COST EFFECTIVENESS ANALYSIS OF MICROSCOPIC OBSERVATION DRUG SUSCEPTIBILITY ASSAY VERSUS GENEXPERT MTB/ RIF IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS IN HIV PATIENTS

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A THESIS SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES, AHMADU BELLO UNIVERSITY ZARIA, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF MASTER OF PUBLIC HEALTH (FIELD EPIDEMIOLOGY) DEGREE

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DECLARATION

I declare that the work in this dissertation "COST EFFECTIVENESS ANALYSIS OF MICROSCOPIC OBSERVATION DRUG SUSCEPTIBILITY ASSAY VERSUS GENEXPERT MTB/ RIF IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS IN HIV PATIENTS" was performed by me in the Department of Community Medicine under the supervision of Prof A.T. Olayinka and Dr. F.J Giwa, with support from Dr. Damian Lawong. The information derived from literature has being duly acknowledged in the text and a list of references provided. No part of this dissertation was previously presented for another degree or diploma at any University.

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CERTIFICATION

This thesis entitled "COST EFFECTIVENESS ANALYSIS OF MICROSCOPIC OBSERVATION DRUG SUSCEPTIBILITY ASSAY VERSUS GENEXPERT MTB/ RIF IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS IN HIV PATIENTS" by Osigwe Ugochukwu Chinedu meets the regulations governing the award of the degree of Master in Public Health of Ahmadu Bello University, Zaria and is approved for its contribution to knowledge and literary presentation.

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ACRONYMS

AFB	Acid-fast bacilli
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-Retroviral Treatment
CFU	Colony Forming Unit
COPD	Chronic obstructive Pulmonary Diseases
CXR	Chest X-Ray
DALY	Disability Adjusted Life Years
DOTS	Directly observed treatment shortcourse
DST	Drug Susceptibility Testing
EPTB	Extra-pulmonary TB
EQA	External Quality Assurance
FM	Fluorescent Microscopy
HC	Health Centre
HIV	Human Immunodeficiency Virus
LED	Light Emitting Diode
L-J	Löwenstein-Jensen solid TB culture
MDG	Millennium Development Goals
MDR-TB	Multi Drug Resistant-TB
MGIT	Mycobacterium Growth Indicator Tube- liquid culture
MODS	Microscopic Observation Drug Susceptibility test
MTB	Mycobacterium tuberculosis
NRA	Nitrate Reductase Assay

NTBLCP	National TB & Leprosy Control Programme
NTBRL	National TB Referral Laboratory
PCP	Pneumocystis carinii (jirovecii) pneumonia
PEPFAR	President's Emergency Plan for AIDS Relief
PTB	Pulmonary Tuberculosis
Rif	Rifampicin
SN-PTB	Smear-negative pulmonary tuberculosis
TB	Tuberculosis
WHO	World Health Organization
ZN	Ziehl-Neelsen staining procedure

SUMMARY

Patients with HIV experience high mortality and severe morbidity if co-infected with tuberculosis. This is especially true in countries of sub-Saharan Africa like Nigeria with high burden of both diseases where diagnostic capacity for TB in HIV positive patients is poor. Early diagnosis and treatment has been identified as an important strategy to mitigate these effects. A cost and cost-effectiveness analyses of TB diagnostic strategies to reduce this adverse outcomes was carried out.

A decision analysis model was developed to estimate the incremental cost, Life years gained, and cost-effectiveness of 3 TB diagnostic algorithms. The base case scenario was an algorithm relying on sputum smear, and chest radiography, which was compared to algorithms featuring newer TB diagnostics (GeneXpert MTB/Rif and MODS). All relevant costs from a National TB programme perspective using the timeframe of the first 6 months of ART was considered. We conducted a one-way sensitivity analysis on parameters in the model.

When considering TB diagnosis and treatment costs, the cost per patient was $126.39 for current practice, $76.96 for the algorithm with Xpert test, and $88.62 for the algorithm with MODS. Life years gained was 0.9 for all 3 algorithms. The results showed that both new TB diagnostic methods were more cost effective than base case scenario. The algorithm with Xpert test was cheapest to achieve similar effectiveness compared with the MODS and base case. Sensitivity analyses indicated that cost-effectiveness findings were robust.

This study showed that Xpert was cost-effective compared to MODS and base case algorithm. Thus, these findings provide support for ongoing efforts to expand TB diagnostic capacity with GeneXpert MTB/Rif.

Key Words: HIV, tuberculosis, tuberculosis diagnosis, cost, cost- effectiveness, sub-Saharan Africa, Nigeria

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND INFORMATION

Tuberculosis (TB) is a highly infectious communicable disease caused by the bacterium Mycobacterium tuberculosis (MTB). It most commonly affects the lungs (pulmonary TB) but may also affect other parts of the body such as the spine, lymph nodes, brain, bone joints, meninges and kidneys (extra-pulmonary TB).[1]

TB is a global health priority. Globally, 9.6 million new cases of TB occurred in 2014 with 1.5 million TB deaths.[2] HIV infection is the most significant risk factor for the development of TB. This is because HIV causes the reactivation of latent TB and predisposes infected individuals to acquire new TB infections. TB on the other hand, is also known to accelerate HIV infection into AIDS. This is one of the reasons why TB/HIV co-infection results in greater morbidity and mortality.[3,4] People living with HIV are 26 times (20 - 30) more likely to develop TB disease than those who are HIV negative.[5,6] Of the estimated 9.6 million incident TB patients in 2014, 12% (1.2 of 9.6 million) are infected with HIV. About half a million of these incident TB patients have multi-drug resistant TB (MDR-TB), which is characterized by rapid deterioration and high mortality in HIV positive patients. Sub-saharan Africa is disproportionately affected with 74% of the 1.2 million HIV positive TB cases and 390,000 deaths in 2014.[2,7] This represented 25% of all deaths attributed to TB and one third of the deaths attributed to HIV/AIDS. In Nigeria, the prevalence of TB was estimated at 330 per 100,000 population[2] while mortality was 44 per 100,000. Nineteen percent of TB cases were HIV positive.[2]

Unfortunately, current TB detection levels are suboptimal as a result of which nearly three million of the incident cases are not diagnosed worldwide.[8] TB diagnosis is challenging and only about 63% of the estimated TB cases are diagnosed.[2] This implies that as much as 37% may go undiagnosed. In Nigeria, case detection stood at 15% for all forms of TB in 2014.[2]Evaluation for TB here relies heavily on detection of acid-fast bacilli by sputum smear microscopy and chest radiography as obtains in most countries of sub-Saharan Africa on account of resource constraints. TB diagnosis among people living with HIV (PLHIV) is problematic because they are likely to have sputum smear–negative TB, and atypical chest radiography findings are more likely especially in persons with advanced HIV infection.[3] Microscopy is still the most accessible method for TB diagnosis in Nigeria. It is still the main stay for diagnosis even though it has a sensitivity of only 40–60% under field conditions, falling as low as 20% in the presence of HIV co-infection (smear negative TB).[9] To improve this, Nigeria initially adopted an algorithm, which began with TB microscopy and, if negative, followed by chest X-ray or culture.[10] However, there was inadequate manpower to implement the algorithm fully, the algorithm resulted in high dropout rates in some regions because it required the patient to visit the clinic at least 4 times before diagnosis is reached (depending on availability of tests results and other factors) and TB culture was not routinely available. TB diagnosis among smear-negative HIV patients was therefore often delayed, which resulted in high mortality rates.

