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THE CONCORDANCE BETWEEN XPERT MTB/RIF, MICROSCOPY AND CULTURE FOR PRESUMED TUBERCULOSIS PATIENTS AT THE CAPE COAST TEACHING HOSPITAL

BY

FRANCIS OBENG BRENYA

A thesis submitted to the Department of Microbiology and Immunology of School of Medical Sciences, College of Health and Allied Sciences, University of Cape Coast, in partial fulfilment of the requirements for the award of Master of Philosophy degree in Infection and Immunity

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DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the result of my original research and that no part of it has been presented for another degree in this university or elsewhere.

Candidate's Signature: …… Date: …….

Name: Francis Obeng Brenya

Supervisors' Declaration

We hereby declare that the preparation and presentation of the thesis were supervised in accordance with the guidelines on supervision of thesis laid down by the University of Cape Coast.

Principal Supervisor's Signature: …… Date: ……

Name: Prof. Samuel Victor Nuvor (Ph.D)

Co-Supervisor's Signature: …… Date: ……

Name: Caleb Agbale Mawuli (Ph.D)

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ABSTRACT

Sputum Smear Microscopy (SSM) is time-honoured tuberculosis (TB) detection tool in resource-constrained settings such as Ghana. However, sensitivity and specificity are low. The purpose of this retrospective study, which included 494 archived samples, was to assess the degree of agreement between TB detection by Xpert MTB/RIF, SSM, and Culture (LJ media) diagnostic tests in presumed TB patients at Cape Coast Teaching Hospital (CCTH). At the CCTH, all archived samples have already undergone Xpert MTB/RIF tests. In this study, all of the archived samples were cultured and microscopically examined. Age, gender, HIV status, and diagnostic test type were among the variables of interest. Using STATA version 16, SSM and microscopy data from positive TB cases diagnosed were compared to Xpert MTB/RIF diagnoses using a two-sample proportional test. Logistic regression was used to determine the strength of the association and the factors associated with positive TB cases. Overall, the proportion of TB cases detected by SSM was 19.3 (13.9 – 25.6 %) compared to 22.2 (17.3 – 27.8). The specificity of Xpert MTB/RIF, as opposed to tradition, changed into additionally lower: 92.5 (89.0 – 95.2%) as opposed to 99.6 (97.6 – 100.0%). (p = 0.001) The kind of diagnostic device used changed into found to be notably associated with the detection of nice TB cases (p = 0.01). This study emphasizes the importance of using Xpert MTB/RIF, as molecular diagnostics are number one in diagnosing TB despite limited resources. It also highlights the importance of using SSM with an MTB/RIF expert and the tradition of selecting different types of NTM-containing mycobacteria.

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DEFINITION OF TERMS

ACF	Active Case Finding
AFB	Acid-Fast Bacilli
ART	Antiretroviral Therapy
BAL	Bronchoalveolar Lavage
BCG	Bacillus Calmette-Guerin
BCR	Benefit-Cost Ratios
BSC	Biosafety Cabinet
CAD	Computer Aided Detection
CCMA	Cape Coast Metropolitan Assembly
CCTH	Cape Coast Teaching Hospital
CDC	Centre for Disease Control
CDR	Case Detection Rate
CI	Confidence Interval
CL3	Containment Level 3
CNR	Case Notification Rate
CSF	Cerebrospinal Fluid
CT	Computer Tomography
DNA	Deoxyribonucleic Acid
DOTS	Directly Observed Treatment Shortcourse
DR-TB	Drug-Resistant TB
DS-TB	Drug Sensitivity Tuberculosis
DST	Drug Susceptibility Testing
EPTB	Extrapulmonary Tuberculosis
FM	Fluorescent Microscopy

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HIV	Human Immunodeficiency Virus
IFN-γ	Interferon gamma
IGRA	Interferon Gamma Release Assays
ICF	Intensified Case Finding
LAM	Lipoarabinomannan
LED	Light Emitting Diode
LF-LAM	Lateral Flow-urine Lipoarabinomannan Assay
L-J	Löwenstein-Jensen
LPA	Line Probe Assays
LTBI	Latent Tuberculosis Infection
MAC	*Mycobacterium Avium Complex*
MDR-TB	Multidrug-Resistant Tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MDG	Millennium Development Goal
MAP	*Mycobacterium paratuberculosis*
MTB	*Mycobacterium tuberculosis*
MTBC	*Mycobacterium tuberculosis Complex*
NAAT	Nucleic Acid Amplification Tests
NALC	N-Acetyl-L-Cysteine
NTM	Non-Tuberculous Mycobacteria
NPV	Negative Predictive Value
NTCP	National TB Control Programmeme
OADC	Oleic Acid-albumin-Dextrose-Catalase
PCR	Polymerase chain reaction
NPV	Negative Predictive Value

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PPV	Positive Predictive Value
PLHIV	People Living with HIV
PNB	Para-Nitrobenzoic Acid
POC	Point of Care
pH	Potential of Hydrogen
PTB	Pulmonary TB
QA	Quality Assurance
RMT-TB	Rapid Molecular Test-Tuberculosis
RIF	Rifampicin
RR-TB	Rifampicin-Resistant TB
SDG	Sustainable Development Goal
SSM	Sputum Smear Microscopy
TB	Tuberculosis
TNF	Tumor Necroting Factor
TST	Tuberculin Skin Test
WHO	World Health Organisation
XDR-TB	Extensively Drug Resistant TB
ZN	Ziehl-Neelson

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DEDICATION

To my lovely and supportive wife (Mrs. Naomi Obeng Brenya), children (Georgina, Golda, Alvin, Elliot, Kristodea and Carlos) and grandmother (Madam Grace Enninful).

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CHAPTER ONE

INTRODUCTION

Chapter One sets out the background of investigation, problem statement, purpose of the study, its implications, interruptions and limitations.

It briefly reviews tuberculosis and outlines the diagnostic procedures available in this setting with treatment options and challenges faced by many clinicians. The chapter subsequently describes the hypotheses, general and specific objectives, significance of the study, limitations and delimitations of the present research. It further provides an overview of the thesis.

Backgroung of the study

Mycobacterium tuberculosis (*M. tuberculosis*), is the reason tuberculosis (TB), is a persistent infectious sickness. The sickness remains a continual chance to humanity and the main purpose of demise on an international scale after one hundred thirty years (WHO, 2020). TB is contagious and might infiltrate a number of organs, maximum significantly the lungs. *Tubercle bacilli* contamination in people does now no longer continually brings about sickness. TB has brought on extra struggling and demise than another infectious sickness, and it stays a prime public fitness subject worldwide.

Clinical sickness can arise while TB resistance is decreased or cell-mediated hypersensitive reaction is increased. When TB is nicely-recognised and treated, the bulk of sufferers may be clinically cured. As a result, early TB detection and analysis are essential. TB is presently recognized clinically commonly via an intensive exam of the sufferers` medical manifestations, imaging data, and laboratory exam results. TB stays one of the main reasons

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for its demise worldwide, thanks to the coming to light of *M. tuberculosis* and HIV co-infection drug-resistance lines (Gandhi *et al.*, 2010; WHO, 2020).

Regardless of the truth strict manipulate techniques and powerful anti-TB tablets have helped to lessen *M. tuberculosis* prevalence, the issue, and cost involved in treating drug-resistant TB makes early analysis essential to make a certain well-timed intervention and save the spread of drug-resistant TB spread (Gandhi *et al.*, 2019; WHO, 2020).

The gold standard diagnostic procedure for detecting *M. tuberculosis* in TB diagnosis is culture. Culture does, however, have a longer turnaround time, as well as difficulties transporting specimens to the laboratory, the requirement for highly skilled personnel, and specialized infrastructure. Before the culture results were available, any suspected tuberculosis patient would have had to start treatment or die (Chiang, Van Weezenbeek, Mori, & Enarson, 2013).

There has been an eccentric evolution in the global TB programme over the last two decades, putting an end to many years of neglect. This evolution has been accompanied by advances in tuberculosis screening and diagnostic technology. Two examples are computed radiography and Xpert MTB/RIF test (Chiang *et al.*, 2013). In 2015, WHO published an approach to combat tuberculosis, which aims to eradicate tuberculosis by 2035. The tuberculosis eradication strategy aims to achieve zero mortality, morbidity or tuberculosis by 2035. The strategic plan requires a 90 % discount in tuberculosis deaths via way of means of 2030 and a 95 % reduction in TB prevalence by 2035, in addition to reduce TB prevalence to 80 % by 2030 and to 90 % by 2035. Early TB prediction, contact screening, and the

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identification of anyone susceptible to TB and drug-resistant TB is key to effective treatment. One approach to achieving this goal is to maximize deployment and adoption of effective strategies. The Xpert MTB/RIF test is a rapid molecular cartridge-based test that is more sensitive than sputum smear microscopy (SSM) and provides more immediate rifampicin resistance results than SSM. In addition, computer-aided digital X-ray detection has the ability to read 98 % of high-quality images at low cost, with instant remote diagnostics available. The findings of Ghana TB prevalence survey were primarily due to an upgrade in diagnostic procedures used in place of the country's SSM and analogue X-ray.

According to the prevalence survey report and recommendations, SSM has been replaced with the initial TB detection test with Xpert MTB/RIF, and Computer-Aided Detection digital X-ray is used to identify and detect TB in the lungs. TB is very common and has risen in Sub-Saharan Africa over the last decade, owing in part to the continent's ongoing poverty and political instability (Mosissa *et al.*, 2016). This has hampered and slowed progress in implementing effective TB control measures. Thirty countries have been identified to account for 87 % of new TB cases in 2019, with Sub Saharan Africa accounting for 66 % (WHO, 2020).

These countries' TB incidence rates are now comparable to those recorded in Europe half a century ago, before anti-tuberculosis drugs were introduced (WHO, 2018). The annual incidence of tuberculosis is decreasing by about 2 %. Globally, TB prevalence declined by 9 %, less than half the target of the End TB Policy of 20 % reduction between 2015 and 2020 (WHO,

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2020). Tuberculosis diagnosis and treatment estimate increased between 2000 and 2019, saving 60 million people.

Rifampicin, isoniazid, pyrazinamide, and ethambutol are used to treat drug-sensitive tuberculosis for two months, followed by four months of rifampicin and isoniazid. These are referred to as first-line drugs.

In 2019, the overall treatment success rate for this regimen in Sub-Saharan Africa was 82 % (Global TB Report, 2020).

MDR-TB is caused by *Mycobacterium tuberculosis*, which is resistant to at least one of the most powerful anti-TB drugs, isoniazid and rifampin. These drugs are used to treat all types of tuberculosis (MDR/RR-TB) (Steingart *et al.*, 2014).

Multidrug-resistant tuberculosis (XDR-TB) is tuberculosis that is not only multidrug-resistant and rifampicin-resistant, but also resistant to all fluoroquinolones and at least one other Group A drug (non-antibiotic drug), caused by a strain (Steingart *et al.*, 2014) .

Non-tuberculous mycobacteria (NTM) are common organisms found in the soil and water in the environment, and over 180 NTMs have been identified, of which 25% are associated with human infections (List of Prokaryotic Names, 2021). Due to advances in NTM diagnostic methods and increased prevalence of immunocompromised people, the incidence of NTM has gradually increased worldwide, with lung infections accounting for 90 % of NTM infections (Emily *et al.*, 2017).

Tortoli and colleagues (2014) identified over 170 *Mycobacterium* species, the *Mycobacteriaceae* family's sole genus. They went on to conclude that organisms in this genus are qualified for causing a wide array of human

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diseases, with some of them acting as strict pathogens. Others, on the other hand, are either opportunistic or non-pathogenic pathogens. The prevalence of NTM lung disease (NTM-PD) in the United States has been estimated at 1–15 cases per 100,000 population (Kendall and Winthrop, 2013). The prevalence of NTM-PD increased from 9.4 per 100,000 in 2009 to 36.1 in 2016.

According to Jeon (2019), the occurrence of NTM lung disease increased from 1.2 in 2010 to 4.38 in 2016 (102 in 2010 and 4.8 in 2016) (Huang *et al.* 2012; Park *et al.*, 2020).

Isolation rates for pulmonary NTM range from 1.3 to 22.2 per 100,000 individuals, depending on geographic region, race, and underlying disease (Perng et al., 2012). NTM is rarely isolated from extrapulmonary sites such as CSF, synovial fluid, soft tissue, muscle, and bone. Many studies have been published on the distribution of her NTM species in lung localization.

The most common species of *M. tuberculosis* that causes lung disease with NTM is *Mycobacterium avium* complex (MAC) (Simons *et al.*, 2011; Zhang *et al.*, 2012; Hoefsloot *et al.*, 2013). However**,** studies backing this claim were conducted in single-center hospitals. Furthermore, there is a lack of understanding of the prevalence of NTM species in extrapulmonary infections. Proper clinical management requires accurate laboratory identification of mycobacteria isolated from clinical specimens. The understanding of clinical significance changes and evolves as new clinical laboratories identify mycobacterial species using molecular or other methods such as mass spectrometry. Due to misdiagnosis or underestimation, many of the newly described mycobacterial species' roles may be underestimated.

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This study serves as a benchmark for archived samples provided to identify tuberculosis using the Xpert MTB/RIF test. To ensure occupational safety and consistency of culture results, this study compared tuberculosis, and co-infection with other mycobacteria.

Mycobacterium tuberculosis complex is an oxygen-dependent obligate aerobic micro-organism that thrives in oxygen-rich tissues like the lungs. These are intracellular pathogens that normally attack mononuclear phagocytes (eg. macrophages) (WHO, 2016). It is hydrophobic, has a high cell wall lipid content, and has a slow growth time of 12 to 18 hours (20 to 30 minutes for *E. coli*). Cells are hydrophobic and lumps, so they are resistant to common spots such as stain (Cavanaugh *et al.*, 2016). *Mycobacteria* are known as "acid production basili" due to a relatively flavorous local rich cell wall that is relatively flavouring to various main dyes. Acidic organic solvents do not destroy stained cells (Cavanaugh *et al.*, 2016).

Potential patients in this study were tested for tuberculosis if they reported symptoms of cough, weight loss, night sweats, and fever. Sputum samples were then collected and cultured in Lowenstein-Jensen medium according to culture diagnostic protocols. Mycobacterial culture is the gold standard for diagnosing active tuberculosis. Eosinophil staining for bacilli is a simple and rapid test, but it has low sensitivity. More than 104 bacilli per ml of sputum can reliably detect active tuberculosis (Matthew *et al*., 2002).

However, results take weeks and are expensive. Sample viability requires a well-equipped laboratory with trained staff and efficient transport systems. A chest x-ray is helpful in diagnosing active tuberculosis but is not specific. To improve the accuracy, speed, and convenience of tuberculosis

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diagnosis, new diagnostic methods, such as molecular techniques and immune responses based on cell-mediated immunity (CMI) or humoral immune responses, are being investigated (Boehme *et al.*, 2010).

WHO recommended Xpert MTB/RIF, a PCR-based molecular assay primarily for the detection of particular strains. Tuberculosis nucleic acids revolutionized the detection of active and rifampicin-resistant tuberculosis. However, this is expensive with a significant savings in technology (Boehme *et al.*, 2010). Interferon-gamma release assay (IGRA), a novel T cell immunoassay with higher sensitivity and specificity than TST, has been used to successfully detect *M. tuberculosis* infection (Dendukuri *et al.*, 2012). IGRA is highly sensitive to detecting latent and active tuberculosis (LTBI and TB) but is less effective in immunocompromised individuals (Syed *et al.*, 2009). In addition, IGRA cannot differentiate between LTBI and active tuberculosis (Dendukuri *et al.*, 2012; Adams *et al.*, 2019), limiting its use in areas with high incidence.

