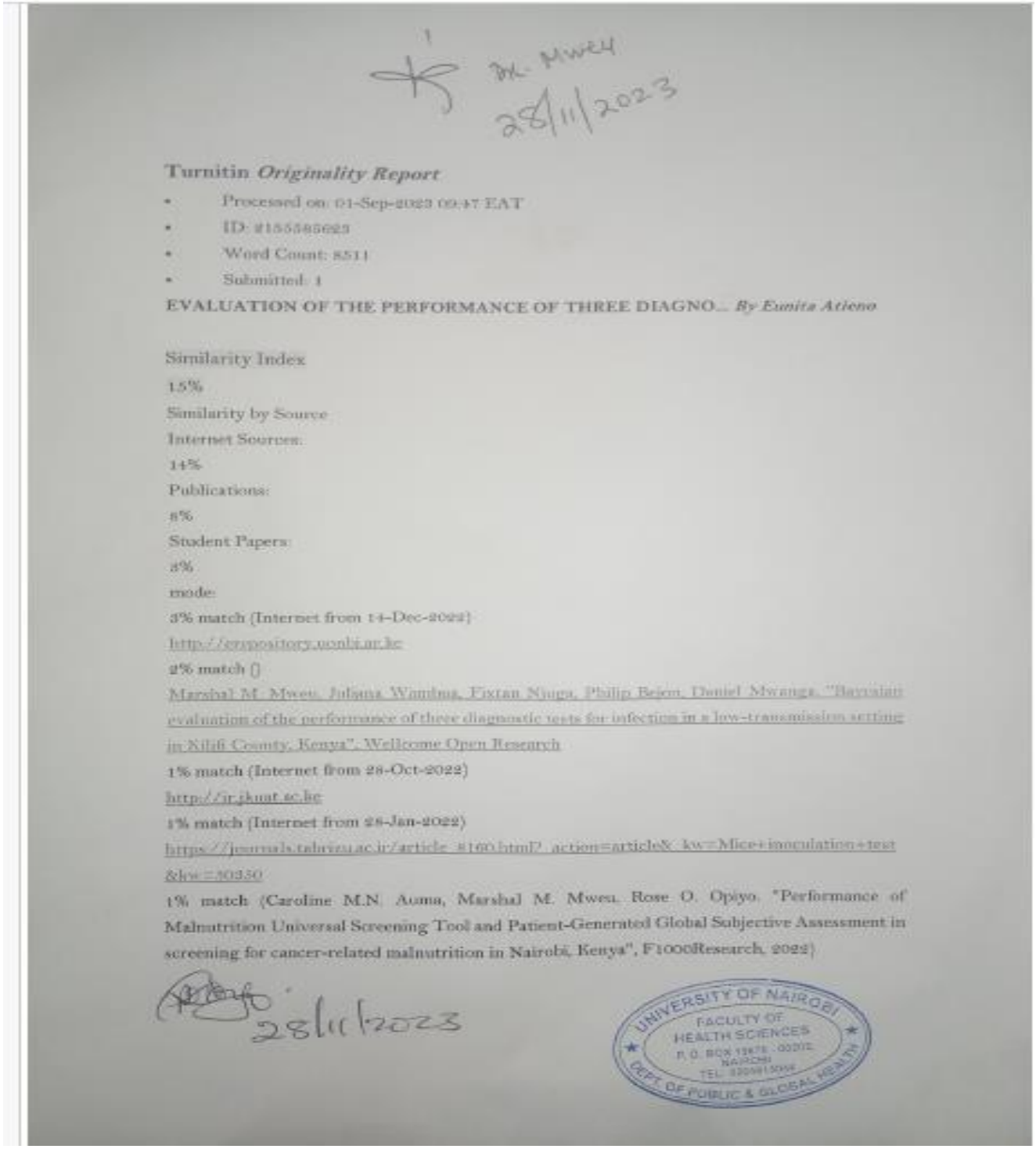
Applicant Identification Number

Director General
NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Verification QR Code

NOTE: This is a computer generated License. To verify the authenticity of this document, Scan the QR Code using QR scanner application.

Appendix 7: Turnitin *Originality Report*



1

DR. MWEU
28/11/2023

Turnitin *Originality Report*

- Processed on: 01-Sep-2023 09:47 EAT
- ID: #1155585623
- Word Count: 8511
- Submitted: 1

EVALUATION OF THE PERFORMANCE OF THREE DIAGNO... *By Eunita Atieno*

Similarity Index

15%

Similarity by Source

Internet Sources:

14%

Publications:

8%

Student Papers:

3%

mode:

3% match (Internet from 14-Dec-2022)

http://erepository.uonbi.ac.ke

2% match ()

Marshal M. Mwesi, Juliana Wambua, Fixtan Njuga, Philip Bejon, Daniel Mwanga. "Bayesian evaluation of the performance of three diagnostic tests for infection in a low-transmission setting in Kilifi County, Kenya", Wellcome Open Research