The World Health Organization (WHO) recommends the classification of any HIV-infected person with current cough, fever, weight loss, or night sweats as a TB suspect[11] and also recommends that sputum mycobacterial culture be conducted for TB suspects in whom sputum smears do not yield a diagnosis.[12] Sputum culture, especially when done in liquid medium, is much more sensitive than acid-fast bacilli smear and can identify more TB cases among TB

suspects. Culture also allows drug-susceptibility testing, which can lead to improved treatment outcomes. However, access to mycobacterial culture is limited in resource-constrained settings like Nigeria because it requires a sophisticated laboratory and highly trained technicians, is expensive, and requires weeks to yield a result.[13]

From 2007, there was an expansion in available TB diagnostics and new tests became available.[14]In the last ten years, the WHO developed many policies based on the new tests to improve TB diagnosis and treatment. These policies include the use of Xpert MTB/Rif test in HIV-positive patients[15]and Microscopic-observation drug-susceptibility test (MODS) to screen for MDR-TB [16]and other policies,[17–19]These new laboratory techniques provide the opportunity to improve TB diagnosis among PLHIV. The Xpert MTB/RIF assay is based on the real-time polymerase chain reaction technique developed on the GeneXpert platform (Cepheid, Sunnyvale, CA) and integrates sample processing and testing in a disposable plastic cartridge containing all reagents.[20] It can be performed on raw sputum by personnel without extensive training and provides a result within 2 hours. The Microscopic-observation drug-susceptibility test (MODS)[21]on the other hand is a non-commercial liquid culture method. The MODS relies on two well-known properties of Mycobacterium tuberculosis (MTB): First, the rate of growth of MTB in liquid medium is considerably higher than that on solid medium. Second, the morphology of MTB in liquid culture is characteristic and recognizable, consisting of so called "cord" like structures. Based on these two characteristics, MTB growth can be detected within 7-10 days using a microscope compared to conventional solid culture that takes 3-8 weeks[22,23]. MODS has been used extensively in different HIV care settings.[24–26]

Improved TB diagnosis and case management has profound implications for program costs especially in resource-constrained settings such as ours and also on the patient outcomes.

Therefore the choice of strategy to implement should involve adequate rigor to ensure that the minimum costs that produces the most benefit is selected. Cost-effectiveness analysis (CEA) provides guidance for strategic prioritization of resources by projecting clinical outcomes from specific strategies and examining the comparative value of different strategies. CEA evaluates both effectiveness (e.g., in years of life saved, YLS) and costs to calculate an incremental cost-effectiveness ratio (ICER, or difference in costs / difference in effectiveness) that quantifies the value of different strategies of care. Guided by recommendations from WHO CHOICE,[27]a strategy is often considered "cost-effective" if its ICER is less than three times the country-specific per capita gross domestic product (GDP) and "very cost-effective" if its ICER is less than the per capita GDP. Such analyses can inform policy and allocation of resources for HIV guidelines and care.

1.2 PROBLEM STATEMENT

TB and HIV are major public health problems in Nigeria. Nigeria has a high burden of both HIV and TB. WHO estimates in 2014 show that Nigeria with a population of 177 million, had a prevalence 330 cases per 100,000 population.[2] The prevalence of HIV on the other hand is 3.1%.[28] This may look small but it represents an estimated 3.5 million people living with HIV in Nigeria. TB is closely related to HIV/AIDS. Together, they constitute a lethal combination of diseases with each making the impact of the other worse. Tuberculosis is prevalent in up to one quarter of persons initiating ART in sub-Saharan Africa and is among the leading causes of death.[29] The mortality rate in this population is high (8-26%) with most deaths (50%-90%) occurring in the first year of anti-retroviral therapy.[29]The mortality rate was 17.9 deaths per 100 person-years for those in whom active TB was diagnosed and treated at baseline or follow-up,

compared with 3.8 deaths per 100 per- son-years for persons without TB in a study in Uganda[30]while a South African study found that patients with active TB had a 15%–20% probability of death in the first year of treatment compared with 7%–8% for those without active TB.[31]

In Nigeria, 19% of TB cases reported were HIV positive in 2014. The incidence of TB/HIV was 59 per 100,000 population while mortality was 44 per 100,000 population.[2]Yet TB is a curable disease. Using combinations of first-line drugs, around 90% of people with drug-susceptible TB can be cured in six months. The rise in TB cases among People Living with HIV (PLHIV) poses an increased risk of TB transmission to the wider community especially from smear negative TB.

TB and HIV account for 5% of all the disability adjusted life years (DALYs) globally. Over 130 million years of healthy life (DALYs) are lost due to illness and premature mortality from TB (43,650,000) and from HIV (91,907,000) each year.[32] In sub-Saharan Africa these DALYs due to TB and HIV are over four times the global average (8800 versus 1900 per 100,000).[33,34] This is because more young adults from the region die from TB or other HIV related causes than elsewhere.

Globally, TB DALYS were estimated to result in economic losses equivalent to 3.4 trillion dollars (US $) between 2006 and 2015.[35] For sub-Saharan Africa, the economic losses were estimated to be 519 billion dollars (US $) during the period. Eighty percent of these economic losses in sub-Sahara Africa were attributed to co- infection with HIV.[35]

With the advent of new TB diagnostics such as liquid culture and molecular tests, which can give a diagnosis within a short time with better specificity and sensitivity, there were proposals to incorporate these new tests into the existing WHO 2007 algorithm to improve TB diagnosis and treatment, particularly for HIV positive patients who were smear negative. In Nigeria, an algorithm using Genexpert MTB/Rif is currently being used to fill this gap. Genexpert MTB/Rif can diagnose MTB and determine resistance to Rifampicin within hours but also has low sensitivity in smear negative TB/HIV patients. The machines and reagents are sourced with support from donor agencies (TB CARE consortium) and so raise concerns about sustainability. The machines are also not yet sufficient to cover the whole country. In 2014, there were only 96 sites for an estimated 177 million population.[2]Some tertiary health centres on the other hand have started the MODS technique and argue that it could be an alternative to Genexpert and advocate for its use or inclusion in the national algorithm especially with donor fatigue setting in. However, the cost effectiveness of these strategies has not been evaluated in this country which would have served as a guide to enable the National TB program managers make an informed choice on a cost effective and sustainable algorithm for diagnosis of TB in HIV patients in Nigeria.