According to WHO recommendations, the most commonly used TB testing methods are the Xpert MTB/RIF Classic and Xpert MTB/RIF Ultra tests. It can be used in laboratories of city hospitals and clinical hospitals in all regions. The success or failure of tuberculosis treatment has a significant impact on tuberculosis management. As a result, completing prescribed medications is very important to TB treatment programmes. The laboratory is considered the backbone of the TB control program. In the late 1990s, many international reviews of Ghana's tuberculosis control programs found that laboratory services were the weakest link and that SSM was the main diagnostic tool for pulmonary tuberculosis in Ghana (Twerefou *et al.*, 2015).

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Many patients with TB are thought to avoid seeking medical attention because of the disease's stigma (Aryal *et al.*, 2012). As a result, adequate training is critical to ensuring and maintaining a reliable and efficient laboratory personnel and TB coordinators in TB diagnosis. However, since most TB centres in Ghana do not have culture facilities except for community hospitals or educational hospitals, continuous negative smear testing is required until infection control measures are lifted, which means whether the patient has recovered. treatment or not. Cape Coast Teaching Hospital (CCTH), part of the Cape Coast Metropolitan Assembly, maintains a TB testing facility.

Problem Statement

The ultimate goal of TB diagnosis is the earliest possible initiation of effective treatment to identify people infected and diseased with tuberculosis as soon as possible and to eradicate further spread of the infection, i.e. the emergence of anti-tuberculosis drug resistance among the populations (Gelmanova *et al.*, 2007).

Tubnerculosis, a comprehensive open health threat, kills thousands of people each year. This is frequently because of the truth that many humans had been residing with undiagnosed TB for a long way too long, and detection and prognosis are often delayed. The number one way of controlling transmission and decreasing disorder prevalence is TB case detection and remedy. The primary means of controlling transmission and lowering disease incidence are TB case detection and treatment (Wallis *et al.*, 2010).

According to the findings of the 2020 Ghana Tuberculosis Prevalence Survey, TB is four times more prevalent than the previous WHO estimate, as

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are the proportions of smear-negative and pulmonary positive cultures. The survey`s findings were largely due to the improved diagnostic techniques used in place of the country`s standard sputum smear microscopy.

Based on data from prevalence studies, qualified laboratory personnel should be involved in TB diagnosis to improve TB detection and diagnosis in larger populations and sputum smear-negative patients. Therefore, the aim of this study was to evaluate the suitability of Xpert MTB/RIF, Culture, and SSM for detection of TB as it can detect a substantial proportion of TB cases that were undetectable with conventional SSM, thus bridging the gap between incidents and reported cases.

Purpose of the Study

Current TB remedy regimens are complicated and require long-time period use of a couple of antibiotics, each of them with specific facet consequences which can cause remedy failure and bacterial resistance, multidrug-resistant strains. The modern TB-HIV epidemic, and its severe social effects have created public fitness dangers in current years. Delays in right prognosis and remedy of tuberculosis sufferers placed the network at hazard. New diagnostic strategies including Cell Mediated Immune (CMI) or molecular techniques primarily based totally on humoral immune reaction and immune reaction are being studied to enhance the accuracy, speed, and comfort of tuberculosis prognosis (Boehme *et al.* , 2010).

WHO-encouraged Xpert MTB/RIF PCR-primarily based totally molecular techniques for detecting *M. tuberculosis*-unique nucleic acids have converted the prognosis of energetic and rifampicin-resistant TB. IGRA has excessive sensitivity in detecting instances of latent TB contamination (LTBI)

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and energetic TB, but the overall performance in immunocompromised people is impaired (Syed *et al.* , 2009). In addition, IGRA can not distinguish among latent tuberculosis contamination and energetic tuberculosis (Wallis *et al.*, 2010; Adams *et al.* , 2019), restricting its use in endemic areas.

Co-contamination with TB-HIV poses full-size diagnostic, management, and monetary demanding situations in lots of countries, specially in Africa, wherein the weight of HIV-associated tuberculosis is highest. HIV contamination will increase the hazard of growing energetic TB by accelerating the development of the disease.

Hypothesis

The researcher hypothesized that a unit Xpert MTB/RIF test would be further accurate than a smear as compared to culture as a gold standard in detecting presumed tuberculosis.

Research Questions

1. What are the accurate results of the Xpert MTB/RIF and SSM, with culture as the gold standard for detecting suspected TB in patients?
2. What are the Xpert MTB/RIF, SSM and culture-positive rates in TB patients?
3. What is the relationship between Xpert MTB/RIF and SSM outcomes as compared to culture as a gold standard?
4. What are the sensitivity, specificity, positive and negative predictive values of Xpert MTB/RIF and SSM compared to culture as the gold standard in our context?
5. What other *Mycobacteria species* can be identified among the presumed TB patients?

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General Objective

The aim of this study was to assess the concordance rate for tuberculosis diagnosis in CCTH-suspected patients with tuberculosis using SSM, Xpert MTB/RIF, and culture as the gold standard.

Specific Objectives

1. Describe the demographic and clinical characteristics of presumed TB patients at CCTH.
2. Determine the test performance characteristics in the three diagnostic tools at the CCTH.
3. Determine if other mycobacterial species have been identified in patients with suspected TB.

Significance of the study

Tuberculosis remains a public health problem because many patients go undiagnosed for too long. Late detection of TB, among other things, spreads the disease to others and increases the risk of financial hardship, poor health, and treatment outcomes.

Timely recognition and treatment of tuberculosis can accelerate progress of tuberculosis management and remission. For this reason, 365 TB SSM Diagnostic Centres were established in Ghana. The first tuberculosis diagnostic test, Xpert MTB/RIF, was installed at 117 sites to replace SSM. Since the introduction of the Xpert MTB/RIF test, the National Tuberculosis Program has modified the National Tuberculosis Diagnostic Algorithm in line with WHO recommendations. Currently, all health sectors in Ghana are actively promoting the discovery or expansion of TB cases, centered on public health facilities. The effectiveness of the Xpert MTB/RIF test has not been

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evaluated or evaluated since it replaced the first tuberculosis diagnostic test in parts of Ghana in 2017. Xpert MTB/RIF, SSM and culture are necessary to increase the reliability and effectiveness of TB diagnosis.

Traditional microscopy is imprecise and culture is the gold standard, but it has limitations. SSM needs time to become aggressive. On the other hand, nucleic acid amplification techniques, due to their rapidity and sensitivity, are useful for early diagnosis and treatment of TB, especially in clinically suspected patients. It also helps prevent the spread of disease. With the widespread availability of the Xpert MTB/RIF test, the bacterial density per unit sputum appears to be lower in non-progressive patients than in advanced patients (Ngabonziza, 2019). A low Bacillus load has been reported to significantly reduce the ability of the Xpert MTB/RIF assay to accurately identify rifampicin-resistant TB.

If the results are inconsistent, either TB-negative or rifampicin-sensitive, a more thorough individual clinical review is needed to determine if multidrug-resistant tuberculosis treatment is needed. .. If successful, the resistance test is skipped. Until then, the 2019 report by Ngabonziza and his colleagues on the gradual switch to previous TB diagnosis will continue.

Delimitations

This study used archival samples of male and female patients aged 1 to 80 years. These were tuberculosis and HIV-infected patients at the Cape Coast Teaching Hospital in the central part of Ghana. These patients were selected for signs of tuberculosis. They had a higher ability to reproduce bacteria and played an important role in tuberculosis infection. All patients were symptomatic at the time of sampling. Due to limited diagnostic data on

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patients, the results of this study provided new insights into the effective diagnosis and treatment of TB infection at CCTH in Cape Coast communities.

Limitations

Only patients with suspected TB were included in the study. TB is approximately 1,627 times more common in HIV-positive patients than in HIV-negative patients. Untreated latent TB infections in HIV-infected patients are more likely to progress to TB than in HIV-negative patients. In an HIV-positive patient, TB is considered the definitive disease in AIDS. Infectious diseases and potentially fatal cancers are the defining conditions of AIDS in HIV-positive patients.

The Organisation of the Study

The research report is divided into five chapters. Chapter 1 (Introduction) is followed by Chapter 2 (Literature Review), Chapter 3 (Methodology), Chapter 4 (Results and Discussion), and Chapter 5 (Conclusion and Summary).

The first chapter contains research background, problem description, research objectives, its implications, interruptions, and limitations.

Chapter 2 was a literature review covering key areas of tuberculosis epidemiology, transmission, diagnosis, and treatment.

Chapter 3 describes research methods and ethical considerations for research and data analysis.

Chapter 4 presents and discusses the results, and Chapter 5 presents conclusions, suggestions, and directions for future research.

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CHAPTER TWO

LITERATURE REVIEW

Introduction

This chapter was a literature review covering key areas of tuberculosis epidemiology, transmission, diagnosis, and treatment. It also defines disease transmission and population impact, and measures to address this challenge.

Mycobacterium tuberculosis

Mycobacterium tuberculosis (*M. tuberculosis*) causes tuberculosis (TB), a chronic infectious disease. The disease is still a persistent threat to humanity and the leading causes of death on a global scale after 130 years (WHO, 2020). TB is contagious and can infiltrate a variety of organs, most notably the lungs. *Tubercle bacilli* infection in humans does not always result in disease. TB has given rise to more hurt and demise than any other communicable disease, and it remains a major public health distress worldwide.

Clinical disease can occur when TB resistance is reduced or cell-mediated allergy is increased. When TB is properly diagnosed and treated, the majority of patients can be clinically cured. As a result, early TB detection and diagnosis are critical. TB is currently diagnosed clinically primarily through a thorough examination of the patients' clinical manifestations, imaging data, and laboratory examination results (Gandhi *et al.*, 2010; WHO, 2020).

Despite the fact that stringent control strategies and effective anti-tuberculosis drugs have helped reduce the spread of TB, the difficulty and cost of treating drug-resistant TB continue to ensure timely intervention and

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prevent the spread. Early diagnosis is essential to prevent drug-resistant TB (Gandhi et al., 2019; WHO, 2020).

Tuberculosis Case Finding

The primary means of controlling transmission and lowering the incidence of TB are case detection and treatment. Patients with positive TB screening test results should be well evaluated. Only set off prognosis and remedy can lessen TB morbidity and mortality. Nonetheless, in most limited resource settings with an increased burden of TB, finding a TB case is accomplished primarily through passive case detection methods.

People with symptoms, unlike finding cases of active TB, which is a systematic screening of active tuberculosis in a pre-determined high-risk population, using rapid testing, screening, or other protocols. Rely on self-reports or referrals to medical facilities (Abebe *et al.*, 2012; Ho, Fox & Maris, 2016).

The Account of TB

On March 24, 1882, Robert Koch announced the discovery of *Mycobacterium tuberculosis*, the causative agent of TB, and has killed 1 of his 7 patients in the United States and Europe. One century since the discovery of Dr. Koch, World Tuberculosis Day was established to educate the world about the global consequences of TB and the possible means of eradicating it (Bell *et al.*, 2018).

Hippocrates, Celsius, and Galen doubt that the importance of tranquility and the need for fresh air were important factors of treatment. In the 16th century, TB was recognised as an infectious disease in the Mediterranean culture and was first called phthisis. In 1679, Sylvius reports

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the pathological and anatomical features of Opera Medica's TB, followed by military TB pathological features in 1702. TB lesion homogenate, rabbit, and guinea pigs successfully inoculate. After that, rabbits and guinea pigs have developed Phthisis-like infections.

French Format Jeanantoine Viremin, doubts that TB was a microbial infection in 1865, despite the fact that Benjamin Marten of English doctor suspected in 1720 is non-communication, to Austin Flint You can learn a lot through the TB Chronicles about leaders and historians in the fight against tuberculosis in 2018.

Types of Mycobacteria

Mycobacteria are small, non-spore-forming, rod-shaped bacteria that live in soil and water. They are aerobic, slow-growing, and self-sufficient. The generation time of these bacteria is about 20 hours. As a result, isolation and identification can take up to 6 weeks (although some species develop in 5-7 days) (Malama *et al*., 2014).

Mycobacteria (0.2–0.6 m in width and 1.0–10 m in length) are rod-shaped bacteria that are catalase-positive, non-motile, and do not form spores. Despite the fact that some mycobacteria are microaerophilic, the vast majority are aerobic (Malama *et al*., 2014).

Mycobacterial colonies vary in morphology from species to species, and some form coarse or even colonies. Colony colours range from white to orange or pink (Iivanainen, 1999). Mycobacteria have four thick layers on the cell membrane. The innermost layer consists of a peptidoglycan layer followed by a lipid layer. Lipids protect bacteria from acidic and alkaline environments. It reduces cell permeability to various primary dyes that must

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bind phenol to penetrate the cell wall. Mycobacteria grow in the form of aggregates floating on the surface of a liquid medium due to the hydrophobic component of the cell wall. Detergents such as Tween® 80 can be added to the medium to promote the spread of microorganisms. Some mycobacteria, such as *M. tuberculosis*, can break down cell walls and form spheroplasts that are not seen in acid-resistant bacterial staining tests.

TB is the main clinical form that causes tuberculosis in humans. *Mycobacterium bovis* causes bovine TB and can sometimes cause human illness, while *Mycobacterium tuberculosis* causes human TB in Central and West Africa (Pande, 2013). Phenotypic differences exist between these pathogenic species, with very similar genetical appearance and are often classified as *M. tuberculosis* complex (MTBC).

Nontuberculous mycobacteria (NTM) pathogens include *Mycobacterium avium* complex (MAC), *Mycobacterium avium bacillus*, *Mycobacterium avium cesus*, and *Mycobacterium avium pyorrhea*. Other NTM species are often opportunistic pathogens, especially in immunocompromised individuals (Holland, 2001). This is important given the recent discovery of NTM-mediated sporulation in various mycobacteria. Due to sporulation, many NTMs can survive the environment and patients in long term, and can lead to skin and lung infections. The utmost communal mode of infection is aerosol (Malama *et al*., 2014).

Mycobacteria belong to the order *Actinomycetales*, and remain the only genus of *Mycobacterium* family. This genus is characterised by the presence of mycolic acid and acid resistance. Over 100 mycobacterial species

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are recognised or proposed, including numerous pathogens and in warm-blooded saprophytes.

TB affects both humans and animals, and archaeologists in Wyoming discovered it in ancient bison bones. These Bisons lived approximately 17,000 years ago. In the United States, *M. bovis* is still present in cattle and deer. Each year, nearly 1 million cattle in America are tested for tuberculosis. Cattle that have been exposed to TB-carrying wildlife, such as deer, are particularly vulnerable. Some animals are capable of transmitting tuberculosis to humans. Many tuberculosis patients, it is believed, do not seek treatment because the disease is stigmatised.

Additionally, a number of misdiagnosed patients by laboratory personnel as a result of incorrect SSM arise and could account for identifying a false negative or false positive result, both of which would be harmful to a section of the population and the patient. An unreal-negative result indicates that a TB patient was not diagnosed and thus remained a source of infection in the population (Desalegn *et al.*, 2018). A false positive result, also, clearly indicates that a non-infected TB suspect is subjected to unnecessary treatment, which can include social stigma, drug waste, and anti-TB drug side effects. As a result, sufficient laboratory personnel and TB coordinator training are required to warrant and keep a dependable and efficient laboratory service capable of producing accurate, timely, and consistent results.