1% match (Internet from 28-Oct-2022)

http://ir.jkuat.ac.ke

1% match (Internet from 28-Jan-2022)

https://journals.tabrizu.ac.ir/article_8160.html?_action=article&_kw=Mice+inoculation+test&kw=30330

1% match (Caroline M.N. Auma, Marshal M. Mwesi, Rose O. Opiyo. "Performance of Malnutrition Universal Screening Tool and Patient-Generated Global Subjective Assessment in screening for cancer-related malnutrition in Nairobi, Kenya", F1000Research, 2022)

28/11/2023

UNIVERSITY OF NAIROBI
FACULTY OF HEALTH SCIENCES
P.O. BOX 19676 - 00202
NAIROBI
TEL: 2726300 Ext 43016
DEPT. OF PUBLIC & GLOBAL HEALTH

Caroline M.N. Auma, Marshal M. Mweu, Rose O. Opiyo. "Performance of Malnutrition Universal Screening Tool and Patient-Generated Global Subjective Assessment in screening for cancer-related malnutrition in Nairobi, Kenya", F1000Research, 2022

<1% match (Internet from 10-Nov-2022)
http://erepository.uonbi.ac.ke

<1% match (Internet from 11-May-2023)
http://erepository.uonbi.ac.ke

<1% match (Internet from 29-Oct-2022)
http://ir.jkuat.ac.ke

<1% match (Internet from 28-Oct-2022)
http://ir.jkuat.ac.ke

<1% match (Internet from 27-Sep-2021)
http://ir.jkuat.ac.ke

<1% match (Internet from 28-Oct-2022)
http://ir.jkuat.ac.ke

<1% match (Internet from 27-Sep-2021)
http://ir.jkuat.ac.ke

<1% match (Internet from 28-Oct-2022)
http://ir.jkuat.ac.ke

<1% match (Internet from 27-Sep-2021)
http://ir.jkuat.ac.ke

<1% match (Internet from 04-Jun-2023)
http://erepository.uonbi.ac.ke:8080

<1% match (Internet from 21-Jun-2023)
http://erepository.uonbi.ac.ke:8080

<1% match (Internet from 05-May-2023)
http://erepository.uonbi.ac.ke:8080

<1% match (Internet from 14-Jul-2023)
http://erepository.uonbi.ac.ke:8080

<1% match (Seon Ah Cheon, Hyun Hee Cho, Jeonghyo Kim, Jaebeom Lee, Hwa-Jung Kim, Tae Jung Park. "Recent tuberculosis diagnosis toward the end TB strategy", Journal of Microbiological Methods, 2016)

Seon Ah Cheon, Hyun Hee Cho, Jeonghyo Kim, Jaebeom Lee, Hwa-Jung Kim, Tae Jung Park. "Recent tuberculosis diagnosis toward the end TB strategy", Journal of Microbiological Methods, 2016

<1% match (Internet from 22-Oct-2022)
http://etd.aau.edu.et

<1% match (Internet from 20-Jan-2023)
https://www.slideshare.net/EngAbdikadirAliBade/challenges-facing-crop-production-among-small-scale-farmers-in-rural-areas-of-dilla-district-somaliland

<1% match (student papers from 23-Sep-2016)
Submitted to International Health Sciences University on 2016-09-23

<1% match (Hend M. El Damaty, Sarah G. Yousef, Yasser S. Mahmmod, Farouk A. El-Balkemy, Marshal M. Mweu. "Sensitivity and specificity of piroplasm indirect fluorescent antibody test and PCR for Theileria annulata infection in clinically asymptomatic large ruminants using Bayesian latent class analysis", Veterinary Parasitology: Regional Studies and Reports, 2021)
Hend M. El Damaty, Sarah G. Yousef, Yasser S. Mahmmod, Farouk A. El-Balkemy, Marshal M. Mweu. "Sensitivity and specificity of piroplasm indirect fluorescent antibody test and PCR for Theileria annulata infection in clinically asymptomatic large ruminants using Bayesian latent class analysis", Veterinary Parasitology: Regional Studies and Reports, 2021

<1% match (student papers from 20-Jun-2018)
Submitted to Mount Kenya University on 2018-06-20

<1% match (Ibrahim Elsohaby, Yasser S. Mahmmod, Marshal M. Mweu, Heba A. Ahmed et al. "Accuracy of PCR, mycobacterial culture and interferon-γ assays for detection of Mycobacterium bovis in blood and milk samples from Egyptian dairy cows using Bayesian modelling", Preventive Veterinary Medicine, 2020)