1.3 JUSTIFICATION FOR THE STUDY

Implementing any health intervention (such as implementing a new algorithm for detecting smear negative TB) entails consuming resources to produce health benefits. While needs are unlimited, resources are scarce, and their allocation to a particular use makes them unavailable for other uses. It is therefore important, in the context of resource constrained settings like Nigeria, with our huge burden of both TB and HIV, for decision makers in healthcare to determine whether the trade-off of resources for health outcomes is worthwhile, or whether a

different approach or policy choice would yield greater benefits for a given resource cost. In the face of multiple options and even more potential algorithms and implementation plans, deciding which novel diagnostic to implement, and how, is not a trivial process. Such decisions must involve careful consideration of available strategies, requiring an understanding of the potential costs, population level impact for each test upon implementation in a given setting and uncertainty around these factors. Economic evaluation can help to make these decision-making processes more transparent and data-driven. In the absence of such evaluations, it is difficult to utilize existing data in a systematic fashion for decision-making.

Cost effectiveness analysis is preferred when comparing options whose outcome are the same. For example, in this study all algorithms will result in earlier diagnosis and treatment leading to more years of life saved for the HIV positive TB patients. It is especially useful when the intervention of interest is both more costly and more effective than the comparator: an incremental cost-effectiveness ratio (ICER), which represents the cost per additional unit of health outcome obtained due to the intervention of interest, can be calculated. Decision makers can then determine, based on their willingness-to-pay or cost-effectiveness threshold, whether this cost is acceptable to them. If the ICER is below the cost-effectiveness threshold, the intervention of interest is cost-effective.

Studies of this nature are uncommon in Nigeria where they are solely needed to make evidence based decisions. As public health leaders and public health laboratory physicians who will have to make these decisions for health programmes and National laboratories, conducting this study will contribute to the literature in the often-overlooked areas of Laboratory management and Health Technology Assessments in an area (TB/HIV) where such information is pertinent.

1.4 RESEARCH QUESTIONS

- Are there new more efficient methods to diagnose TB in HIV patients?
- What are the costs and outcomes of each method?
- How do the costs and outcomes compare?
- Which is the most cost effective method?
- What factors influence the costs/effectiveness of these methods?

1.5 OBJECTIVES

1.5.1 GENERAL OBJECTIVE:

To determine the cost effectiveness of MODS assay versus Genexpert MTB/Rif in the diagnosis of PTB in HIV positive patients.

1.5.2 SPECIFIC OBJECTIVES:

1. To undertake a cost analysis of MODS Assay and Genexpert MTB/Rif
2. To determine the per unit cost of MODS Assay and Genexpert MTB/Rif
3. To determine the cost- effectiveness of MODS Assay versus Genexpert MTB/Rif compared to the base case

CHAPTER TWO

LITERATURE REVIEW

2.1 MYCOBACTERIUM TUBERCULOSIS

Mycobacteria are subdivided into three groups: The Mycobacterium tuberculosis complex (MTC), Mycobacterium leprae and Non-tuberculosis mycobacteria (NTM).[36] In humans, disease from Tuberculosis (TB) is caused by Mycobacteria from the MTC group within which, Mycobcaterium. tuberculosis (MTB) is the principal agent. MTB can be distinguished from other agents within the MTC group by its ability to reduce nitrate to nitrite.[37]

Mycobacteria are non-motile and non-spore forming aerobic rods measuring 0.2-0.6 x 1 -10 µm in size. Their envelope structure consists of mycolic acids of 60 to 90 carbons, with a high content (61-71%) of guanine and cytosine in their DNA.[38] Species variations are characterized by variation in sugar substitutions in the cell wall of the mycobacteria. Further, their cell wall is rich in lipids, making the surface hydrophobic and resistant to many disinfectants, including common antibiotics and common laboratory stains.[36–38] Once stained, they cannot be decolorized with acid solutions, and are therefore described as acid-fast. This acid fast property is used to detect mycobacterium in sputum smear. Other important wall components include the glycolipid trehalose dimycolate,[39] which is thought to induce cord-like growth of mycobacteria on artificial media and lipoarabinomannan (LAM) a glycolipid which may play a role in virulence.[40]The cord like growth of MTB is the characteristics that distinguishes it in liquid culture. This characteristic is used to detect MTB in MODS. The last diagnostic method (Xpert) does not use a physical characteristic rather it identifies and amplifies the nucleic acid in the DNA of the MTB.

Mycobacteria grow extremely slowly with a generation time of 18-24 hours because of their complex cell wall.[41] In addition, Mycobacteria are fastidious in nature, requiring specially

enriched media for growth and enhanced by the presence of 5-10% CO2 in a limited temperature range of 35-37oC.[36–38,41]

2.2 GLOBAL TB CONTROL

The WHO launched the DOTS strategy in the early 90s in response to the global burden of tuberculosis. The strategy aimed to use cure of the infectious cases as prevention for TB transmission.[42,43] The target was to detect at-least 70% of those infectious cases and cure at-least 85% of them by the year 2000. The DOTS strategy relied on smear-microscopy for TB detection and a standardized short course regimen for TB treatment.

Reports on the DOTS strategy revealed suboptimal progress towards the set targets.[44,45] For example, a report of the DOTS strategy in 1998 showed that only a handful of countries had achieved the set detection and treatment success targets for TB.[7] In addition, there were persistent difficulties in TB diagnosis coupled with high TB mortality rates. It is during this period, that the momentum to set up new global initiatives for TB control picked up.

This momentum led to the creation of the STOP TB partnership and development of the first Global plan to Stop TB 2000-2005.[46] The first 'Global plan to Stop TB 2000-2005' was intended to expand DOTS coverage, address HIV associated TB and drug resistant TB, and to pursue innovative research for new TB diagnostics, drugs and vaccines.[47] In parallel, the Global Fund was established in 2002 to increase resources to fight AIDS, Tuberculosis and Malaria.[48] The second 'Global plan to stop TB 2006-2015' set out the actions and funding needed to accelerate progress in TB control.[49] The targets in the second plan included reduction of the global TB prevalence and mortality by half relative to the 1990 levels by 2015. The key strategies in the second plan for achieving the set targets included scaling up existing interventions and the

introduction of new technologies, notably new TB diagnostics. It is two of these new diagnostics, which came up post 2007 whose cost effectiveness over the 'traditional' smear based algorithm that is being considered in this study.

2.3 EPIDEMIOLOGY OF HIV ASSOCIATED TB

Worldwide, an estimated 35 million people are infected with HIV.[28] As is the case for TB, HIV infection is most common in young adults aged 15-49 years. Since 2010 however, the number of new HIV infections has continued to decline by 13%.[28] In addition, since 2005, AIDS related deaths have fallen by 35% after the global scale-up of HIV antiretroviral treatment (ART) through various global initiatives such as the '3 by 5 initiative' and PEPFAR.[50,51]

Only 15 countries account for 75% of the global HIV burden. Except for five of them (Brazil 2%; China 2%; India 6%; Russia 2%, United States 4%), the rest are from sub-Saharan Africa-making the region account for 70% (25 out of 35 million) of the global HIV burden.[28] Within sub-Sahara Africa, ten countries(Ethiopia, Kenya, Malawi, Mozambique, Nigeria, South Africa, Uganda, Tanzania, Zambia and Zimbabwe) account for 80% of all people living with HIV with slightly more women (58%) than men having the HIV infection.[28]