TB Epidemiology

Each year, tuberculosis accounts for about 5 % of all deaths in Ghana (Ohene *et al.*, 2021), the affliction of TB is declining much more slowly, and the incidence of tuberculosis has increased by an average of 2.5 % year over

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year. In Ghana, the majority of tuberculosis cases are at work age (73 % of new cases aged 1544 in 2018). Up to 68 % of people who develop tuberculosis for the first time have not been treated for any year. Approximately 15 % of those who applied for treatment had inadequate adherence and results or disappeared.

Approximately 15,800 Ghanaians die from TB each year, one-third of the world's population is infected with TB, and nearly two million people die each year. More than 1.5 million TB cases are reported each year in sub-Saharan Africa (WHO, 2019), and Ghana reports an additional 46,000 new cases. In fact, only about 33.3% of the estimated tuberculosis cases are diagnosed in hospitals and clinics each year. Only 14,022 cases of all types of TB have been recently reported, making it the most officially recorded case in the country (NTP Annual Report, 2020).

An additional 190,000 TB deaths will occur if global TB detection increases by 25 % in 3 months compared to pre-pandemic detection rates (Ohene *et al.,* 2021). The mechanical modeling tool has been used to assess costs and advantages of three arbitrations to moderate the burden of TB in Ghana. In perilous populations, they used consulting to enhance compliance and results for aggressive business discovery (ACF), transfer of sputum system and level of patient education and tuberculosis treatment. According to their analysis, until the end of 2019 by the end of 2019, the expansion of ACF could have a major impact on reducing TB burden and mortality. They also found that by 2020, 33 % of the TB governance in the high-risk population were notified and have been registered for treatment. This model predicts that the expansion of molecular tests of Xpert MTB/RIF in 6 years to 2025 is to

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prevent the burden and mortality of tuberculosis to prevent 4,832 TB cases and 3,087 TB mortalities. Intervention cost-benefit analysis and intervention cost-benefit analysis. In the Ghana Priorities series, these are the most important BCRs. For active case detection, the BCR is as low as 38, is still significant. The sputum transport system provides the greatest net profit.

Improved Adherence to Treatment

The STREAM study is a multicenter, contemporary, non-inferiority study comparing short-term treatment with WHO-recommended treatment in patients with MDR pulmonary tuberculosis without fluoroquinolone or kanamycin resistance (Moodley & Godec, 2016). WHO is proposing smaller MDR-TB treatment regimen of 9 to 12 months for patients with multidrug-resistant TB instead of the traditional 20 to 24 month regimen. However, this recommendation was conditional due to uncertain evidence. Treatment of non-adherence is a major barrier to TB control in most high-burden countries, leading to asymmetric drug use and selection of drug-resistant mutations. The 9-month course of oral bedaquiline treatment is called "first cycle treatment". Another option is 6 months of treatment with bedaquiline as second-line treatment. This is because these short-term therapies, especially oral therapies, are as effective as traditional therapies while improving adherence.

The only new TB drugs developed four decades ago are bedaquiline and delamanid (WHO, 2018). Both are prohibitively expensive, preventing the majority of developing countries' national tuberculosis programs from being implemented.

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Challenges in Diagnosing Tuberculosis

Four critical steps must be taken to address the significant challenges posed by TB. Priorities such as money, laboratory capacity, treatment adherence, and the development of new low-cost drugs must all be critically examined and considered. One significant difficulty in TB diagnosis is that drug resistance in TB must be diagnosed in the laboratory because a drug-resistant MTB strain does not cause clinical signs or symptoms.

Globally, only 57 % of patients with pulmonary TB reported to WHO were bacteriologically confirmed (WHO, 2016). About 4,444 undiagnosed cases of TB disease, including those caused by drug-resistant strains, will spread throughout the community. The immediate priority is to identify and treat all cases as quickly as possible, including those of drug resistance. Therefore, in clinical practice, it is important to detect tuberculosis as quickly as possible and rule out drug resistance. National testing capacity needs to be improved to detect drug resistance to primary and secondary drugs in all cases of tuberculosis. The Universal Drug Susceptibility Test (DST) has been part of the WHO TB Control strategy since 2015 (WHO, 2016).

SSM, a common first-line TB diagnostic test, is quick, widespread, specific, and limited, making it affordable in resource-constrained high-burden countries. Microscopy, on the other hand, cannot differentiate between mycobacteria that are drug-resistant and those that are drug-sensitive.

New drug resistance cases in communities experimentally treated with standardized first-line drug regimens often fail, increase resistance, and lengthen the chain of infection (Ramalho *et al.*, 2015). For this reason, drug resistance testing should be conducted as soon as possible. Based on a

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phenotypic culture, DST is a traditional diagnostic strategy for drug-resistant tuberculosis. The main limitation is the slow processing time of this strategy. Cultured DST in clinical isolates can take up to 16 weeks. However, the more serious problem is that most exposed countries have few (or no) reference laboratories. Furthermore, for TB, the infrastructure for transporting samples to centralized or reference laboratories located outside of the country is frequently insufficient.

Disease Transmission

New infections are still being caused by TB transmission, and the infected population is a never-ending source of new TB cases. Countries must treat ongoing cases and prevent the spread of infection if they are serious about ending the global tuberculosis epidemic. This requires a shift in finding strategies from passive to intentionally active. This includes proactively screening, diagnosing, and treating patients at high risk of tuberculosis to increase their infectivity and prevent them from interfering with the chain of infection. Passive case detection prolongs the duration of infection, delays diagnosis, and leads to inevitable infection to the family and community until the case is identified and treated (Kranzer *et al.*, 2013).

Social Problem with Medical Repercussions

Nonetheless, the disease`s remedy has been in the main biomedical because of the improvement of powerful TB drugs. TB Control Programmes in high-incidence international locations often lack skilled fitness employees, laboratory facilities, powerful second-line drugs, and good enough investment to offer the nice care viable to sufferers with drug-resistant TB.

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In the past decade, new tools for the identification and treatment of drug-resistant TB have been introduced into the medical field. These are Line Probe Assays (LPA) Xpert MTB/RIF (Cepheid, Sunnyvale, California, USA) with GenoType MTBDRplus VER 2.0 and GenoType MTBDRsl VER 2.0 and Hain Lifescience, Nehren, Tübingen, Germany. The Xpert MTB/RIF is an automated cartridge-based nucleic acid amplification assay. It can be applied to due diligence factors as molecular biology laboratories and highly skilled staff do not need to provide molecular results. The main drawback of today's Xpert MTB/RIF devices is that they require power and the cartridge must be stored below 28oC. The main drawback is the need for specialized laboratories and highly skilled workers (Köser *et al.*, 2013).

Measures to address the challenge

Almost 90% of the 4,444 national TB programmes in well-funded low-income countries rely on 4,444 donors worldwide. In 2016, investment in lower and middle income countries plummeted from the required $83 billion to nearly $2 billion. Compared to the WHO guideline of at least 6 % of GDP, government spending on fitness in 2014 fell significantly in 150 countries. Multidrug-resistant tuberculosis consumes a significant portion of the tuberculosis budget in high-burden countries, as treatment costs for drug-related cases ranged from $ 100 to $ 500 in most high-burden countries, but in MDRTB patients. Treatment costs typically ranged from $ 5,000 to $ 10,000. (WHO, 2016).

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Enhanced Laboratory Capacity

An increased global laboratory capacity is urgently required, particularly in high-burden countries to reach out to more TB patients as soon as possible, treat and screen them for drug resistance (Udwadia *et al.,* 2013).

Measures Taken to Curb TB Over the Years

This includes bringing the worldwide TB burden right all the way down to ranges similar to the ones discovered high-profit international locations. The End Tuberculosis Strategy dietary supplements and expands at the efforts of UN Sustainable Development Goal 3. This includes decreasing the worldwide TB burden to ranges similar to high-profit international locations. Despite this, little interest has been paid to TB laboratory offerings due to the fact that Ghana carried out the DOTS manage method in 1994.

Development of Diagnostic Tests for TB

SSM is the primary procedure for the identification of pulmonary TB in Ghana because TB Control Programme prioritises, identifies and treat infectious pulmonary TB cases. As a result, the NTP trains laboratory personnel in SSM, teaches biosafety techniques, and implements a quality assurance system to support the country's TB microscopy services.

Developing a quick and accurate diagnostic test for TB that reduces the time required to start treatment is a significant approach for controlling the onset of TB. The WHO-approved Xpert MTB/RIF test (Cepheid, USA) is a real-time polymerase chain reaction (RT-PCR) test designed to reduce time to treatment shows sputum samples within 2 weeks (Boehme *et al.*, 2011; Calligaro *et al*., 2017).

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Clinical Diagnosis of TB

TB prevalence is prompted through chance elements inclusive of TB publicity and susceptibility, in addition to socioeconomic status (poverty, housing, nutrients and get right of entry to to healthcare). The majority of TB sufferers have fever, adynamia, anorexia, weight loss, night time sweats, and signs and symptoms precise to the affected site (WHO, 2020). The majority of sufferers have pulmonary tuberculosis, with the closing 15 % having extrapulmonary TB (WHO, 2021).

Tuberculosis of the lungs

Cough is an important sign of pulmonary tuberculosis and the occurrence of cough in all population groups should be considered. All contact with tuberculosis patients, HIV / AIDS patients, and prisoners must be tested for TB (Rueda *et al*., 2013).

TB testing should be performed on patients seeking care at any healthcare facility, as well as diabetic patients with cough lasting two weeks or longer. Doctors must look for cases in the general population when a cough lasts three weeks or longer. Coughing may be dry at first, but as the disease progresses, drool, hemoptysis, and other symptoms may develop.

Extrapulmonary Tuberculosis

TB outside the lungs is frequently misdiagnosed. Objective samples are collected at the suspected infection site using invasive procedures. As a result, a clinical diagnosis is inadequate, and additional testing is required to confirm and refine the diagnosis. All clinical samples should be subjected to bacterial, molecular, and histopathological testing, as well as imaging exams on the patient (Goletti *et al.*, 2018).

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Pleural Tuberculosis

Depending on the amount of pleural fluid present, patients may develop a tickle in the throat, pleuritis, and palpitations. Lymph node TB is the dominanrt type of extrapulmonary TB in HIV patients. Women and children are especially vulnerable.

The lymph node chains in the cervix, supraclavicular, and mediastinum on one or both sides (usually asymmetric) are the most commonly affected lymph node chains. Scrofuloderma features swollen, coalescing lymph nodes that attach to the level of the corpus cavernosum, forming a fluid-filled fistula (Fichman, 2022). Pleural tuberculosis is the most common extrapulmonary tuberculosis, except in HIV-infected persons.

Cutaneous Tuberculosis

Progression of cutaneous TB progresses from neutrophilia to extrinsic necrosis and acid-fast bacilli (AFB). Granulomas with caseous necrosis develop in 3 to 6 weeks and may or may not have AFB. Endogenous tuberculosis of the skin can cause caseous necrosis and granulomas with AFB. Granulomas can replace nonspecific, persistent inflammatory infiltrations as the lesion progresses, resulting in a deficiency of AFB. In skin tuberculosis caused by hematogenous dissemination, there are nonspecific foci of inflammation with necrotizing vasculitis, signs of thrombosis, and numerous AFBs. Bazins erythema induratum and erythema nodosum (a skin condition of distant testicles) are caused by tuberculosis (Nihues *et al*., 2015).

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Bacteriological Diagnosis of TB

Sputum Smear Microscopy (SSM)

SSM is the required diagnosis in TB because it identifies active TB patients who are part of the disease's transmission chain. The AFB smear test is straightforward and inexpensive (Nihues *et al*., 2015). In the presence of extensive cavitary lesions, direct SSM examination of spontaneous sputum has a sensitivity of up to 80 %. In patients with minor lesions, it ranges from 40-60 % on average, with smears being positive in only 20 % of those patients (Nihues *et al*., 2015).

Fluorescence microscopy detects mycobacteria 10 % better than standard light microscopy. Sputum centrifugation or sedimentation can also be used to boost smear microscopy sensitivity by 10-20 % (Sotgiu and Migliori, 2019). The use of the hypertonic saline solution to induce sputum improves SSM and culture yield for patients with negative sputum smear results.

In cases of TB hemoptysis, bronchoscopy can also help rule out alternative diagnoses and identify smear-negative pulmonary tuberculosis (Conde *et al.*, 2009; Rodrigues *et al.*, 2012). Although its sensitivity is lower, SSM of the collected material is also recommended in cases of suspected extrapulmonary TB. A needle puncture aspiration test or lymphadenectomy is used to diagnose tuberculous lymph nodes. In pleural tuberculosis, pleural fluid is a lymphocyte-dominated exudate, but the detection rate of AFB is low (5 %).

Nevertheless, SSM has a low sensitivity range of 2060% in patients with co-infected HIVTB (Méndez Samperio, 2017). SSM requires 2-3 sputum samples for best results and takes at least one sputum sample early in the

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morning (Sotgiu and Migliori, 2019) to increase the amount of sputum produced.

Culture of Mycobacteria

Mycobacterial culture of the respiratory material has about 80% sensitivity and 98% specificity. In the case of sterile lung tuberculosis, mycobacterial culture increases the detection of disease by 2040%. Disease management and prevention center (WHO, 2018). Löwensteinjens and Ucitaudoh's Paths, such as Ucitaudoh media, are the most commonly used cultural procedure because they have high cost-effective and low pollution rate (WHO, 2018). Meanwhile, mycobacteria appear in 2-8 weeks in solid medium. Therefore, for faster results (10- 42 days), liquid medium, such as Becton Dickinson Mycobacteria Growth Indicator Tube (MGIT; Sparks, MD, USA) should be used in non-radioactive automated systems (WHO, 2018).

Species Identification

Species identification involves the use of biochemical, phenotypic, and molecular methods to distinguish between mycobacteria of the *Mycobacterium tuberculosis* complex and nontuberculous mycobacteria. The ratio method, performed on solid media and providing results within 42 days of culture, is one of the currently available antimicrobial susceptibility testing methods. The automated method works in liquid media and provides results within 5-13 days. Drugs tested included streptomycin, isoniazid, rifampicin, ethambutol, and pyrazinamide. Second-line drugs are being tested against multidrug-resistant tuberculosis (MDR-TB) (WHO, 2018). According to WHO, solid or liquid media are the gold standard for diagnosing tuberculosis (Sotgiu et al., 2020).

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Molecular Testing of TB

Xpert MTB/RIF Assay

Molecular biology strategies in biopsy maceration influenced *Mycobacterium tuberculosis* DNA and rifampicin resistance in conjunction with Cepheid's Xpert MTB/RIF Ultra (Cepheid). *M. tuberculosis* were observed in 25.71 %, 20.71 %, and 17.85 % of a hundred and forty sufferers with lymph node TB using Xpert MTB/RIF, traditional PCR, and MGIT 960 cultures, respectively (Rawat *et al*., 2018).

WHO accredited the Xpert MTB/RIF take a look at in 2011 for the speedy prognosis of TB and the recognition of rifampicin resistance in HIV-superb sufferers with supposed tuberculosis. For person sputum samples, the sensitivity of the take a look at is set 90%. Rifampicin resistance was 95 % sensitive (Ministério da Sade, Brazil, 2019). In Ghana, the rapid molecular TB diagnostic is Xpert MTB/RIF.