Ibrahim Elsohaby, Yasser S. Mahmmod, Marshal M. Mweu, Heba A. Ahmed et al. "Accuracy of PCR, mycobacterial culture and interferon-γ assays for detection of Mycobacterium bovis in blood and milk samples from Egyptian dairy cows using Bayesian modelling", Preventive Veterinary Medicine, 2020

<1% match (Internet from 19-Feb-2023)
http://dspace.muhas.ac.tz:8080

<1% match (Internet from 16-Dec-2022)
http://dspace.muhas.ac.tz:8080

<1% match (Internet from 05-Nov-2022)
https://wellcomeopenresearch.org/articles/4-67/v1

<1% match (Internet from 26-Feb-2023)
http://ir.mu.ac.ke:8080

<1% match (Internet from 26-Feb-2023)
http://ir.mu.ac.ke:8080

<1% match (student papers from 25-Jan-2023)
Submitted to Muhimbili University of Health and Allied Sciences on 2023-01-25

<1% match (Internet from 10-Jun-2021)
https://ir-library.ku.ac.ke/bitstream/handle/123456789/20470/Effects%20of%20Children%20Diarrhoeal%20Diseases%e2%80%a6%e2%80%a6%e2%80%a6%e2%80%a6%e2%80%a6%e2%80%a6%e2%80%a6%e2%80%a6%e2%80%a6%e2%80%a6%e2%80%a6...pdf?isAllowed=y&sequence=1

<1% match ()
Mweu, Marshal M., Murunga, Nickson, Otieno, Juliet W., Nokes, D. James. "Accuracy of diagnostic tests for respiratory syncytial virus infection within a paediatric hospital population in Kilifi County, Kenya", 'F1000 Research Ltd', 2020

<1% match (Ibrahim Elsohaby, Jawher I. Alahadeb, Yasser S. Mahmmod, Marshal M. Mweu et al. "Bayesian Estimation of Diagnostic Accuracy of Three Diagnostic Tests for Bovine Tuberculosis in Egyptian Dairy Cattle Using Latent Class Models", Veterinary Sciences, 2021)
Ibrahim Elsohaby, Jawher I. Alahadeb, Yasser S. Mahmmod, Marshal M. Mweu et al. "Bayesian Estimation of Diagnostic Accuracy of Three Diagnostic Tests for Bovine Tuberculosis in Egyptian Dairy Cattle Using Latent Class Models", Veterinary Sciences, 2021

<1% match (Internet from 26-Oct-2021)
http://elibrary.buse.ac.zw:8080

<1% match (Aboma Zewude, Temesgen Mohammed, Lemma Terfassa, W. Garrett Hunt et al. "Evaluation of Mycobacterium tuberculosis lipoarabinomannan antigen assay and rapid serology blood test for the diagnosis of bovine tuberculosis in Ethiopia", BMC Veterinary Research, 2019)
Aboma Zewude, Temesgen Mohammed, Lemma Terfassa, W. Garrett Hunt et al. "Evaluation of Mycobacterium tuberculosis lipoarabinomannan antigen assay and rapid serology blood test for the diagnosis of bovine tuberculosis in Ethiopia", BMC Veterinary Research, 2019

<1% match (G. Franzo, J. Segalés, F. Klaumann, M. Legnardi, M. M. Mweu, Y. S. Mahmmod. "Diagnostic accuracy of two DNA-based molecular assays for detection of porcine circovirus 3 in swine population using Bayesian latent class analysis", Letters in Applied Microbiology, 2019)
G. Franzo, J. Segalés, F. Klaumann, M. Legnardi, M. M. Mweu, Y. S. Mahmmod. "Diagnostic accuracy of two DNA-based molecular assays for detection of porcine circovirus 3 in swine population using Bayesian latent class analysis", Letters in Applied Microbiology, 2019

<1% match (Marshal M. Mweu, Juliana Wambua, Fixtan Njuga, Philip Bejon, Daniel Mwanga. "Bayesian evaluation of the performance of three diagnostic tests for Plasmodium falciparum infection in a low-transmission setting in Kilifi County, Kenya", Wellcome Open Research, 2019)
Marshal M. Mweu, Juliana Wambua, Fixtan Njuga, Philip Bejon, Daniel Mwanga. "Bayesian evaluation of the performance of three diagnostic tests for Plasmodium falciparum infection in a low-transmission setting in Kilifi County, Kenya", Wellcome Open Research, 2019

<1% match (student papers from 21-Jun-2016)
Submitted to London School of Hygiene and Tropical Medicine on 2016-06-21

<1% match (Robert F. Miller, Laurence Huang, Peter D. Walzer. "Pneumocystis Pneumonia Associated with Human Immunodeficiency Virus", Clinics in Chest Medicine, 2013)
Robert F. Miller, Laurence Huang, Peter D. Walzer. "Pneumocystis Pneumonia Associated with Human Immunodeficiency Virus", Clinics in Chest Medicine, 2013