Not surprising therefore, 80% of the 1.1 million TB patients co-infected with HIV globally, are from sub-Sahara Africa.[2] On average, 40% of TB patients in sub-Sahara Africa are co-infected with HIV, with the levels of TB-HIV co-infection highest in Southern Africa (68%) compared to Eastern (40%) and Western Africa (25%). The epidemiology of HIV-associated TB has therefore remained un-changed since its earlier descriptions.[52,53] Even in the era of ART, TB remains the main cause of mortality among HIV patients in sub-Saharan Africa.[54–56] ART however, reduces the risk of TB by 66% and the risk of death by 50% in people living with HIV.[57,58] Thus, since

2013, the WHO recommends initiation of ART in HIV patients with CD4 count of 500 compared to CD4 count of 350 previously.[59]

The risk of TB starts to increase soon after infection with HIV. The risk of TB doubles within one year and is sustained or increased during the following years.[60]In addition, HIV increases the risk of progression of latent TB to active TB while on the other hand, TB increases progress of HIV infection to AIDS.[61,62]The rapid progression to AIDS explains why there are more deaths among TB patients co-infected with HIV during TB treatment compared to TB patients who are not infected with HIV. At a global level, the proportion of TB patients who died in 2013 during TB treatment were more than three times higher among HIV-positive TB patients than in those who were HIV-negative (11% versus 3.4%).[63] In sub-Saharan Africa, HIV-positive TB patients were twice more likely to die during TB treatment compared to HIV-negative TB patients (10% versus 5%).[63]

The poor treatment outcomes for TB in HIV-positive patients compared to those who are HIV negative is also related with the difficulty of diagnosis and the treatment delays that are associated with smear-negative TB.[64–66] Smear-negative TB is a common clinical problem in HIV patients and was described several years before. In one review, researchers described the dis-proportionate increase in smear-negative TB with the advent of the HIV epidemic and the higher mortality among this group compared to smear-positive patients.[64] A subsequent review proposed the use of clinical algorithms for diagnosis of smear-negative TB since additional tests to TB microscopy were generally unavailable or inaccessible then.[67] This was followed by a third review which proposed the urgent need to change the existing policies for the diagnosis of smear-negative TB in HIV patients from resource limited settings.[68]

2.4 PATHOGENESIS OFHIV ASSOCIATED TB

TB is caused by the bacterium Mycobacterium tuberculosis-which is spread from person to person through the air. Pulmonary TB is therefore the most common form of the disease. It is also the most important for transmission control using the strategy of early diagnosis and treatment. Diagnosis of pulmonary TB is mainly achieved by examination of sputum as cough is the commonest sign/symptom.[69] TB microscopy is the most common method for sputum examination. However, HIV reduces the sensitivity of TB microscopy.[64,67,68] How this occurs is briefly described thus:

In the normal host, on inhalation of the TB bacilli, they are engulfed and immediately killed by alveolar macrophages. This is achieved using different bactericidal mechanisms such as reactive nitrogen and oxygen intermediates.[70] However, the bacilli may survive in 25-50% of the infected individuals and continue to divide within macrophage cytoplasm.[71] The macrophages then present the Mycobacterial antigen to CD4+ lymphocytes, which become activated and initiate a cell-mediated response. The sensitized lymphocytes produce various cytokines such as TNF-α, IFN-γ, IL-6 and IL-12 which attract and activate more macrophages, enhancing their ability to kill the Mycobacteria.[71] Such activated macrophages become enlarged and differentiate into what are known as epitheliod macrophages to form a granuloma. The granuloma is a compact aggregate of epitheliod cells populated with many other cell types such as neutrophils, dendritic cells, natural killer cells and fibroblasts.[72] It is generally believed that the main purpose of the granuloma is to 'wall off' the bacteria in the host resulting in containment or cure in 90% of individuals.[70,71] This view has recently been revisited however, and the granuloma is now thought to have a role in the dissemination of TB infection.[72] Considering that the granuloma is mainly a protective structure in the host, and that the CD4+ lymphocyte plays an important role

in the formation of the granuloma, HIV has a detrimental effect on the formation of the granuloma by depletion of host CD4+ lymphocytes.[73,74] This results in poor containment of the TB bacilli resulting in uncontrolled spread of the TB bacilli in the lung and elsewhere in the body. In addition, the poorly formed granuloma results into less cavitatory disease in the lungs. This results in less numbers of bacilli in the expectorated sputum than would normally be the case in the normal host. These numbers are often below the detection limit of microscopy (5000-10,000 bacilli per ml) which results in smear-negative TB.[75,76] The situation is made worse by the weak respiratory effort in patients with advanced HIV disease resulting in sputum of poor quality with subsequent smear-negative results.[77]

2.5 OVERVIEW OF TRADITIONAL TB DIAGNOSTICS

2.5.1 MICROSCOPY

Microscopy is the main method for the laboratory diagnosis of pulmonary tuberculosis (PTB) for more than 100 years. This is achieved by direct microscopic examination for tubercle bacilli in sputum specimens stained using the Ziehl-Neels[n (ZN) procedure.[78] Sputum examination by microscopy is simple, inexpensive and efficient in detecting those cases of pulmonary tuberculosis that are most infectious. Smear microscopy is also used to monitor treatment of patients and to establish cure. However, between 5,000-10,000 bacilli/ml of sputum are required for direct microscopy to be positive. But only a proportion of tuberculosis patients harbour such large enough numbers of organisms to be detected in this way.[77] Thus, the sensitivity of microscopy may be as low as 20% especially in HIV patients who have pauci-bacillary forms of TB.[9] In addition, it is virtually impossible to distinguish between the MTC and NTM forms of mycobacteria using the microscopy test which may result into incorrect treatment of NTM as MTC.[64,79] Further, the yield of TB microscopy is highly dependent on skills of the operating

technician and on the quality of reagents, which may vary from one setting to another.[77]This low sensitivity which results in missed cases or more commonly smear negative TB in PLHIV led to the introduction of newer diagnostics to detect MTB.

2.5.2 CHEST X-RAY

Like microscopy, chest X-ray has been used for over a century to diagnose pulmonary TB (PTB). In the pre-HIV era, PTB typically appeared on chest X-ray as cavitation with apical or bilateral distribution.[67] Interpretation of chest X-rays of individuals suspected to have PTB can be difficult. It is even more difficult among patients infected with HIV because they have atypical appearance of TB on chest X-ray.[80]Moreover, chest X-ray can appear normal in nearly one-third of HIV-positive patients with TB as their immunity deteriorates even further.[81,82]Studies that have evaluated the diagnostic value of chest X-ray in smear-negative patients found that it has low to moderate sensitivity and specificity of 28-78%, and 59-75% respectively.[83,84]Nonetheless, chest X-ray is useful for diagnosis of extra-pulmonary TB such as pleural or pericardial TB and other non-tubercular chest diseases such as *Pnuemocystis Carinii*Pneumonia or Kaposi's sarcoma, which are both common among people living with HIV.[85]

A correct diagnosis of PTB on chest X-ray is dependent on the reader's expertise because interpretation is currently not well standardized. Efforts are underway presently to introduce standardized scoring systems for interpretation of chest X-ray and thereby increase its sensitivity and specificity. These will combine clinical presentation and chest X-ray appearance. Available evidence indicates that the score systems could improve sensitivity remarkably (93-98%) although specificity could still remain low (35-50%).[86,87] A major limitation of chest X-ray is

that it is not widely available in the peripheral health facilities, and even where it is available, the quality of the X-ray is often poor.