The Implementation of Xpert MTB/RIF Assay Test by TB Control Programmes

The introduction of Xpert MTB/RIF has modified TB screening and diagnosis algorithms in many countries. The approach in these countries to conducting TB diagnostic testing is different. The Xpert MTB/RIF test has been introduced in Ghana, South Africa, Brazil, Swaziland and Moldova as the first line of protection for all suspected tuberculosis patients. However, in the Philippines, 4,444 smear-negative and chest X-ray-negative patients are being tested.

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Outcome of Xpert MTB/RIF analysis

In South Africa, Swaziland, Brazil, Moldova and high-threat groups, Xpert MTB/RIF is used because the first diagnostic take a look at for all sufferers with suspected tuberculosis. Due to accelerated sensitivity to SSM, Xpert MTB/RIF has been proven to growth the range of identified instances of TB with the aid of using sufferers. This take a look at has growth the range of instances of rifampicin-resistant TB. This is due to the fact the usa can now discover instances of rifampicin-resistant tuberculosis at its decentralized level.

Line Probe Assay (LPA)

In addition to identifying *Mycobacterium tuberculosis* complexes in other assays, WHO has approved a line probe assay (LPA) to detect resistance to rifampicin and isoniazid as well as resistance to fluoroquinolone and injectables (WHO, 2018). It is a constituent of respiratory substances. According to meta-analysis, the sensitivity and specificity of the linear probe for detection of rifampicin resistance were 96.7 % and 98.8 %, respectively, and the sensitivity and specificity for detection of isoniazid resistance were 90.2 % and 99.0 %, respectively (Nathavitharana, 2017).

Granulomas are the most common finding of caseous necrosis, and the results of SSM, culture, and molecular biology methods, whether present or not, vary due to the difficulty of such procedures. The results of epidemiological, clinical and radiological studies are often used to make a diagnosis (Hu *et al.*, 2018).

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Radiological Diagnosis of TB

Chest X-Ray (CXR) and Chest Computed Tomography (CT)

X-ray imaging is the method of choice for the initial evaluation of patients with suspected TB because it is easy to perform, inexpensive, and requires a low dose of radiation. Despite its low diagnostic specificity, radiography is very useful for identifying clinical symptoms of tuberculosis, evaluating potential comorbidities, and tracking the progress of tuberculosis treatment.

X-rays and, if necessary, chest CT are included in the basic approach for patients with respiratory disease. These procedures are important as they provide important information about the manifestation of TB extent, and course during treatment. CXR can also be used to screen for tuberculosis, which is particularly prevalent among prison inmates (Hu *et al.*, 2018). The primary routine X-ray procedures for include postero-anterior and left lateral views, nodule(s), and one or greater cavities.

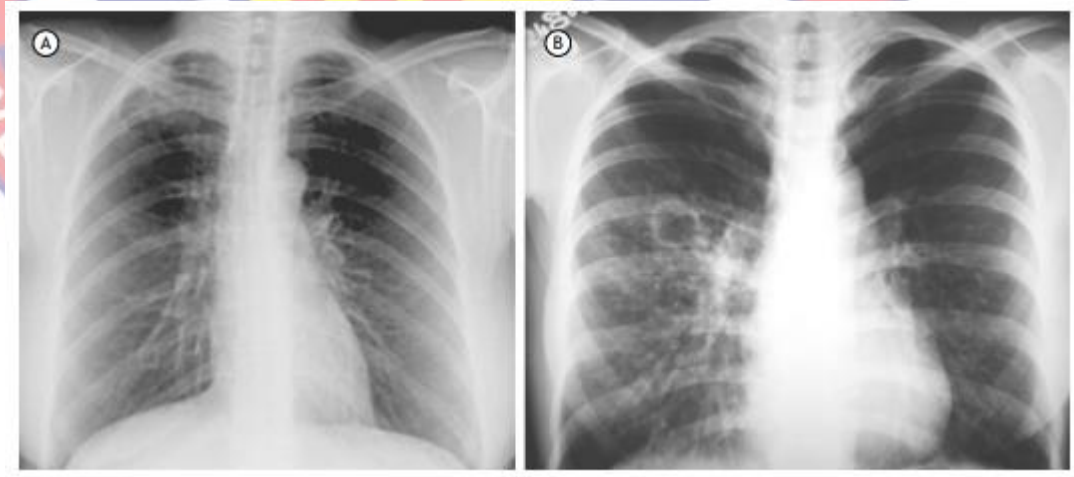

Figure 1: Tuberculosis CXR results. A small cloudy mass in the right subclavian region of A. ***Thick-walled cavity in the middle third of the right lung in B, with small conjunctival nodules, also called satellite lesions, usually indicating disseminated bronchial disease.***

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Chest CT is becoming more popular for TB diagnosis and monitoring, despite the fact that CXR is the most commonly used imaging modality. Chest CT is more sensitive and accurate than CXR for detecting early changes that CXR misses. Patients should be evaluated if they have poorly defined or ambiguous respiratory symptoms and changes, as well as a clinical and epidemiological perspective suggestive of TB. Patients with suspected TB whose CXR was inconclusive, patients with diffuse disease, patients with endobronchial abnormalities, and patients with respiratory disorders and extensive sequelae should all have a chest CT. Chest CT is becoming more popular for TB diagnosis and monitoring, despite the fact that CXR is the most commonly used imaging modality.

Patients with suspected TB whose CXR was inconclusive, patients with diffuse disease, patients with endobronchial abnormalities, and patients having pulmonary symptoms and extensive sequelae should all have a chest CT.

CT patterns reveal TB, including bronchial abnormalities such as fusion (with or without air bronchography), caries, hiatus nodules (a type of tree in the kidney), nodules and wall thickening and dilatation (Yuan *et al*., 2014).

Other Diagnostic Methods

Histology

Necrotised or granuloma and rental pig cells are pathological discovery in tuberculosis samples of infected organs. The increase in tuberculosis is usually diagnosed with organisational testing. On the other hand, organizational conclusions can provide diagnosis of possibilities because

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reproductive donation lesions can be caused by various diseases, including donation, rolling, mold infection and syphilis. Ziehl Neelsen dyeing for fresh samples and acid salt for mycobacterial culture is sent to the histological sample (evidence of level D) HIV and severe immune disabilities are rare in typical parenting.

Laboratory Examinations

Adenosine deaminase, an enzyme secreted by activated lymphocytes, helps detect pleural, peritoneal, or meningeal TB. Pleural or ascites adenosine deaminase level >45 U/L. The presence of IFN in serum, pleural effusion, or bronchoalveolar lavage fluid confirms the presence of tuberculosis but does not always indicate active disease.

TB Diagnosis in Children

According to WHO, more than 1 million children are diagnosed with TB each year, accounting for about 10 % of all TB cases. Each year, about 200,000 children and adolescents aged 0 to 14 die as a result of TB. Children under the age of five are responsible for roughly 80 % of those fatalities, with HIV-infected patients accounting for the remaining 17 %.

Every year, 25,000 children below age of 14 are diagnosed with MDR-TB, with only 5 % receiving treatment. This public health challenge could be explained by challenges with detection, tracing contacts, and access to healthcare institutions (Aurilo *et al.*, 2020). Treatment for TB is almost always initiated based on clinical history, symptoms, signs, radiological findings and, if possible, tuberculin skin test (TST) results (Carvalho *et al.*, 2018). The diagnosis of pulmonary TB in children is based on clinical and radiological history, epidemiological history of exposure to adult TB (usually active TB),

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and interpretation of individual TST results. A tertiary hospital study found positive results for RMTB in 33 % and 64 % of children with pulmonary TB.

However, in both groups, cultures were approximately 42 % positive and 10 % of patients tested positive for rifampin resistance. Rifampin resistance was found in 17 % of patients tested for *M. tuberculosis* according to a previous study (Aurilo *et al.*, 2020). In 2017, WHO recommended that Xpert MTB/RIF Ultra is more sensitive than Xpert MTB/RIF, has promising applications in low bacterial cases such as children and HIV/AIDS patients, and is more reliable for diagnosing TB (Ssengooba *et al*., 2020).

However, the clinical manifestations of TB-HIV infected patients may vary depending on level of immunosuppression. In general, invasive procedures like thoracentesis and lumbar puncture, and biopsies of lymph nodes, are required as part of the diagnostic workup.

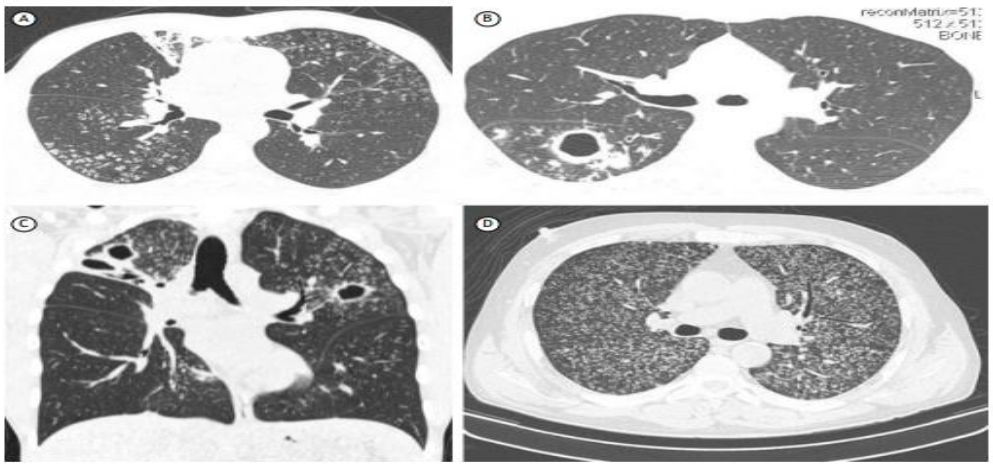

Figure 2: CT results of tuberculosis. The pattern of trees in the buds is formed by diffuse conjugated tubercles, some of which are dichotomous. *A thick-walled cavity is present in the apical segment of the right lower lobe in B (same case as Figure 1B), accompanied by significant thickening of the satellite nodules and bronchial walls. Coronal reconstruction in C shows a thick-walled cavity on both sides with satellite nodules. D is distinguished by the presence of a colony pattern of diffuse micronodules.*

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Table 1: The Various Laboratory TB Diagnostic Tests

Test	Assay Method	Use	Sensitivity (%)	Specificity (%)	TAT
Microscopy					
Conventional sputum smear microscopy	*Mycobacteria* can be seen directly under a light microscope.	Diagnosis of active TB	32–94	50–99	Same day
LED Fluorescence Smear Microscopy	Direct Imaging of *Mycobacteria* using Fluorescence Microscopy	Active TB ailment diagnosis	52–97	94–100	Same day
Culture-based techniques					
DST in combination with liquid culture	LJ medium is used for culturing mycobacteria.	• Diagnosis of active tuberculosis • Diagnosis of drug-resistant tuberculosis	• 89 (smear positive) • 73 (smear negative)	>99	10-21 days*
Solid Culture on LJ media	LJ medium is used for culturing	• Diagnosis of active tuberculosis	• 75.8	>98	17–56 days*

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	mycobacteria.	• Diagnosis of drug-resistant tuberculosis			
Drug Susceptibility Testing (DST)	Microscopic examination after sample inoculation on medium	•Drug resistance	• 98 for RIF resistance • 91 for INH resistance	99	5–38 days
Nitrate reductase assay (NRA)	On solid culture, *M. tuberculosis* has the ability to reduce nitrate.	Drug resistance	• 97 for RIF resistance • 97 for INH resistance	99	10–23 days
Antigen detection techniques					
LAM lateral flow assay	Antigen detection	Diagnosis of active TB in HIV-positive individuals	• 44 % (all) • 54 % (in HIV-positive)	• 92 (all) • 90 (in HIV positive)	Same day
Molecular techniques (NAAT)					
Xpert MTB/RIF	NAAT (qPCR)	• Diagnosis of active TB •Drug resistance	• 98 (smear-positive & culture	• 99 (RIF resistance)	Same day

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		(rifampicin)	positive) • 67 (smear negative & culture-positive) • 94 (RIF resistance)		
First-line LPA (GenoType MTBDRplus and NIPRO)	NAAT (LPA)	Diagnosis of active tuberculosis •Drug resistance (isoniazid and rifampicin)	•98 (RIF resistance) •84 (INH-resistance)	• 99 (RIF resistance) • >99 (INH resistance	1-2 days
Second-line LPA (GenoType MTBDRsl)	NAAT (LPA)	Drug resistance (fluoroquinolones and second-line injectable drugs)	•86 (fluoroquinolone resistance) • 87 (second-line injectable drugs	•98 (fluoroquinolone resistance) •99 (second-line injectable drugs)	1-2 days

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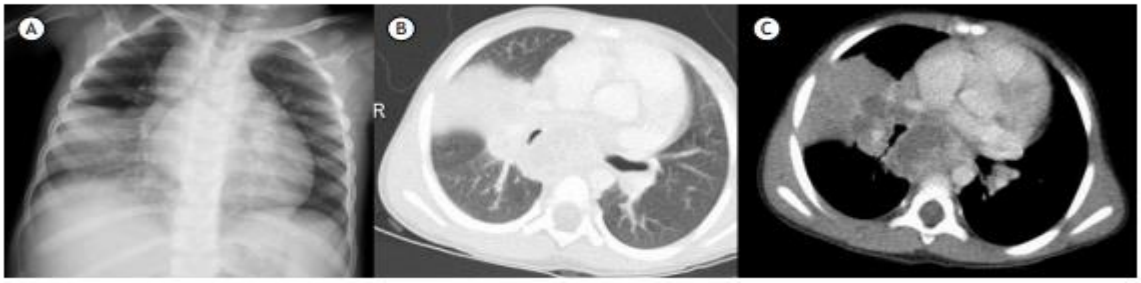

Figure 3: A 4-year-old boy and a 9-month-old girl with tuberculosis. ***X-ray A shows lymph node enlargement, darkening in the lower right middle third of the image and enlargement of the right paratracheal bundle. Enlarged lymph nodes on chest CT (pulmonary septum) B cause obstruction and external obstruction of the middle bronchi suggestive of middle lobe syndrome. A chest CT scan (mediastinum) showed variable-density lymphadenopathy in patient C's right portal vein and posterior mediastinum.***

Children with tuberculosis must have a tenacious cough and have a past contact with tuberculosis in adults (Carvalho *et al*., 2018). Almost always these are cases of primary tuberculosis. However, some results are controversial. A prolonged cough (more than 15 days) in children is considered a sign of pulmonary tuberculosis. Children who cough for several days may have undiagnosed pulmonary tuberculosis. Children are more likely than adolescents to have a history of tuberculosis and have some radiological features, such as enlarged unilateral portal lymph nodes and secondary findings.

Children have more contact with people with tuberculosis (usually adults) than adolescents in their daily life. Despite having greater social freedom, they are more likely to engage in rebellious or challenging behaviour, as well as refuse TB treatment. According to studies, less than 30

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% of children who have contact with TB patients become infected, casting doubt on the traditional model of TB transmission.

Malnutrition is another important aspect of treating tuberculosis in children. Depending on the epidemiological scenario, malnutrition has been studied as either a cause or a result of TB (Aurilio *et al.*, 2020).

Adolescents are more susceptible to TB than adults. In this age group, extensive TB is common, with more than half having active TB (Barreto *et al.*, 2011; Carvalho *et al.*, 2018). Over time, the scoring system for interpreting TST results has evolved.