<1% match (Toft, N.. "Evaluation of three serological tests for diagnosis of Maedi-Visna virus infection using latent class analysis", Veterinary Microbiology, 20070225)
Toft, N.. "Evaluation of three serological tests for diagnosis of Maedi-Visna virus infection using latent class analysis", Veterinary Microbiology, 20070225

<1% match (Internet from 07-Mar-2023)
https://pdfs.semanticscholar.org/3db3/10fce0d472abe04d26d447b91d7f44331fb2.pdf

<1% match (Asikiya Hanson, Amala Smart Enoch, Gloria N. Wokem. "Tuberculosis-Candida Co-Infection in Patients having Pulmonary Tuberculosis Attending DOTs Clinic in Rumuigbo Model Primary Health Centre in Port Harcourt, Nigeria", International Journal of TROPICAL DISEASE & Health, 2019)

Asikiya Hanson, Amala Smart Enoch, Gloria N. Wokem. "Tuberculosis-Candida Co-Infection in Patients having Pulmonary Tuberculosis Attending DOTs Clinic in Rumuigbo Model Primary Health Centre in Port Harcourt, Nigeria", International Journal of TROPICAL DISEASE & Health, 2019

<1% match (Hailemariam Mengistu, Minuta Abebe, Bewoket Gezahegn, Alehegn Tadesse, Worku Yismake, Desta Moges. "Performance evaluation of laboratory professionals on tuberculosis microscopy at Hawassa Town, Southern Ethiopia", African Journal of Microbiology Research, 2015)

Hailemariam Mengistu, Minuta Abebe, Bewoket Gezahegn, Alehegn Tadesse, Worku Yismake, Desta Moges. "Performance evaluation of laboratory professionals on tuberculosis microscopy at Hawassa Town, Southern Ethiopia", African Journal of Microbiology Research, 2015

<1% match (Internet from 18-Oct-2022)
http://ir-library.egerton.ac.ke

<1% match (student papers from 27-Aug-2018)

Submitted to National postgraduate Medical College of Nigeria on 2018-08-27

<1% match (Internet from 14-Apr-2016)
http://bmcresnotes.biomedcentral.com

<1% match (Internet from 15-Oct-2022)
http://dspace.knust.edu.gh

<1% match (Internet from 19-Mar-2023)
http://www.suaire.sua.ac.tz

<1% match (Enoe, C.. "Estimation of sensitivity and specificity of diagnostic tests and disease prevalence when the true disease state is unknown", Preventive Veterinary Medicine, 20000530)
Enoe, C.. "Estimation of sensitivity and specificity of diagnostic tests and disease prevalence when the true disease state is unknown", Preventive Veterinary Medicine, 20000530

<1% match (Internet from 22-Nov-2022)
https://cgspace.cgiar.org/bitstream/handle/10568/21400/21400.pdf?isAllowed=y&sequence

=1

<1% match (Internet from 25-Apr-2022)
https://link.springer.com/chapter/10.1007/978-3-030-81107-5_8?code=f5c0ab64-79db-4f16-a99a-07573744e93f&error=cookies_not_supported

<1% match (Ibrahim Elsohaby, Marshal M. Mweu, Yasser S. Mahmmod, J. Trenton McClure, Greg P. Keefe. "Diagnostic performance of direct and indirect methods for assessing failure of transfer of passive immunity in dairy calves using latent class analysis", Preventive Veterinary Medicine, 2019)

Ibrahim Elsohaby, Marshal M. Mweu, Yasser S. Mahmmod, J. Trenton McClure, Greg P. Keefe. "Diagnostic performance of direct and indirect methods for assessing failure of transfer of passive immunity in dairy calves using latent class analysis", Preventive Veterinary Medicine, 2019

<1% match (Internet from 20-Nov-2021)
https://elibrary.pu.ac.ke/bitstream/handle/123456789/799/BOB%20OPIYO.pdf?isAllowed=y&sequence=1

<1% match (Internet from 09-Oct-2022)
https://journals.plos.org/plospathogens/article/file?id=10.1371%2Fjournal.ppat.1000133&type=printable

<1% match (Internet from 10-Nov-2022)
http://ulspace.ul.ac.za

<1% match (Internet from 07-Nov-2022)
http://umispace.umi.ac.ug

<1% match (student papers from 30-Sep-2014)
Submitted to The Robert Gordon University on 2014-09-30

<1% match (Internet from 26-Nov-2022)
https://afribary.com/works/an-investigation-of-teachers-attitude-towards-children-with- learning-difficulties-a-case-study-of-koutulai-schools-kachumbala-sub-county

<1% match (Internet from 27-Jul-2023)
https://pgsdspace.ictp.it/xmlui/bitstream/handle/123456789/689/Yaqub.pdf?isAllowed=y&sequence=1

<1% match (Internet from 19-Jul-2020)
http://ugspace.ug.edu.gh