2.5.3 SOLID CULTURE

Culture is the "gold standard" for TB diagnosis. Culture requires fewer bacilli (10-100/ml) for detection and therefore allows for detection of pauci-bacillary forms of PTB that are associated with HIV.[41] In addition, culture allows for species identification and drug susceptibility testing which have become important because of the increasing cases of drug-resistant TB.[63] However, implementing TB culture requires sophisticated infrastructure and highly skilled staff thus limiting the technology to mainly referral or research facilities.

Until 2007, solid media (egg or agar-based) was the main type of media used for TB culture. The advantages of egg-based media include ease and ability to be prepared in-house, it allows for observation of colonies of mixed cultures and contaminants, and it may be stored for several weeks.[63] Löwenstein-Jensen (L-J) medium is the most commonly used egg-based solid medium for TB culture. L-J media containing glycerol is used to promote growth of M. tuberculosis, while L-J containing sodium pyruvate without glycerol is used to promote growth of M. bovis. Alternatively to reduce costs, L-J media without asparagin (Ogawa media) may be used. A disadvantage of egg-based media is that when contamination does occur, it may involve the entire slant surface causing the entire culture to become lost. In addition, if specimens contain few bacilli it may take three to eight weeks before cultures become positive.

Agar-based media are less likely than egg-based media to become contaminated.[88]The most common are Middlebrook 7H10 and 7H11, which can be prepared in the laboratory using commercially available agar-powdered bases.[88] After preparation, the media is enriched with

addition of Oleic acid, Albumin, Dextrose and Catalase (OADC). Because of the transparency of 7H10 and 7H11 plates, microcolonies of MTB with typical cord formation can be detected and counted using a microscope as early as one week after incubation.[41] Also, visibility of colonial morphology on agar plates is better than on egg-containing slants, aiding the identification of mycobacteria. A disadvantage of Middlebrook media is that the surface dries more rapidly than egg-based media. Culture is not readily available and requires technical know how to perform. It also takes a long time for the results to become available which means it is not readily available to the clinician to make clinical decisions on a patient in a timely manner. This leads to delays in diagnosis, increased morbidity and mortality. The newer diagnostics currently available were designed with these fallbacks in mind. They are expected to be methods that will require low expertise and produce results in a timely manner while also being cheap enough to be made available at lower levels of healthcare delivery were they are needed.

2.6 OVERVIEW OF NEW TB DIAGNOSTICS

TB diagnostics expanded tremendously from 2007 with new tests becoming available.[14]Between 2007 and 2015, the WHO developed many policies based on the new tests to improve TB diagnosis and treatment. These policies include; use of Xpert MTB/Rif test in HIV-positive patients,[15] use of LED fluorescent microscopy as an alternative to Ziehl-Neelsen microscopy, MODS and Nitrate Reductase Assay (NRA) to screen for MDR-TB,[89] and use of liquid medium for TB culture and DST among others.[19] All these were in response to the shortfalls of the older more traditional methods of TB diagnosis. The 2 considered in this study are:

2.6.1 GENEXPERT MTB/RIF TEST

Previously, molecular diagnostics for TB were limited to research laboratories. The introduction of the automated molecular test (Xpert MTB/Rif or GeneXpert) was considered a “game

changer" in the use of molecular TB diagnostics because it provided a practical alternative to TB microscopy and culture. While thousands of MTB must be present in each millilitre of sputum sample for PTB to be diagnosed using the microscope, GeneXpert can detect MTB at much lower concentrations of about 100-200 bacilli per millilitre of sputum and is able to distinguish between MTB and NTM with very high specificity. GeneXpert relies on real time polymerase chain reaction (PCR) to amplify a portion of the Mycobacteria gene where many of the mutations for resistance to the anti TB drug rifampicin, occur (81 base pair long rpoB hot spot region)[90].

If present, fluorescent dyed molecular probes of 16-20 base pairs long, are used for detection of the amplified Mycobacterial DNA in the clinical sample[91]. The steps involved to process the sample, amplification of nucleic acid and detection of the target sequences are automated. This is achieved by the use of single-use disposable GeneXpert cartridge that holds the PCR reagents and hosts the PCR process. GeneXpert simultaneously detects Mycobacterium tuberculosis and 'drug resistance' within two-three hours. Moreover, being an automated test, it does not require highly skilled staff to operate. Thus, the WHO currently recommends GeneXpert as the primary diagnostic test for HIV associated TB in adults or in children suspected of having TB or individuals suspected of having multi drug-resistant TB. The test is currently implemented on a global scale. However, concerns have been raised about the cost-effectiveness of the GeneXpert because of its high cost but limited impact on patient morbidity and mortality.

2.6.2 MODS ASSAY

The Microscopic-observation drug-susceptibility test (MODS) is a common non-commercial liquid culture method, used mainly to screen for multi drug-resistant TB [90]. The MODS relies

on two well-known properties of Mycobacterium tuberculosis (MTB): First, the rate of growth of MTB in liquid medium is considerably faster than that on solid medium. Second, the morphology of MTB in liquid culture is characteristic and recognizable, consisting of so called "cord" like structures. Based on these two characteristics, MTB growth can be detected within 7-10 days using a microscope compared to conventional solid culture that takes 3-8 weeks.

An advantage of MODS is the incorporation of anti-TB drugs into broth cultures at the onset of the test, which enables direct susceptibility testing from sputum samples. MODS entails the observation of Middlebrook 7H9 cultures (using tissue-culture plates) with an inverted light microscope to detect the characteristic tangles (cording) of MTB in liquid media. Drug - containing and drug-free control wells allow concurrent DST for rifampicin and isoniazid. A study evaluating MODS for diagnosis of TB reported 98% sensitivity for MODS compared with 84% sensitivity for L J while speed of detection was found to be seven days compared with 26 days for L J.[23]

The MODS methodology is straightforward and the standard operating procedure is simple to follow. The method is associated with a significantly lesser workload than conventional cultures and contamination rate was reported to be 50% that of L J medium[92,93]. Biosafety concerns, which are a major issue with other liquid cultures, do not arise when using MODS. This is because inoculated MODS plates are permanently sealed in zip-lock polythene bags through which microscopic examination takes place thereby preventing any spillage of the MTB culutre. Furthermore, it has a low frequency of cross-contamination and aerosolisation because the method employs direct DST which does not require any secondary sub-culture or any other manipulation[93]. However, it is recommended to use a biological safety cabinet. MODS has been used in different HIV care settings for diagnosis of MTB. A commercially available 'MODS test

kitTM' has now been developed to address the difficulties faced by many laboratories in low and middle income countries to procure the consumables required for the test. However it requires the use of an inverted microscope, which is not readily available at centers were Tb diagnostics are routinely carried out (smear). The cost may be prohibitive in low-income settings.