Even in patients who have been vaccinated with BCG at birth, a 5 mm TST induration in children indicates a *M. tuberculosis* infection. Children and adolescents with slowly developing pneumonia caused by common germs should be suspected of having lung TB. Clinical and radiological dissociation is fairly common. Radiological findings may remain unchanged or worsen while symptoms improve. In adolescents, traditional bacteriological or molecular methods can be used to make a diagnosis.

The SSM method is widely used in the industry (Addo *et al.*, 2010). Their study concluded that regular SSM and QA training, as well as laboratory personnel re-training, is essential for an effective and efficient TB control program. Clinical symptoms of TB in HIV-infected people may vary depending on the level of immunosuppression.

Children plague-ridden with HIV are more likely to develop extrapulmonary tuberculosis and disseminated tuberculosis. In general, invasive procedures like thoracentesis and lumbar puncture, as well as lymph node and pleura biopsies, are required for an accurate diagnosis. Detecting

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lung TB in HIV-infected children can be more difficult. HIV-related lung diseases that must be distinguished include pneumocystosis, other mycoses, and lymphocytic interstitial pneumonia. Furthermore, anergy caused by HIV can impair the sensitivity of TST.

Tuberculosis Screening and Diagnosis Protocol in Ghana

TB can be diagnosed and treated in any patient or person because it is a community health challenge. In Ghana, Sputum Smear Microscopy (SSM) is the main method for diagnosing tuberculosis, especially pulmonary tuberculosis. SSM is widely available in most public health facilities in the United States. Because of their ease of use and low cost, the SSM diagnostic test has been the primary choice for screening and diagnostic testing for suspected TB cases.

Treatment for DS-TB

Drug-susceptible tuberculosis (DS-TB) is treated with a standard daily medication regimen for 6-8 months in a primary care hospital (PHC). Despite the increasing number of patients undergoing treatment in Ghana, the published literature does not describe the characteristics of drug-sensitive patients, methods of identification, or treatment outcomes in routine public sector treatment programmes. Mostly not included. Even where clear national guidelines are in place, the published literature indicates that performance and outcomes vary from country to country. Treatment success rates range at the district level from just under 83 % in Western Cape to less than 58 % in Limpopo and from 90 % in Tungul, KwaZulu-Natal to just 47 % in Bembe, Limpopo (Massyn *et al*., 2016).

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Table 2: First-Line Medications for Treatment of Drug-Susceptible TB

Inform the patient about possible side effects of the drug at the beginning and during treatment.

DRUG	DOSAGE MG/KG[2] [TYPICAL DOSE]		ADVERSE REACTIONS	COMMENTS
	Daily	DOSAGE 3x/wk[3]		
Isoniazid (INH)	5 mg/kg [normally 300 mg]	15 mg/kg [usually 900 mg]	Side effects include hepatitis, rash/allergy, peripheral neuropathy, mild central nervous system effects, drug interactions, and optic neuritis.	Add 25-50 mg of pyridoxine (vitamin B6) per day to pregnant women suffering from malnutrition, alcoholism, diabetes and other conditions related to neuropathy. Patients with peripheral neuropathy should take 100 mg per day.
Rifampin RIF	10 mg/kg [normally 600 mg]	10mg/kg [typically 600 mg]	Gastrointestinal intolerance, hepatitis, drug interactions, rash, thrombocytopenia, and flu-like	Inform the patient of the expected orange coloration of the body fluid. Drug interactions may require monitoring and dose adjustment (eg

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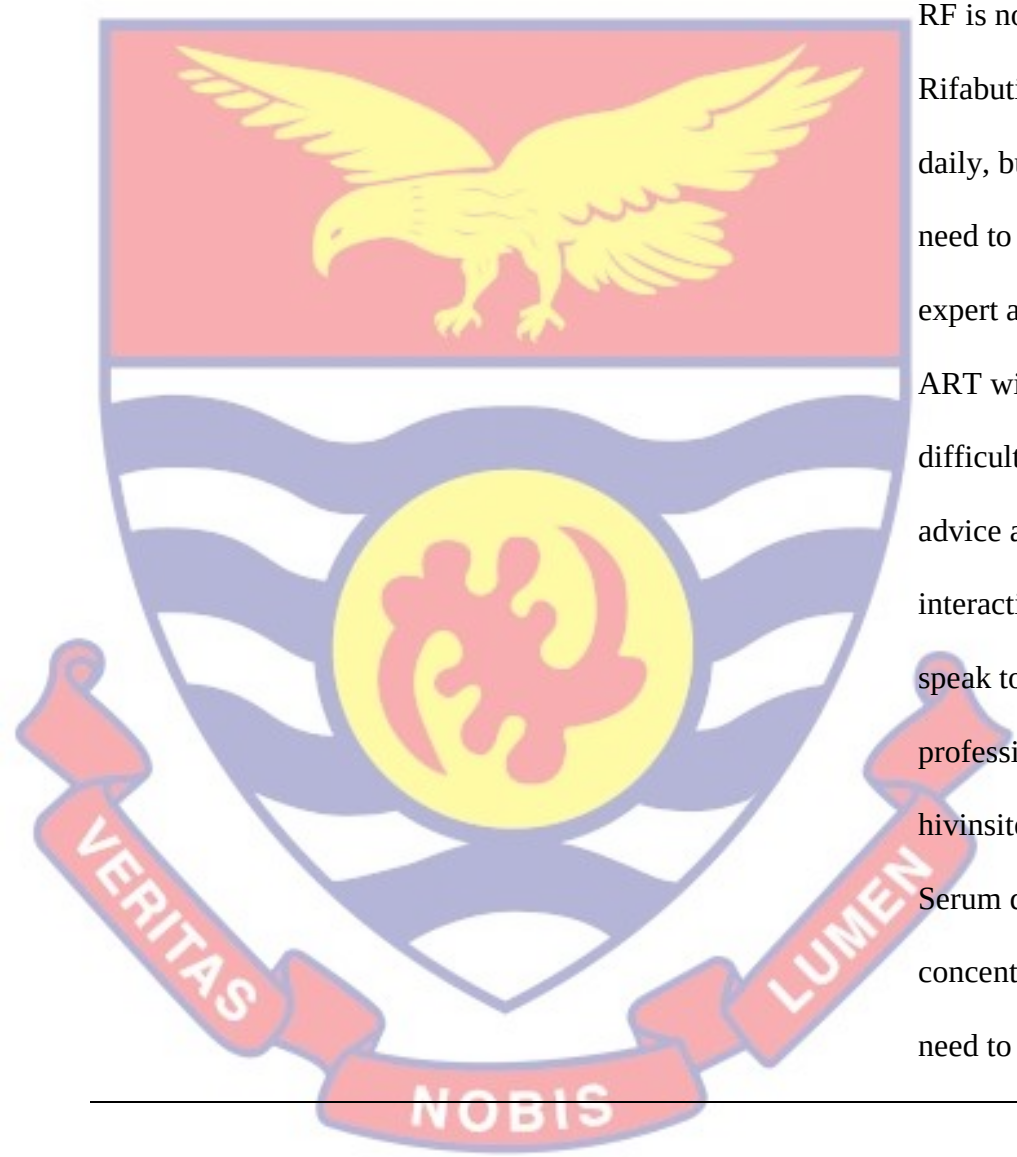
symptoms may occur.	methadone). Women taking hormonal contraceptives should use a blocking method. RF is not an option. Rifabutin can be used daily, but dosage may need to be adjusted. Get expert advice. Using ART with rifamycin is difficult. For up-to-date advice and drug interaction information, speak to an HIV professional and visit hivinsite.ucsf.edu/insite. Serum drug concentrations may need to be monitored.



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DRUG	PATIENT WEIGHT[1]	SUGGESTED DOSAGE		ADVERSE REACTIONS	COMMENTS
		Daily	DOSAGE 3x/wk[3].		
Pyrazinamide PZA	40-55 kg	1000 mg	1500 mg	Hepatitis, gastrointestinal disorders, rash, arthralgia, hyperuricemia, gout (rare), photosensitivity	Patients with creatinine clearance <1. For 30 mL/min or hemodialysis, reduce dosing interval to 3 weeks (use standard dose). Her use of PZA for pregnant women in the United States is controversial (see Special Circumstances section). Closely monitor elderly patients for side effects, drug interactions, or hypersensitivities. If for any reason she does not take PZA, the treatment period will be extended for her to
	56-75 kg	1500 mg	2500 mg		
	76-90 kg	2000 mg	3000 mg		

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					9 months.
Ethambutol EM	40-55 kg	800 mg	1200 mg	Optic neuritis	Dosing interval should be reduced to 3 times weekly in patients with creatinine clearance <30 mL/min or on hemodialysis (standard capacity).
	56-75 kg	1200 mg	2000 mg		
	76-90 kg	1600 mg	2400 mg		

1. Fixed-dose anti-tuberculosis drugs (FDCs) can be used when possible.

2. Dosages of INH and RIF can be based on the actual body weight of non-obese patients. PZA and EMB dosages are based on estimated lean body mass. The optimal dose for obese patients has not been established. See Table 3 in ATS/CDC/IDSA Recommendations.

3. For other intermittent therapies, see ATS/CDC/IDSA dosing guidelines (Akobeng, 2007).

Table 2 Preferred treatment for culture-positive drug-sensitive pulmonary tuberculosis

Daily dosing with case management and DOT is preferred throughout treatment. For non-HIV-infected patients, intermittent dosing with DOT 3 times a week during the persistence phase is reasonable. Pyridoxine (vitamin B6) is given with isoniazid to all retirees at risk of neuropathy and retirees with peripheral neuropathy (see previous table for details).

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INTENSIVE PHASE		
4-Drug Combination	Interval & Doses (Minimum Duration) with DOT	Recommendation
INH	Daily: at least 56 doses 7 days per week (8 weeks) or at least 40 doses 5 days per week (8 weeks)	Preferred
	OR	Some patients may be considered: HIV-free and low risk of recurrence (known drug-
	Intermittent: 3 times a week, at least 24 times times (8 weeks).	

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<table>
<tr><td colspan="2">CONTINUATION PHASE[1]</td><td rowspan="2"></td><td rowspan="2">susceptible tuberculosis with no holes or smears at the start of treatment).</td></tr>
<tr><td>2-Drug Combination</td><td>Interval & Doses (Minimum Duration) with DOT</td></tr>
<tr><td>INH/RIF</td><td>Daily[1]: At least 126 doses 7 days a week (18 weeks)
or
At least 90 doses 5 days a week
(18 weeks)

OR

Intermittent:[3] 3w/wk for a minimum of 54 dozes (18 weeks)</td><td colspan="2"></td></tr>
<tr><td colspan="2">RIF

PZA

EMB[2]</td><td colspan="2"></td></tr>
</table>

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1. *Follow tuberculosis program guidelines for defining daily naps. Many programs using 5 DOTs per week to meet the daily dose definition opt for 2 additional doses with self-administered therapy (SAT). However, the SAT dosage is not included in the totals given. In difficult cases, some experts prefer the maximum doses mentioned above for daily treatment.*
2. *Other intermittent dosing options may be available under certain circumstances. Twice a week is generally not recommended as skipped doses are equivalent to once a week. However, twice-weekly doses can be used during the maintenance phase if program conditions are met to compensate for the missing dose. See recommended treatment section of ATS/CDC/IDSA guidelines.*
3. *In certain circumstances with cavitation in the initial complete control and positive cultures 2 months post-treatment, extend the continuation phase to 7 months for a total of 9 months (31 weeks) of daily treatment is needed. Yes (National Tuberculosis Control Program).*

Treatment For DR-TB

Define your daily dose according to TB programme guidelines. Many programmes that use a 5-day/week DOT to meet the daily dose definition also choose to provide two additional doses through self-administered therapy (SAT). However, the SAT dozen is not taken into account when counting the total offering. In complicated cases, some experts prefer the maximum doses mentioned above for daily treatment.

Twice-weekly dosing is normally not recommended. A missed dose is equivalent to a once-a-week dose, which is inferior. However, WHO recently

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published integrated treatment guidelines for drug-resistant tuberculosis (DR-TB) (WHO, 2018). These include new drug classifications for rifampicin-resistant (RR) and multidrug-resistant tuberculosis (MDR-TB) and recommendations for short-term (including parenteral) or long-term (including parenteral) alloral therapy.

A powerful diagnostic tool for detecting secondary drug resistance is now available in just hours. The challenge for national TB programs is therefore to integrate these new recommendations into national anti-TB chemotherapy regimens that have significantly improved outcomes for TB patients. Between 1946 and 1976, several antituberculosis drugs were discovered, including aloniazid (H) and rifampicin (R), the most effective.

Similarly, randomized controlled trials combining multiple agents have strengthened the evidence for both of these basic principles of antituberculous chemotherapy. These include:

1) use of at least two drugs (to avoid selection of naturally resistant mutants)a

2) for a period of time sufficient for healing and prevention of recurrence (to effectively sterilize the infected tissue) (Caminero *et al.*, 2013); A randomized controlled trial showed that dual therapy is effective in all forms of tuberculosis, even when neither drug is resistant (Caminero *et al.*, 2013). Based on these findings, 9-month two-drug regimens (isoniazid and rifampicin) or 6-month three-drug regimens have been used since the 1980s.

Rifampicin and pyrazinamide are extremely sterile (Caminero *et al.*, 2010). The use of rifampicin shortened the regimen from 18 to 24 months to 9 months, and the use of pyrazinamide reduced the treatment duration to six

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months (WHO, 2016). Using sterilising drugs reduces treatment duration, according to several randomized controlled trials (Caminero *et al.*, 2013).

At that time, ofloxacin and levofloxacin (Lfx) were the only fluoroquinolones recommended for the treatment of DR-TB, both of which exhibited moderate bactericidal activity and limited ability to shorten regimens. Pyrazinamide has been routinely used in patients with multidrug-resistant tuberculosis, but early use increases the risk of pyrazinamide resistance in nearly all cases, and new evidence suggests shortening treatment duration for patients with RR/MDR-TB. It was not considered an effective primary therapy because of its support. 2016).

In 2016, WHO recommended its use in certain conditions, including hypersensitivity to fluoroquinolones and use of injection drugs. This regimen was shortened to 9–11 months due to the high bactericidal activity of high-dose moxifloxacin (Mfx) and clofazimine (Cfz) (Htun *et al.*, 2018). In the absence of tolerance, the regimen contains pyrazinamide, which may affect the duration of treatment. A 2017 meta-analysis of studies on this shorter regime confirmed its efficacy, which was confirmed in nine African countries (Trébucq *et al.*, 2018). Finally, pyrazinamide and ethambutol were not required to improve regimen efficacy. Their role was to shorten the regimen (in the case of pyrazinamide) and protect rifampicin if isoniazid resistance existed (for ethambutol). As a result, two highly effective drugs given over a sufficiently long period of time are sufficient to cure nearly all drugsusceptible cases.

Drug resistance, on the other hand, is frequently more complicated, as research has shown that drug resistance can develop even when the treatment

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regimen is properly prescribed and followed. Because of the variability in individual pharmacokinetics (Dheda *et al*., 2018).

TB lineage also contributes to the growth of drug resistance. For decades there were no sterilizing drugs other than rifampicin and pyrazinamide, so patients with RR and MDR-TB were treated with less potent drugs for 18–24 months (or when adverse events of rifampicin occurred). There are conditions to treat missed doses, and twice-weekly dosing is possible in the continuation phase.