2.7 KEY ECONOMIC CONCEPTS

2.7.1 SCARCITY AND OPPORTUNITY COST

The fundamental economic problem is that, while human needs and wants are unlimited, resources are scarce and finite. Budget constraints exist for governments as they do for individuals. Consequently, allocating resources to a particular use renders them unavailable for other uses: for example, resources allocated to public health are not available for education; resources spent on TB control cannot be spent on childhood immunizations or malaria. These forfeited benefits represent an "opportunity cost," equivalent to the value that could have been derived from allocating the resources in question to another purpose. This concept of scarcity and opportunity cost is the underlying reason why making a choice between two alternatives is very important and belies all economic evaluation.

2.7.2 ECONOMIC EVALUATION

Scarcity and opportunity costs make it imperative that choices must be made regarding resource allocation, for which criteria and decision rules are needed. A key criteria is that efficiency (i.e., the amount of benefits, or utility, derived from the use of a given amount of resources) be maximized, thereby minimizing opportunity costs. Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and their consequences [94] and seeks to assess whether a policy, program or technology represents relative "value for money". The intervention of interest is compared to a baseline, which does not have to be an active

strategy, and can be the status quo or "doing nothing". One of the goals of economic evaluation in health care is to assess systematically the relative efficiency of different health care interventions, policies or strategies to assist decision makers in deciding what course of action to follow. While economic evaluation could be envisioned as a normative tool for decision making, many practitioners present it as an aid to decision making, and recognize that other concerns, such as equity, and social and political factors, influence policy choices[95].

Different types of evaluation methods are available to assess the worth of health interventions. All use similar methods to identify and measure costs, and differ primarily in the way they handle the measurement of health outcomes. In this study we have selected the cost effectiveness analysis (CEA). The others include cost-benefit analysis (CBA) and cost-utility analysis (CUA).

2.7.3 COST-BENEFIT ANALYSIS

Seeks to weigh all benefits and costs of an intervention to calculate its net present value (NPV). In CBA, all outcomes (including such hard-to-value benefits as cases of disease averted, prolongation of human life, or changes in levels of pain and suffering) are included and are assigned a monetary value. The use of a common metric of dollars allows for comparison of strategies and interventions that have different outcomes or are related to different policy areas, such as education, health and safety.

2.7.4 COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis (CEA) is a form of economic evaluation in which a health intervention or policy is compared to one or more alternatives in terms of its costs and benefits, the latter being measured in terms of a common, natural units (such as the number of TB cases, the number of healthy days, or the number of years of life that will result). The Panel on Cost-

Effectiveness in Health and Medicine recommended the use of CEA over CBA precisely "because of its focus on health, rather than economic outcomes of investments in different types of preventive, curative and rehabilitative interventions. Although cost-benefit analysis is better suited to making intersectoral comparisons, the panel was asked to direct its attention to CEA, given its broader acceptance in the medical and public health community[96].

2.7.5 COST-UTILITY ANALYSIS

This uses similar methods as CEA, but includes a quality-of-life adjustment in the measurement and valuation of health outcomes. It is useful when both changes in mortality and morbidity must be taken into account; when improvements in quality of life, not just life expectancy, are relevant to the analysis; or when the interventions being compared have different outcomes that cannot be compared directly. Disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs) are commonly used metrics to summarize quantity and quality of life into a single value that can be compared across patient groups and disease conditions.

2.7.6 DECISION ANALYSIS MODELING

Decision analysis is a systematic approach to decision making under uncertainty. All three types of economic evaluation can incorporate the use of decision analysis methods to clarify the probabilities, costs and outcomes of the interventions being compared. Which diagnostic algorithm to implement is a complex question that requires considering many parameters with uncertain value, and drawing on evidence from a range of sources. Decision analysis help disaggregate complex problems into series of smaller elements whose dynamics can be more readily described and quantified. The most essential elements can then be combined into a model of the original problem, using tools such as decision trees. The model explicitly identifies the sequence of events and the linkages between these events. Models must strike a fine line between

simplifying complex real-life situations to increase understanding while making sure to reflect essential processes, and are therefore most useful as aids to decision making. Its purpose is to synthesize evidence and assumptions in a way that allows decision makers to gain insight into the implications of those inputs for valued consequences and costs. Its outputs are always contingent on its inputs, which is why it is so important that its inputs be as transparent and accessible as is practical.[95]

2.7.8 DECISION TREES

Decision trees are a visual representation of a decision analysis model, and are widely used in economic evaluation. It proceeds from left to right, starting with a decision node (square) that reflects the choice alternatives addressed in the model. The number of arms that originate from this initial decision node reflects the number of strategies (at least two) under investigation. From that point on, each possible chain of events in each arm is represented with a different pathway through a series of chance nodes (circles) that reflect the points of uncertainty in the tree. The branches issuing from each chance node represent the possible events patients can experience at that point in the tree[94]. For example, patients who have a sputum smear test done are either Smear positive or smear negative, Start treatment or not etc. The pathways are mutually exclusive (a given patient can only follow one of the pathways) and exhaustive[94] (a given patient must follow one of the pathways).

A decision tree intended for CBA, CEA or CUA also includes health and cost outcomes. An outcome is the expected value of a chain of events. Health outcomes in a decision tree are defined differently depending on the type of economic evaluation method used. In this study, which is a CEA: the outcome of interest is the number of life years (LY) gained following treatment of TB cases detected. Each pathway resulting in a case of TB successfully treated is

assigned an outcome value of 1, while pathways where TB is not successfully treated resulting in death have a value of 0.Cost outcomes represent the costs incurred by the patient or group of patients following a particular pathway. In this study, the cost per pathway will include the cost of diagnosing TB and the cost of treatment for those who are diagnosed with TB.

Decision trees use concepts from statistics and basic probability theory to calculate the expected value of each course of action. The likelihood of the events at each chance node is represented as a set of probabilities. These are conditional probabilities, as they depend on the patient having followed the specific path that led to a particular node. The model weighs outcome value of each pathway by its probability, and then sums up expected values for each strategy under consideration. Model results highlight the sequence of decision that will maximize value (measured in monetary terms or in terms of health effects), minimize costs and balance multiple attributes.

2.7.9 COST MEASUREMENT

The perspective of the study is the viewpoint from which it is conducted. Possible perspectives include, for example, that of the health system, the agency implementing a policy or program like in this study, may be the study sponsor, patients and the society at large. The perspective determines what costs and effects are considered relevant and included in the scope of the study. Patient costs (e.g. transportation to the hospital) will be included in a study conducted from a societal perspective, but will be left out if the analysis is conducted from the viewpoint of the health system or health programme. Analysts are expected to specify clearly which perspective(s) they are adopting. Some have recommended that all studies include the societal perspective, at least in a sensitivity analysis, because it is the broadest and is always relevant.[94]

2.7.10 COST IN ECONOMIC EVALUATION

Economic evaluations aim to assess the opportunity cost of implementing a project, program or policy. Here cost is that which arises from the consumption of resources that cease to be available for other uses. That means cost is thought of in terms of resources used(including time), rather than just expenditures or budgeted funds. This is particularly important when the study is conducted from a societal perspective.

2.7.11 COST ANALYSIS

After determining the study question, the interventions to be compared and the study perspective, the analyst must 1) establish a cost inventory listing the resources used in the implementation of each intervention or alternative under consideration; 2) determine the quantity of resources used; and 3) assign a value/unit cost to each resource. Combining these three elements of information will allow the total cost of an intervention to be calculated. Techniques used to estimate the resource cost of health care services include microcosting (i.e., determining what resources are necessary for the service to be performed—in terms of staff time, materials, etc.) and costing each component separately; or using the market price of a comparable good, service or resource.

2.7.12 UTILITY MAXIMIZATION AND WILLINGNESS-TO-PAY

Willingness-to-pay is the maximum amount a person would be willing to pay, sacrifice, or exchange in order to receive something they desire: therefore, individuals' willingness- to-pay for various goods and services reflects the utilities they would derive from their consumption/possession.

The utility obtained from consuming an additional unit of a good or service (marginal utility) decreases as the total quantity consumed increases. If each additional unit provides less

satisfaction, the consumer will be willing to pay less to obtain it. Utility is maximized when the last dollar spent on each good or service in the consumer's "basket" yields the same marginal utility. Economic evaluation relies on the Von Neumann-Morganstern definition of utility: it is a measure of preference that is made under conditions of uncertainty.

2.7.13 TIME PREFERENCE (DISCOUNTING)

In addition to preferences for different goods and services, individuals and society have a positive rate of time preference: they have a preference for benefits now as opposed to benefits in the future and a preference to pay for things later as opposed to now. In economic evaluation, time preference is taken into consideration through discounting. It is particularly important when the costs and benefits of a program do not always occur at the same time. Costs and health outcomes are discounted according to how far in the future they are expected to occur. It is standard practice to discount costs and health outcomes at the same rate, and to explore the impact of different discount rates on results[95]*. Studies that have a public health significance usually use a discount rate of 3% this can be varied from 0-7% in sensitivity analysis.

2.7.14 THE INCREMENTAL COST-EFFECTIVENESS RATIO

The incremental cost-effectiveness (ICER) ratio is a tool to relate the difference in health outcomes to the difference in costs and evaluate the incremental cost-effectiveness of an intervention. The ratio includes incremental costs in the numerator, and incremental effects in the denominator. It represents the cost per additional unit of health (TB case prevented, or QALY saved) obtained thanks to the intervention of interest. The ICER is a positive number, and the lower the number, the more cost- effective the intervention is.

Guidelines warn against using the average cost-effectiveness ratio (i.e., an intervention total costs divided by its total effects) to measure cost-effectiveness. Such an approach may be convenient, as it does not require a comparison treatment but is misleading because it implies comparing the intervention of interest to "an alternative that is costless and results in immediate death" and "does not reliably indicate the way to achieve the greatest health benefit from a given expenditure. The use of average cost-effectiveness ratios has been shown to lead to inappropriate rankings of program alternatives.

Economic evaluations can compare more than two policies, programs or interventions. One of these could be the standard of care or a "do nothing" strategy. In such a situation, it is not appropriate to compare every strategy to one baseline. Nor is it necessary to calculate a separate ICER for every possible pair of interventions. The recommended approach is to rank all interventions in order of increasing health effect. Then interventions that are strictly dominated (i.e., those that are more expensive and less effective than at least one alternative) should be eliminated. ICERs can then be calculated between each intervention and the next more expensive strategy. The final step in the ranking involves eliminating from consideration those strategies in a situation of extended dominance, i.e., those for who the ICER is higher than that of the next, more expensive, alternative.

2.7.15 SENSITIVITY ANALYSIS

The need for sensitivity analyses arises because of the various types of uncertainty, random and non- random, inherent in any model. Models usually incorporate data from multiple sources that were collected in different circumstances and under different assumptions. Even when the data comes primarily a one trial, observational study or project, sampling variability makes estimates

of event/transition probabilities, costs and effects uncertain. There may also be uncertainty about the structure of the model, and the generalizability of the parameters from one setting to another.

Sensitivity analysis helps determine whether a model is sensitive to a particular uncertainty (i.e., whether varying a parameter's value results in a change in the relative efficiency of the interventions; and if a model is sensitive to a particular uncertainty, at what value of the parameter the model recommends a change in strategy. By assessing the impact that uncertainty about the model and its parameters has on analysis results, sensitivity analysis helps ascertain whether these results are robust.

2.7.16 DETERMINISTIC SENSITIVITY ANALYSIS

Deterministic sensitivity analysis is conducted by varying one (one-way sensitivity analysis) or more parameter at a time. This type of analysis is deterministic because there is no randomness in the expected value calculation, as each parameter is handled as a point estimate. Every path through the model has a deterministic weight in the expected value calculation based on its path probability. Results do not change when the analysis is repeated using the same parameters. Threshold analysis is a form of one- way sensitivity analysis. It seeks to identify more precisely the parameter value at which the conclusion about which strategy is optimal changes by varying the value of the parameter of interest in very small increments.

Deterministic sensitivity analysis is informative when there is a need to isolate the contribution of one or two parameters to overall variation in model results. However, it quickly reaches the limits when multiple parameters need to be varied simultaneously, especially when the results of the sensitivity analysis need to be displayed graphically.

2.7.17 PROBABILISTIC SENSITIVITY ANALYSIS

In many situations, it is useful to introduce random, or stochastic, elements intosome parts of the analysis. Second-order Monte Carlo simulation is a technique that incorporates uncertainty in all model parameters. It provides the same information as deterministic sensitivity analysis, but it can also be used to quantify the level of confidence that can be placed in the models' results.

In probabilistic sensitivity analysis, some or all of the cost and effect parameters in the model are represented by distributions instead of being represented as point estimates. During the Monte Carlo simulation, the model is run repeatedly (10,000 times, for example) using sampled values for each parameter, and expected values for cost and health effect are recalculated.

2.8 EMPIRIC REVIEW OF COST EFFECTIVENESS OF NOVEL DIAGNOSTICS FOR TB DIAGNOSIS

2.8.1 COST ANALYSIS/ UNIT COSTS OF MODS/ GENEXPERT

From the studies involving Xpert, the cost per test ranged from $15-$39 depending on the cost of cartridge and the site of placement of the machines ie point of care clinics or sub-regional laboratories.[110,112,114,121] Xpert was also found to be cost effective to diagnose both TB and MDR-TB compared with current practices for all individuals suspected of having TB and HIV positive individuals suspected of having TB[97–99,102,114]. Though implementing Xpert was more costly than current practice using WHO 2007, the increased costs represented a small share of available TB funding (PEPFAR operational plans as at 2011 and National health spending of the countries involved.)

2.8.2 COST EFFECTIVENESS OF MODS/GENEXPERT

Models used in economic evaluations provided comparisons of the cost-effectiveness and impact on TB incidence and mortality of various novel or hypothetical diagnostics and strategies.