In certain circumstances, including patients with cavitation on initial CXR and positive cultures after 2 months of treatment, the continuation phase was extended to 7 months for a total of 9 months (31 weeks) of daily treatment. (National Tuberculosis Programme).

As a result, almost any drug-sensitive case can be treated if two very efficient drugs are taken for an adequately widespread era. Drug resistance, on the other hand, is frequently more complex as it has been shown that drug resistance can occur even with the correct prescription/administration of a treatment regimen. There is variability in individual pharmacokinetics (Dheda *et al*., 2018).

In addition, drug penetration and *Mycobacteria* strain characteristics differ in lung invasion. Tuberculosis (ie strains) accordingly contributes to the development of drug resistance. For decades, in the absence of other bactericidal agents other than rifampicin and pyrazinamide, RR and MDR-TB (or if side effects of rifampicin did occur) were treated with less effective drugs for 18-24 months.

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Challenge of Treatment Concerning Diagnostics

As a result, if two powerful drugs are taken long enough, almost all drug-sensitive cases can be treated. It has been shown that it can also occur with the administration of therapeutic regimens. There are differences in individual pharmacokinetics (Dheda *et al*., 2018). Furthermore, the drug permeability and lung infiltration properties of mycobacterial strains differ. In the absence of other antibacterial agents, except rifampicin and pyrazinamide, RR and MDR-TB (or if side effects of rifampicin appeared) were treated with less potent drugs for 18-24 months.

Tuberculosis Screening and Diagnosis Protocol in Ghana

Tuberculosis is a serious public health threat, so all patients who come to hospital should be diagnosed and treated. SSM is a simple tuberculosis diagnostic test widely used in public health facilities in Ghana. This is also possible at a fair price. However, the emergence of the Xpert MTB/RIF as the preferred primary diagnostic test has led to a rethinking of TB screening and diagnosis in various populations, as shown below.

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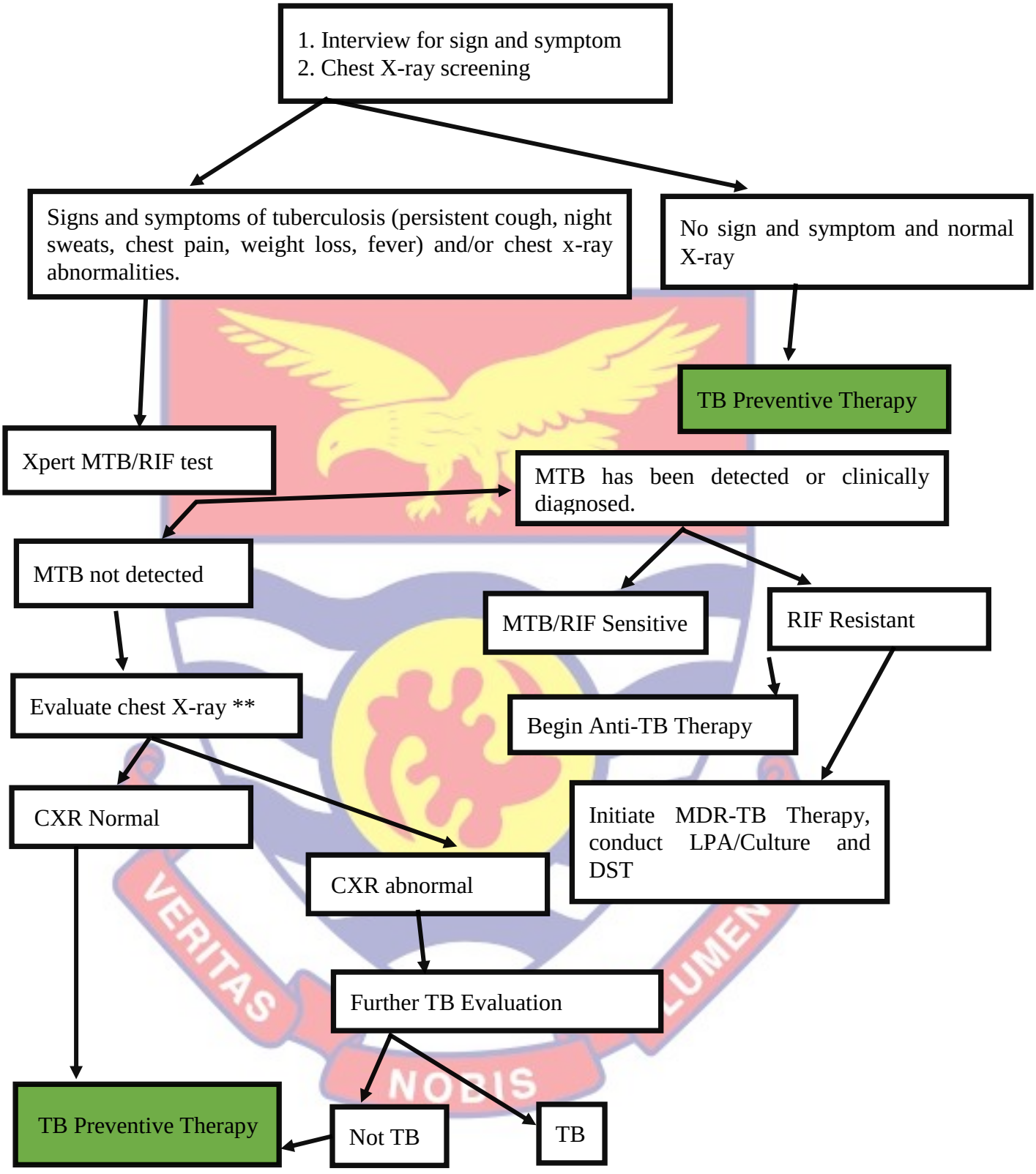

Figure 4: Algorithm for screening and diagnosing tuberculosis in HIV-infected people (Ghana National Tuberculosis Control Programme).

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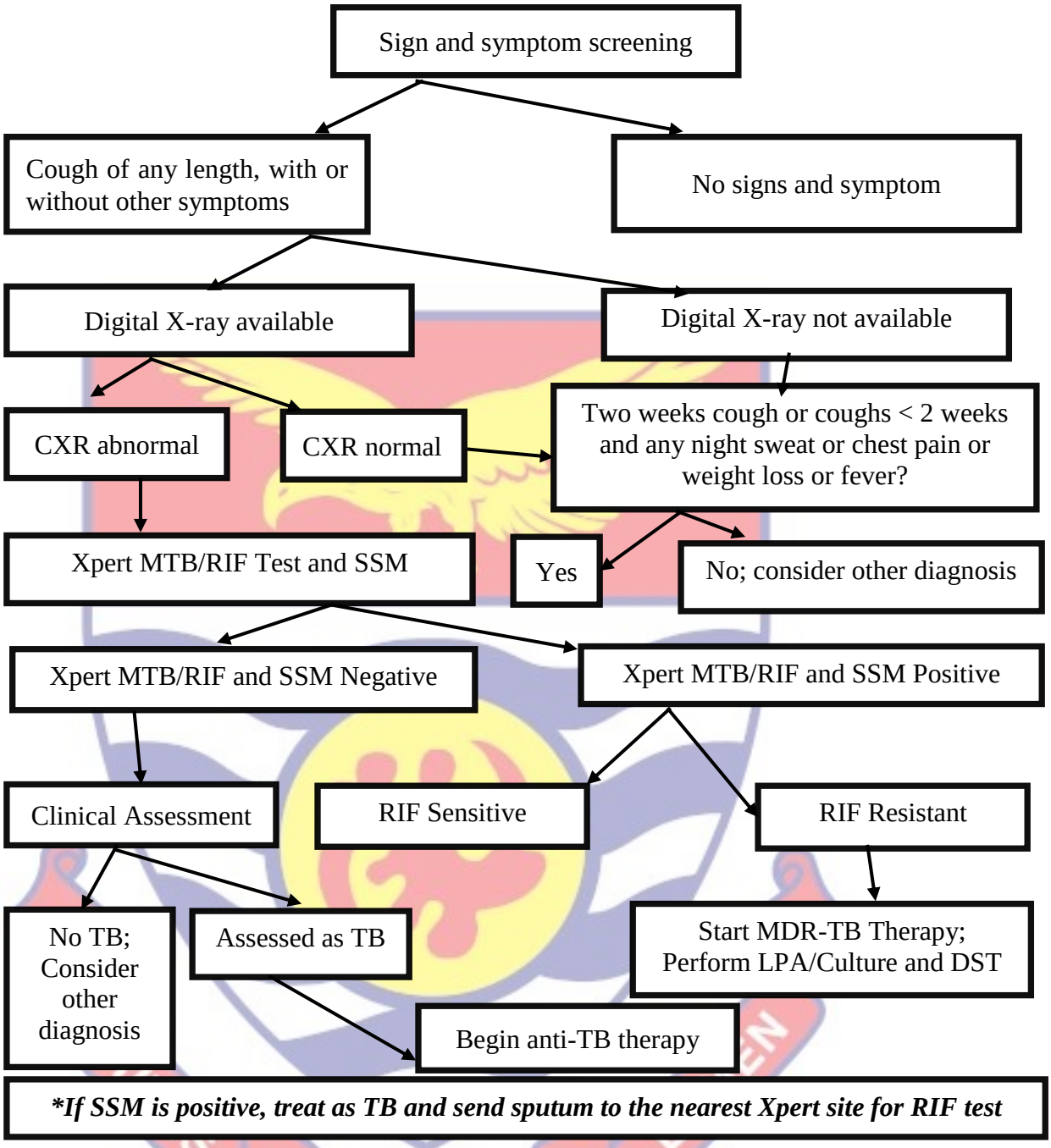

Figure 5: TB screening and diagnostic algorithm for facility-based case detection (Ghana's National Tuberculosis Control Programme).

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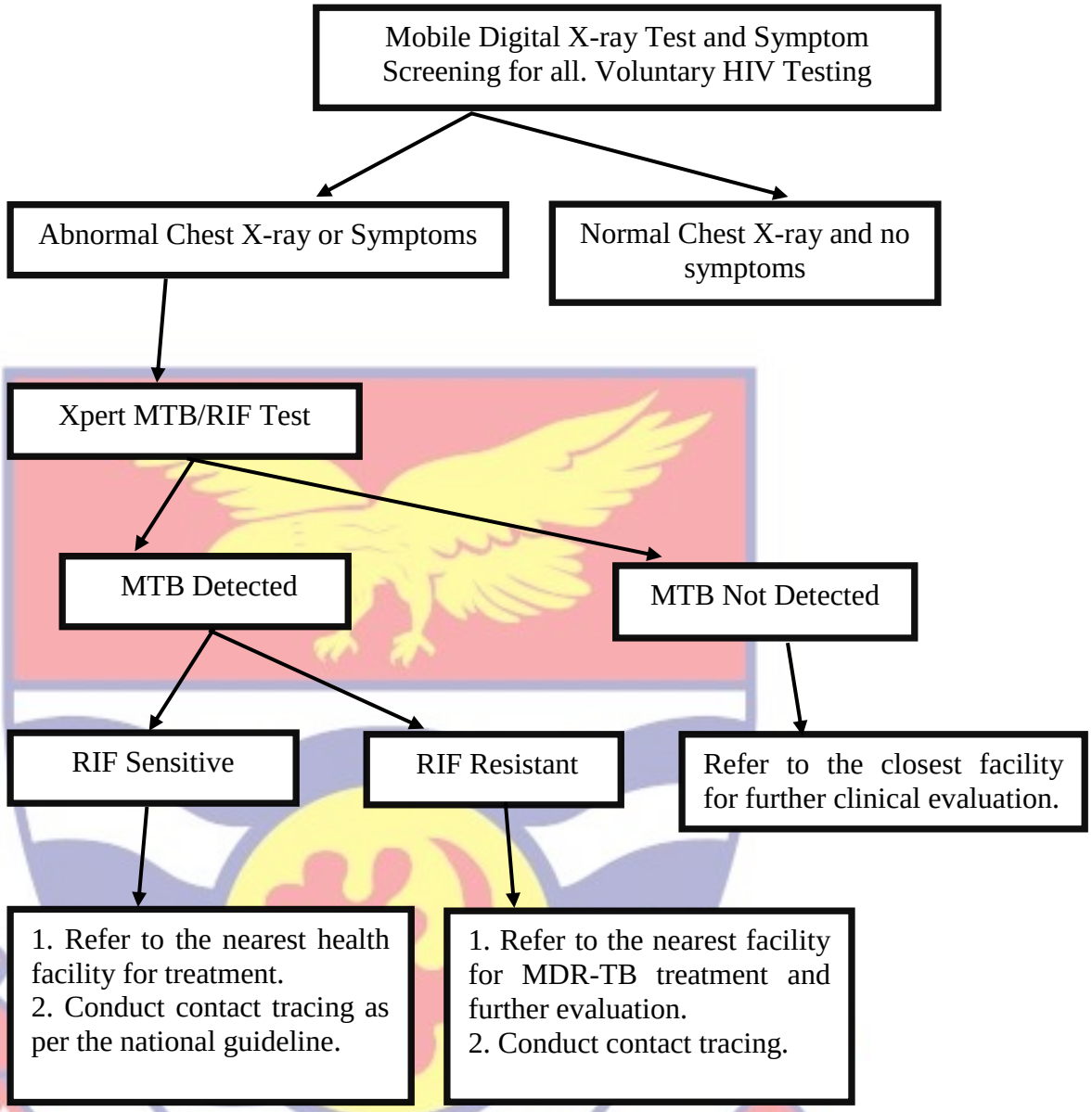

Figure 6: Community Targeted Screening Algorithm for TB Screening and Diagnosis (Ghana National Tuberculosis Control Programme)

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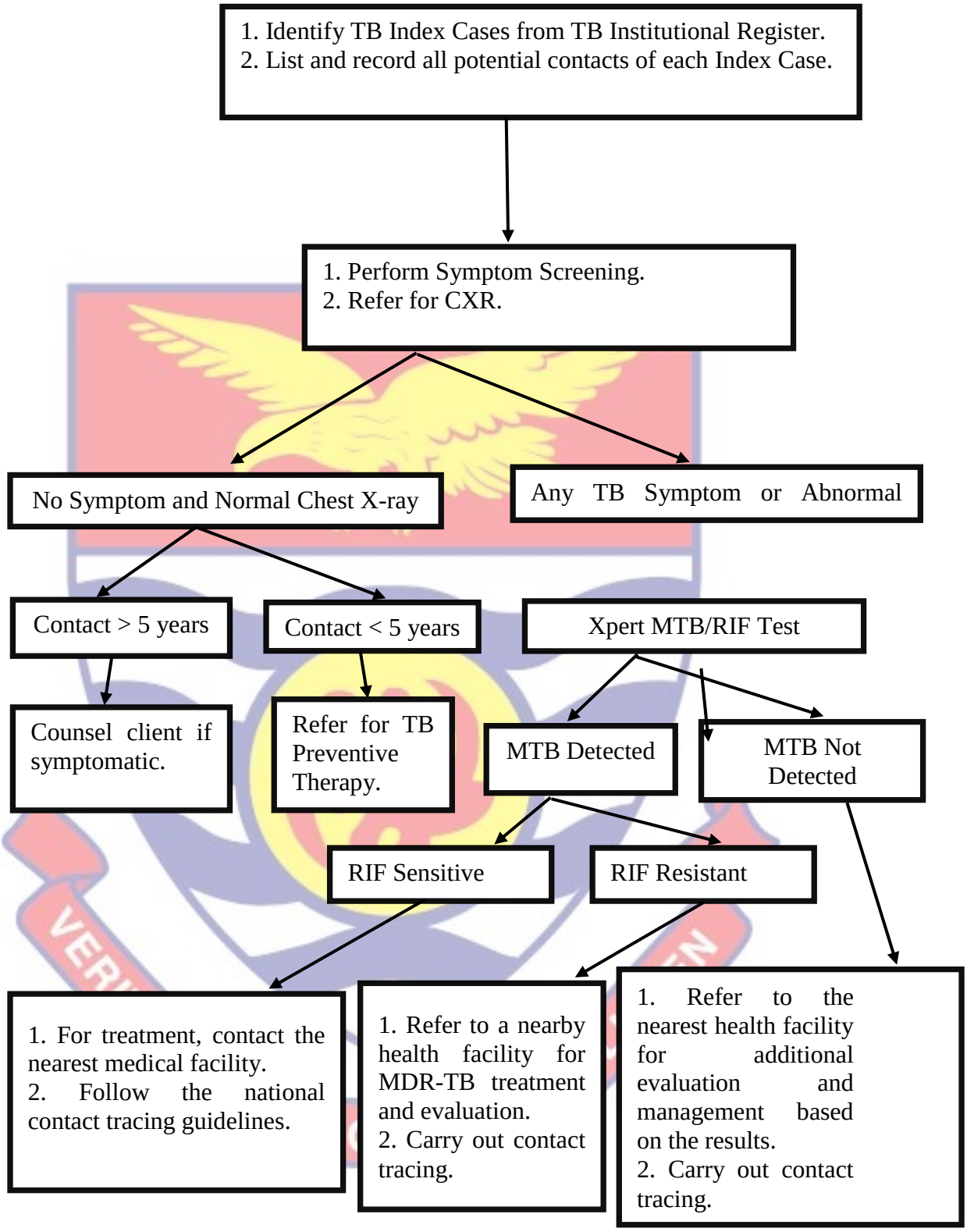

Figure 7: Algorithm for screening and diagnosing tuberculosis among known tuberculosis contacts (Ghana National Tuberculosis Programmeme)

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With the release of Xpert MTB/RIF, a look at the changes in TB screening and diagnosis, and all cases with suspected TB shows that cases were confirmed by X-rays, and then Xpert MTB/RIF if the X-rays were abnormal. Changes to these TB screening and diagnostic algorithms will affect the number of laboratory diagnostic requests for suspected cases. As a result, laboratories will receive fewer requests for TB cases than when SSM was used as a screening and diagnostic tool.

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CHAPTER THREE

MATERIALS AND METHODS

Introduction

Chapter 3 describes research methods and ethical considerations for this research and its data analysis. The methods used in this study, which followed presumed tuberculosis patients once a month for ten months, are described in this chapter. The 494 archival samples used in the analysis were properly stored in 5 mL sterile Falcon tubes and kept at a temperature of -20 ^{o}C in the Cape Coast Teaching Hospital Laboratory until they were used. These samples were gathered between December 2020 and October 2021.

Study Area

Cape Coast is the capital of the Central Region of Ghana and is located at the southernmost tip of the country. Central Regional Hospital, now known as Cape Coast Teaching Hospital (CCTH), is its 400-bed referral hospital in the Cape Coast suburb of Abura. It has been converted into a teaching hospital in collaboration with the University of Cape Coast, College of Health and Allied Sciences and School of Medical Sciences.

CCTH became the first hospital in a state-of-the-art regional hospital chain established by the Ministry of Health on 12 August 1998, and was fully operational the following year. The hospital's TB Referral Clinic is managed by a team of clinicians, pharmacists, nurses (clinical and community health), and disease control officers. The center provides medication administration, contact tracing, and palliative care, as well as counseling and adherence

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services and diagnostic services like Xpert MTB/RIF, SSM, and culture.

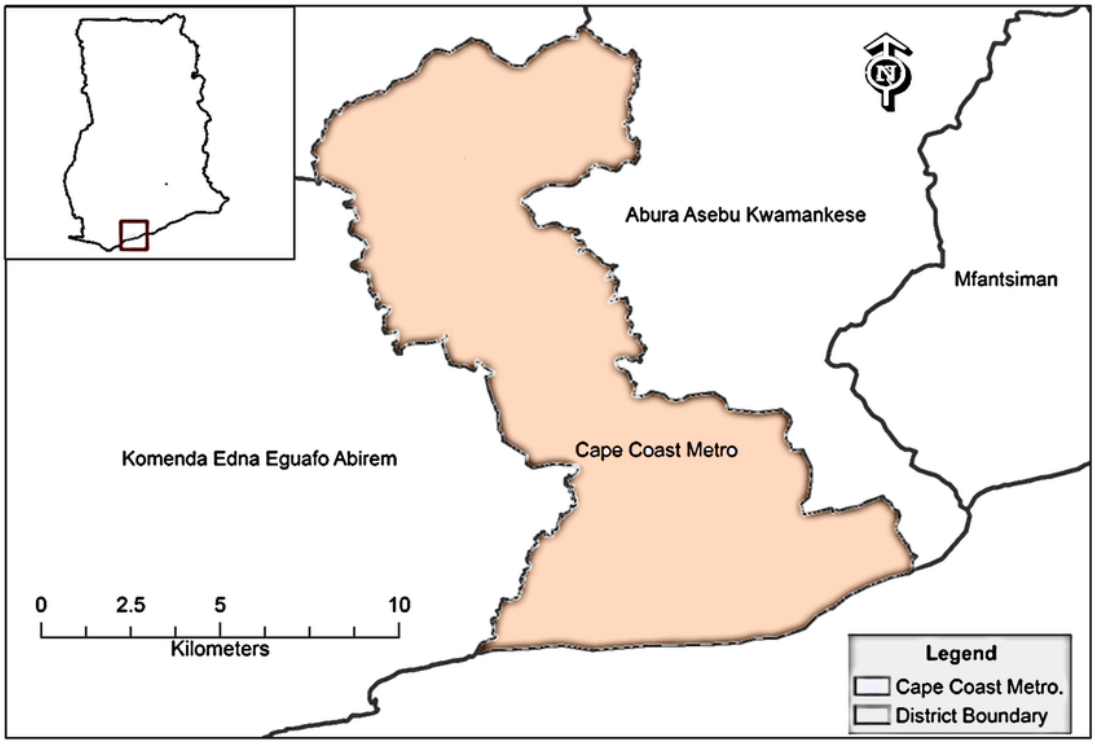

Figure 8: **Map of Cape Coast Metropolitan Area. Source: http//www.researchgate.net**

Study Population

At CCTH, 494 samples from patients with suspected tuberculosis were collected for this study. The age of the initial patient cohort ranged from 1 year to her 80 years. All 494 samples were tested on the Xpert MTB/RIF prior to storage. All 494 archival samples collected between December 2020 and October 2021, which already had Xpert MTB/RIF tests conducted on them, underwent culture and SSM in this study.

Research Design

This research made use of previously archived samples. In a retrospective study, patients suspected of having tuberculosis were sampled daily for ten months (December 2020 to October 2021).

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Approval and Ethical Considerations Ethical Acceptance

The study received ethical approval from the Cape Coast Teaching Hospital Ethical Review Committee under Protocol ID Number: CCTHERC/EC/2022/003.

Sample Size

A total sampling method was used because this was a retrospective study. To demonstrate statistical power, at least 200 individual samples were analyzed.

Sampling Procedure

Investigator used archived samples from 494 suspected TB patients who visited Cape Coast Teaching Hospital between December 2020 and October 2021. During the period indicated above, all suspected cases of TB were recorded in the TB laboratory registry of Cape Coast Teaching Hospital where the sample was taken. Xpert MTB/RIF diagnostic testing had already been performed on all 494 specimens stored prior to storage.

Data Collection Methods and Tools

On all 494 archived samples, an initial Xpert MTB/RIF analysis was performed. For this study, the archived samples were also cultured with Lowenstein Jensen media and SSM. The patients' information came from the Xpert/Microscopy register, which is currently being used at the laboratory to record all information about suspected tuberculosis patients. The register is only accessible to laboratories that perform SSM or Xpert MTB/RIF and SSM and is primarily used to record TB diagnoses.

The data in these patient registers was displayed as a line list. Appendix I structured data extraction was used to collect information on

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presumptive TB cases. Age, gender, institutional referrals, and diagnosis are all factors to consider.

Archived Sputum Samples

CCTH's primary tuberculosis diagnostic tools are Xpert MTB/RIF, SSM and Culture. Mycobacterium tuberculosis is an excellent nitrate reducer. Data from these patient registries were presented as lists of strings, with each row representing a case/observation and multiple columns representing different variables.

Information from these patient registries was presented as a linear list with each row representing a case or observation and multiple columns representing different variables. In Appendix I, structured data extracts to collect information on suspected TB cases were used. The time to report or receive test results was obtained from the laboratory registry of TB patients. All variables required to achieve the study's objectives were included in the extraction form. These archived samples were sputum preserved and stored in 5 mL Falcon tubes at -20 ^{o}C. The CCTH Laboratory conducted all the Xpert MTB/RIF analysis on all archived samples. An adequate volume of raw sputum samples was collected in accordance with the institution's standard procedures. Before processing, re-suspended residues were kept at 2–8 °C for up to seven days. This method was used to prepare expectorated or induced sputum sediments.

Xpert MTB/RIF analysis required a minimum of half mL of re-suspended sputum sediment after digestion, decontamination and concentration. The pellet was resuspended in 67 mM phosphate-water buffer using the method of Kent and Kubica. After re-suspension, at least 0.5 mL of

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the re-suspended pellet was stored for Xpert MTB/RIF analysis. Disposable gloves were worn for protection.

A sample ID was printed on each Xpert MTB/RIF test cartridge. At least 0.5 mL of the entire resuspended pellet was transferred to a conical screw cap tube using a transfer pipette for Xpert MTB/RIF analysis. A 1.5 mL volume of sample reagent was transferred to the 0.5 mL resuspended pellet using a transfer pipette. Three times the volume of resuspended pellet was added to the larger volume pellet. The tube was capped and shaken for at least 10 seconds. Samples were incubated for 15 minutes at 20-30°C. Samples were shaken for at least 10 seconds between incubation times of 5 to 10 minutes.Culture

Lowenstein Jensen (LJ) medium was purchased for these archival samples. A representative of 45 mg sample from the primary culture was collected in a loop and placed in a McCartney bottle with 1 mL of sterile distilled water (SDW) and 63 mm glass beads. Before incubation at 37 °C, sputum was diluted and plated on LJ medium. The growth of *M. tuberculosis* was monitored at 1 week, 2 weeks, 3 weeks, etc. The mycobacteria were carefully poured into a clean, transparent McCartney bottle. The bottle was shaken for 20-30 seconds, then continuous shaking was done slowly with 45 mL distilled water. Small particles were sunk. The turbidity of the bacterial suspension was then attuned with distilled water according to McFarland standards to reach a *M. tuberculosis* concentration of 1 mg/mL.

Mucoid/mucopurulent sputum was primarily made up of recently discharged bronchial tree material, with very little oral or nasal material. Five to seven days after inoculation, cultures were examined once a week for up to

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eight weeks. On LJ medium, the colonies were non-pigmented, rough, and dry. The existence of malachite green, one of the medium's colorus, was responsible for its green hue.

Sputum Smear Microscopy

Ziehl-Neelsen (Acid Fast) Staining Procedure

Before removing the screening sputum sample from the Bio Safety Cabinet (BSC) in the Containment Level 3 (CL3) Laboratory, decontamination, culture inoculation, and smear preparation procedures were completed. The slides were stored in the CL3 Laboratory's BSC prior to heat fixation. Using a pencil, the frosted end of the slide was labeled with the patient screening number, lab accession number, and date. The germ-free deposit was vortexed and thoroughly mixed to re-suspend it. Then, 30 L of well-mixed re-suspended pellets from the decontaminated sputum sample were transferred to a glass slide using a pipette with a sterile aerosol-resistant tip.

Using a continuous rotational movement, each patient's sputum was spread evenly across the central area of the slide. The smear size that was recommended was 20 mm by 10 mm. Slides were air-dried in the dryer for about 30 minutes, with the smeared surface facing up. Then, the dried smear was heat-fixed. Smears were stained with Carbol-Fuchsin and heated until vapors began to rise (i.e., approximately 60 °C).

The heated dye was placed on a glass slide for 5 minutes and rinsed by clean water. The smear was bleached with 3 % v/v for 25 minutes in acid alcohol until it was pale pink. More bleach was added to thick slides or slides that were still discoloured. Stain was removed from the slides with clean

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water, and the backside of the slides were cleaned, and the smear was placed on the air dryer. Each smear was inspected and recorded under a microscope by a 100x oil immersion objective (10x eyepiece for a total magnification of 100x).

Statistical Analysis

This study used both descriptive and analytical statistics. STATA version 16 was used to analyse all data, which allows the data to be organised and summarised numerically and graphically.

Study Variables

Dependent Variables

SSM test result positive or negative, MTB detected, MTB not detected, SSM test result not received were the dependent variables obtained from SSM. A positive or negative smear result was obtained using the Xpert MTB/RIF test previously conducted on all archived samples by the CCTH Labooratory but entirely, other variables remained autonomous.

Independent Variables

Demographic variables were age, gender, requesting institution, appearance of sputum or sample, and processing time for reporting test results.

Key definitions

1. A positive culture was used to diagnose disease and is therefore the gold standard in this definition and Xpert MTB/RIF and SSM tests are associated to the standard (Akobeng, 2007).
2. The percentage of patients with a positive test result was called sensitivity.

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3. The proportion of people with a negative test result who do not have the disease was referred to as specificity.
4. The positive predictive value was the percentage age of people who have the disease and have a positive test result.
5. The proportion of people over the age of 40 that test negative but do not have TB was referred to as the negative predictive value.

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CHAPTER FOUR

RESULTS AND DISCUSSION

Introduction

This chapter presents and explains the results, and Chapter 5 presents conclusions, suggestions, and forthcoming research guidelines. The objective of this study was to see how much concordance there was in tuberculosis diagnosis at CCTH between December 2020 and October 2021 using Xpert MTB/RIF, SSM, and Culture. The researcher used both prospective and retrospective study designs to work on 494 archived samples of people with presumptive tuberculosis who were tested for tuberculosis in the CCTH Laboratory. All of these patients' records remained reviewed for this study, as shown in the tables and graphs below. In course of the study period, all 494 (100%) of the archived samples of all patients were tested. Xpert MTB/RIF checks had already been finished on all the archived samples. In this study, SSM and Culture checks were used on all samples.

Data Analysis

The results of the data analysed are presented in the tables below. Table 1 provides demographic and clinical data, and Table 2 provides descriptive statistics for various test types. The relationship between culture and Xpert MTB/RIF results is shown in Table 3.

Table 4 shows the relationship between culture and microscopy and Table 5 shows the relationship between SSM and Xpert MTB/RIF. Table 6 shows the sensitivity, specificity, and positive and negative predictive values.

Table 7 shows the mycobacterial characteristics of the culture results,

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and Table 8 shows the odds ratio of NTM samples from patients who tested positive for PTB and EPTB.

Results

The sensitivity, specificity, negative predictive value, and positive predictive value (with 95 % confidence intervals) of Xpert MTB/RIF and pulmonary tuberculosis microscopy were determined using culture as the gold standard. All data were analyzed using STATA software (version 16.0), $p < 0.05$ was considered statistically significant.

Sociodemographic characteristics

The majority of the samples, 304 (61.5%), belonged to participants aged between 20-49 years. Mean age was 36.5 years with a standard deviation of 17.8. There were more males, 312 (63.2%), than females, 182 (36.8%). Samples of HIV-positive participants were 139 (27.7%). The HIV status of 37 (7.9%) individuals could not be retrieved. Although many of the participants were classified as pulmonary TB (75.1%), the classification of 13 participants was still undetermined. Table 1 summarises the sociodemographic characteristics.

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Table 3 - Demographic and Clinical Characteristics

Parameter (N=494)	PTB		EPTB		Disseminated TB		Others		Mean	SD	Median	QR	P-value
Age (years)	n	%	n	%	n	%	n	%					
0-19	86	17.4	18	16.8	0	0.0	85	17.7	36.5	17.8	37.0	25-48	<0.001
20-49	305	61.7	62	58.0	2	66.7	295	61.6	36.5	17.8	37.0	25-48	<0.001
≥ 50	103	20.9	27	25.2	1	33.3	99	20.7					
Total	**494**	**100.0**	**107**	**100.0**	**3**	**100.0**	**479**	**100.0**	36.5	17.8	37.0	25-48	<0.001
Sex													
Male	312	63.2	67	62.6	3	100.0	307	64.1	36.5	17.8	37.0	25-48	<0.001
Female	182	36.8	40	37.4	0	0.0	172	35.9	36.5	17.8	37.0	25-48	<0.001
Total	**494**	**100.0**	**107**	**100.0**	**3**	**100.0**	**479**	**100.0**	36.5	17.8	37.0	25-48	<0.001
HIV Status													
Positive	108	29.3	29	27.1	0	0.0	137	28.6	36.5	17.8	37.0	25-48	<0.001
Negative	234	63.4	67	62.6	3	100.0	304	63.5	36.5	17.8	37.0	25-48	<0.001
Unknown	27	7.3	11	10.3	0	0.0	38	7.9	36.5	17.8	37.0	25-48	<0.001
Total	**369**	**100.0**	**107**	**100.0**	**3**	**100.0**	**479**	**100.0**	36.5	17.8	37.0	25-48	<0.001

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Test positivity rate for the different tests

Overall, the test positivity rate of microscopy was 52.8% while that of Xpert and culture were 37.9% and 23.5% respectively. Table 2 summarises the test positivity rate of the three tests as used.

Table 4: Test positivity rate for the different tests

Type of test	**Microscopy**		**Xpert MTB/RIF**		**Culture**		
Results	n	%	n	%	n	%	P-value (< 0.001)
Positive	261	52.8	187	37.9	151	34.7	
Negative	233	47.2	307	62.1	284	65.3	
Total	**494**	**100**	**494**	**100.0**	**435**	**100.0**	

Comparison of Xpert MTB/RIF to Culture as the gold standard

Only 58 of the 59 positive culture samples were also positive for microscopy, while 1 negative culture sample out of a total of 203 negative microscopy samples had a p-value of <0.001.

Table 5: Association between Culture and Xpert MTB/RIF results

Type of test		Culture			
		Positive	**Negative**	**Total**	**p-value**
Xpert MTB/RIF	**Positive**	36	151	187	<0.001
	Negative	23	284	307	
Total		**59**	**435**	**494**	

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Comparison of Microscopy to Culture as the gold standard

With a p-value of <0.001, only 118 of the 261 samples positive for microscopy were also positive for Xpert MTB/RIF, while 69 of the total negatives for culture were negative for Xpert.

Table 6: Comparison of Microscopy to Culture as the gold standard

Type of test		Culture			
		Positive	**Negative**	**Total**	**p-value**
Microscopy	**Positive**	58	203	261	< 0.001
	Negative	1	232	233	
Total		**59**	**435**	**494**	

Diagnostic accuracies for the detection of pulmonary tuberculosis of the tests

Table 5 summarises the sensitivity and specificity of the various tests in identifying patients with pulmonary tuberculosis among patients with presumed pulmonary tuberculosis. The sensitivity of the Xpert MTB/RIF results to the culture gold standard was lower than that of microscopy, which was 19.3 % (95 % CI, 13.9–25.6 %) versus 22.2 % (95 % CI, 17.3–27.8 %). The Xpert MTB/RIF specificity versus culture was also lower, with 92.5 % (95 % CI, 89.0–95.2 %) versus 99.6 % (95 % CI, 97.6–100.0 %) for microscopy versus culture.

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Table 7: Diagnostic accuracies for the detection of pulmonary tuberculosis of the tests

Type of TB Test	**Sensitivity (%)**	**(95 % CI)**	**Specificity (%)**	**(95 % CI)**	**PPV (%)**	(95 % CI)	**NPV (%)**	(95 % CI) (%)
Xpert MTB/RIF	61.0	(47.44-73.5)	65.8	(61.1-70.2)	19.5	(16.0-23.5)	92.6	(90.0-94.5)
Microscopy	98.3	(90.9-100.0)	53.3	(48.5-58.1)	22.2	(20.5-24.1)	99.6	(97.1-100.0)

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Microbiological outputs of culture results

The cultures of the various disease states produced either positive or negative results. As a result of the positive results, two additional mycobacteria species, as shown in Table 7, were grown. The table shows the likelihood of isolating NTM species if a patient has pulmonary tuberculosis rather than extrapulmonary tuberculosis.

Table 8: Mycobacterial characteristics of the culture results

Type of test	MTB Positive (n)	MTB Negative (n)	NTM (n)	P-value (<0.001)
PTB	48	314	7	
EPTB	11	49	50	
Total	**59**	**363**	**57**	

Odds ratio of NTM positive with PTB and EPTB

Out of the 116 samples that were positive on culture, 59 (50.9%) were *Mycobacterium tuberculosis* (MTB) positive, while 57 (49.1%) were positive for nontuberculous mycobacteria (NTM). Table 6 presents the odds of isolating NTM from samples labelled extrapulmonary TB (EPTB) compared to pulmonary tuberculosis (PTB).

Table 9: Odds ratio of NTM positive with PTB and EPTB

	OR (95% CI)	**P-value (<0.001)**
EPTB	45.36 (19.61-104.95)	
PTB	1	

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Discussion

Over the past decade, there has been improvement in TB diagnosis with the approval of Xpert MTB/RIF as the preliminary diagnostic test for active TB diagnosis (WHO, 2022). In this study, the test positivity rate for microscopy was 52.8 %, Xpert was about 38 %, and culture was 23.5 % (Table 2) among the patients eligible for Xpert in our setting. These test positivity rates are higher than those reported in Benue State in Nigeria, at 16 % for SSM and 15.1 % for Xpert in a similar population of patients with presumed TB (Ejeh *et al*., 2020). To improve the test positivity rate for the various tests employed in the field, the test positivity can be improved by using an initial screening tool in a clinical population to avoid wastage in a resource-limited setting.

This study defined a positive Xpert assay as Xpert MTB detected trace and above. The laboratory algorithm for implementing Xpert recommends further evaluating patients with trace results to ascertain tuberculosis (WHO, 2021). Since this is a laboratory study, no positive result was excluded.

The pooled sensitivity and specificities of Xpert MTB/RIF (Ultra) have been reported as 68 % and 98 %, respectively (WHO, 2021). Its predictive values depend on the population's prevalence (WHO, 2021). In this study, culture positives were used as the gold standard, the sensitivity of Xpert was 61.02 % (95 % CI, 47.44-73.45) and specificity of 60.05 % (95 % CI, 54.92-65.03), while the positive and negative predictive values were 19.25 % (95 % CI, 15.81-23.23) and 90.80 % (95 % CI, 87.65-93.31). These test characteristics values were much lower than those reported by Gelalcha *et al*. in Ethiopia, who reported a sensitivity of 93.3 % (95 % CI, 81.7-98.6), and a

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specificity of 98.0 % (95 % CI, 95.6-99.2 %) (Gelalcha *et al*., 2017). It has to be investigated further why the test in our setting detected only 3 out of 10 people with the disease.

The pooled sensitivity reported by WHO in their guideline for using Xpert shows a range of test characteristics (WHO, 2021). This means these tests can have different characteristics in different settings and different populations, and these must be studied to interpret results in context. However, it is important to note that Xpert's PPV is much higher than culture, meaning a presumed TB test with positive Xpert results is more likely to have TB than a positive culture.

Similar derivations can be made according to the microscopy results, which had a much higher sensitivity and lower specificity; 98.31% (95 % CI, 90.91-99.96) and 61.38 % (95 % CI, 56.26-66.31), the sensitivity of SSM using ZN Staining, as reported by Ngabonziza *et al*. in Rwanda, was 48 % (95 % CI, 37.0-60.4) (Ngabonziza *et al*., 2016).

Smear microscopy results have long depended on the operator's expertise and the microscopy method used (WHO, 2022). Although fluorescent microscopy has been touted as a possible replacement for SSM by ZN Staining, the study by Ngabonziza *et al*., did not reveal a significant improvement in sensitivity (55.1 % SSM vs 37.7 % LED) (Ngabonziza *et al*., 2016). Therefore, this study advocates regular training of microscopists to improve the outputs as the world looks to continue the utilisation of microscopy for TB monitoring and identifying other non-TB mycobacteria.

This study presents that the risk group for TB positivity in our setting was >20 years, with the year group 20-49 years having the higher risk for

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microscopy, Xpert and culture. When the study compared Xpert vs culture and Xpert vs microscopy, the odds of TB were still higher in the 20–49 year group.

In this study, sex and HIV status were not associated with an increased risk for TB positivity. Being HIV positive was even associated with a lower risk for TB positivity. Tuberculosis has long been known as one of the important causes of mortality in people living with HIV (PLHIV), causing 214 000 deaths in this population in 2020 globally (WHO, 2021). And the relative risk for TB disease among HIV patients has been reported to be 22 (Glaziou *et al*., 2018). The result of this study should therefore be interpreted in the local context. Based on the findings of this study, it is essential to not just concentrate on PLHIV during TB control activities.

This study also identified the presence of nontuberculous mycobacteria (NTM) amongst LJ-positive cultures at 49.1 % (overall prevalence 57/494, 11.5 %). Between PTB and EPTB, sputum samples were more favourable for NTM in the samples of patients classified as EPTB than TB. It may be possible that these were very sick patients with both pulmonary and extrapulmonary manifestations; of note, all the culture-positive NTM samples were SSM-positive and Xpert-negative. This can be an important finding in the context of Xpert-negative, smear-positive samples being NTMs requiring further assessment.

It is also difficult to ascertain whether these NTM samples were contaminants, although all standard operating procedures were followed to limit contamination. There is also the possibility that these were colonisations. However, the results of this study concur with the reported increase in

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isolation of NTMs amongst pulmonary samples of presumed TB patients in Tanzania and Cote D'Ivoire, respectively, at 1.9 % and 10.2 % (Hoza *et al*., 2016; Afr *et al*., 2021). The health service must therefore pay more attention to the emerging problem of NTM and determine its clinical significance in enhancing patient care.

Strengths and Limitations

This study employed consecutive samples from patients with presumed TB to measure the sensitivities and specificities of the routine tests used in diagnosing TB. This is a strength as the study was able to measure the correlation between these tests and how it is measurable one was used instead of the other in the field.

The study has several limitations in that it did not have funding to have molecular characterisation for the NTM species. Also, it would have been advantageous to present both the clinical and the laboratory data, but the study was limited to the tests employed in routine care. Moreover, as this is a single-centre study, it was difficult to generalise the findings of this study.

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CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

This chapter presents the summary, conclusions and recommendations of the research.

Summary

The purpose of this study was to validate the Xpert MTB/RIF consensus rate using SSM and cultures to detect TB at Cape Coast Teaching Hospital in Central part of Ghana. SSM, culture, and Xpert MTB/RIF tests all showed statistically significant differences in the proportion of tuberculosis detected. If more patients miss the detection of tuberculosis in our setting as a consequence of using standard Xpert MTB/RIF as primary diagnosis, this needs to be further evaluated for clinical importance.

Conclusion

This study has presented the test performance of Xpert, SSM and culture at a tertiary facility in a high-burden TB country. The test positivity rate is much higher on our site. The study has further shown that the test positivity rate of Xpert for TB diagnosis is much higher than culture on the sputum of presumed TB patients.

Therefore, Xpert should be considered as the gold standard for tuberculosis diagnosis. Sensitivity, specificity, and predictive value are much lower than similar regions in our environment, and further studies are needed to confirm these results.

Recommendations

This survey should be repeated periodically to see if the test performance has improved in our environment. This study also showed

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increased segregation of NTM. Although this study was unable to identify much more NTMs, further studies are needed to determine the clinical significance of these few NTM isolates.

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APPENDIX I: LABORATORY DATA EXTRACTION SHEET

LABORATORY DATA EXTRACTION SHEET **FACILITY NAME:** **DATE:**

Patient ID	Age	Sex	Patient address	Referring facility	Reasons for examination	Specimen type	Specimen appearance	Lab results	Sample receipt time	Report pick up time

Reasons for examination: 1 - TB diagnosis 2 - Drug resistance 3 - fellow-up
Specimen type: 1- Sputum 2 - Pleural aspirate 3 - Gastric content 4 - Biopsy 5 - others
Specimen appearance: 1 - Muco-purulence 2 - Blood stained 3 - Muco-salivary 4 - Salivary
Reasons for examination: 1 - TB diagnosis 2 - Drug resistance 3 - Follow up monitoring
Lab results (Microscopy): 1 - Smear positive 2 - Smear negative
Lab results (GeneXpert): 1 - MTB detected only 2 - MTB not detected 3 – Rifampicin resistance detected 4 - indeterminate 5 – Error

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APPENDIX II: ETHICAL CLEARANCE

In case of reply the reference number and the date of this letter should be quoted

Our Ref.: CCTH

Your Ref.:

P. O. Box CT.1363
Cape Coast
CC-071-9967
Tel: 03321-34010-14
Fax: 03321-34016
Website:
www.ccthghana.org
email:
info@ccthghana.com

10th January, 2022

Dr. Tabitha Botchway
Department of Internal Medicine
Cape Coast Teaching Hospital
Cape Coast

Dear Madam,

ETHICAL CLEARANCE – REF: CCTHERC/EC/2022/003

The Cape Coast Teaching Hospital Ethical Review Committee (CCTHERC) has reviewed your research protocol titled, **"The Concordance between XPERT MTB/RIF, Culture and Microscopy for Presumed TB Patients at the Cape Coast Teaching Hospital)"** which was submitted for Ethical Clearance. The ERC is glad to inform you that you have been granted provisional approval for implementation of your research protocol.

The CCTHERC requires that you submit periodic review of the protocol and a final full review to the ERC on completion of the research. The CCTHERC may observe or cause to be observed procedures and records of the research during and after implementation.

Please note that any modification of the project must be submitted to the CCTHERC for review and approval before its implementation.

You are required to report all serious adverse events related to this study to the CCTHERC within ten (10) days in writing. Also note that you are to submit a copy of your final report to the CCTHERC Office.

Always quote the protocol identification number in all future correspondence with us in relation to this protocol.

Yours sincerely,

Prof. Ganiyu Rahman
Chairman ERC

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