Twenty-four (24) studies were found that demonstrated the cost-effectiveness of novel diagnostics, often highlighting the settings and implementation strategies and/or algorithms in which those tests were most cost-effective.[97–120]Among cost-effectiveness models, the most frequently studied diagnostic assays included Xpert MTB/RIF (n = 8) and alternative Nucleic Acid Amplification Tests (NAATs) (n = 9). None considered MODS. Sixteen (16) of the cost-effectiveness models compared new assays to an existing baseline and generated an incremental cost-effectiveness ratio (ICER), of which 69% concluded that novel TB diagnostics were likely to be cost- effective relative to that baseline. Some technologies including NAATs implemented in low TB prevalence settings were judged not to be cost-effective[105,108], and serology was shown to be more costly and less effective than existing diagnostics such as sputum smear microscopy[106]. Cost-effectiveness studies also highlighted barriers or challenges associated with the rollout of novel diagnostic tests including operational barriers or increased indirect costs, associated with HIV or multi-drug resistance (MDR) care.[97,103]Evaluations of hypothetical point of care (POC) tests suggested that a highly specific, low cost POC test would be highly cost-effective, with the greatest impact in settings with poor infrastructure and resource constraints[115].

Twenty out of 24 studies (83%) were cohort models i.e. identified a particular group/population to which the algorithm was applied. They either included a decision analysis framework[99–101,103–115,117,120], or Markov approach[98,102,104]. The majority of cost-effectiveness models 67%, took their study population as people with TB symptoms or in the case of DST individuals diagnosed with TB[99–101,103–115] remaining studies assessed HIV populations initiating ART[102,116,117], the general population[97,118,119]or a prison population with high MDR prevalence[98,120]. Most models assessed populations in high TB burden settings, however 5 studies were set in low TB burden countries[105,107,108,111,120]. Eight of 24 (33%) studies evaluated Xpert[97–99,102,110,112,114,118], while 9

studies (37.5%) evaluated an alternative NAAT. Effectiveness measures in these analyses included health utility measures [quality-adjusted life years (QALYs), 4/24 (17%), or disability-adjusted life years (DALYs), 7/24 (29%)] and cases detected. Several studies also calculated total program and/or implementation costs. The cost-effectiveness studies were performed from a health care provider, health system or TB program. Only one study included patient costs,[103] and these were restricted to an approximate estimate of cost of travel to the health facilities. No study reported taking a societal perspective. Less than half (11/24, 46%) employed an empirical costing component in the analysis. Fifteen of 24 studies (62.5%) included HIV in the model, and 11/24 (46%) accounted for drug susceptibility status.

All economic studies performed sensitivity analyses, and 13/24 (54%) assessed sensitivity to more than one variable at a time. Fourteen of 24 (58%) explicitly modelled false positives (which may have an impact on costs as patients then receive unnecessary treatment and follow-up), 14/24 (58%) studies explicitly modelled false negatives (which may have an impact on health outcomes as they remain undiagnosed, untreated and potentially infectious), Only three studies allowed false negatives to re-enter the diagnostic pathway, in two cases entering the same diagnostic pathway as those entering for the first time[104,118] and in the third a second pathway for false negatives was modelled[116].

LIMITATIONS

Most models did not consider costs incurred by TB patients throughout the diagnostic and treatment process, and no cost-effectiveness studies were conducted from the patient or society perspective. Estimation of patient costs may be important in models considering placement of machines because if patient for example, costs of transport and TB diagnosis are catastrophically high, the incremental impact of point-of-care diagnostics (i.e., that do not require multiple visits

to healthcare facilities to initiate treatment) may be much greater than if patient costs are low. Also TB is a disease of poverty, closer evaluation of the patient-level costs of TB diagnosis may reveal that these costs are a critical barrier to the impact of novel diagnostic tests.

Some studies using health systems, health care provider or TB program perspective did not include all relevant costs. Some studies included only test costs and salaries, omitting overhead costs; likewise costs associated with HIV care post-TB diagnosis and MDR-TB treatment post-diagnosis with Xpert or other new diagnostics, were not included. This can have important implications for estimated ICERs and model conclusions, and should be carefully considered in cost-effectiveness studies. Cost-effectiveness analyses should always carefully consider relevant costs and endeavour to include clear explanations of which costs are and are not included and why.

Sensitivity analyses were frequently limited to one- or two- way analyses. More recent models increasingly include multi-way sensitivity analyses as well. However, thorough investigation and discussion of both uncertainty in model structures and parameter values (both point estimates and associated ranges) should be undertaken.

CHAPTER THREE

METHODOLOGY

3.1 PROJECT SCOPE/DESIGN

A decision analytic model was developed to estimate the incremental cost, Life years (LY) gained and cost-effectiveness of novel TB diagnostic algorithms for patients with HIV ready to initiate ART compared to a baseline. Our model followed a cohort of HIV positive TB suspects through the diagnostic and treatment pathway, estimating costs and health gains. In the diagnostic pathway, the TB cases among the HIV positive individuals with suspected TB were either diagnosed as having TB or not, depending on the test sensitivities in the pathway. Similarly, those with suspected TB who were not TB cases may have been diagnosed as having TB, depending on the pathway's test specificities. A diagnosis of TB was followed by treatment. The HIV positive cases with suspected TB completed the pathway when they were cured (treated successfully) or not cured (treatment failed).

3.2 MODEL DESCRIPTION

Tuberculosis suspects in the base case are evaluated with sputum smear and persons with smear-negative results subsequently undergo chest radiography (WHO 2007 algorithm). The second algorithm, recently adopted in Nigeria, (henceforth, "algorithm with Xpert"), stipulates that HIV positive TB suspects are evaluated with sputum smear and with the Xpert MTB/RIF test irrespective of smear result. If a discrepancy occurs between the result of the smear and the Xpert, the Xpert result is followed. The third algorithm (referred to as "algorithm with MODS"), stipulates that the TB suspects are evaluated with a sputum smear and MODS assay. Like in the algorithm with Xpert, MODS is performed in addition to smear irrespective of smear results. The pathway depends on the result of the MODS assay in case of any discrepancies. Regardless of

the diagnostic algorithm, we assumed that persons with TB in the model started ART, and received TB treatment according to the WHO Directly Observed Therapy Short-course guidelines. Thus, for TB treatment, we applied similar unit costs for Directly Observed Therapy Short-course therapy to each algorithm. All diagnosed TB cases were assumed to be treated and similar efficacy parameters for TB treatment was assigned to all diagnostic algorithms. Models are elaborated in Appendix 1-3

3.3 STUDY AREA/SETTING

Diagnostic costs were collected at the Lagos University teaching hospital. This is a 761-bed tertiary health centre located in a densely populated part of Lagos. It is a referral centre and so has most of the 20 million population of Lagos under its catchment area. It has a purpose built TB laboratory that serves a DOTS centre and the entire hospital. The main mode of TB diagnosis was smear microscopy until 3 years ago when the MODS technique was introduced. The GeneXpert machine was also installed recently. The lab has a safety chamber and was equipped to carry out MTB culture (LJ) prior to the introduction of these novel diagnostics.

3.4 COSTING STUDY

A micro-costing (bottom up) approach is used. This approach identifies all the inputs required to perform a test or deliver treatment and their quantities, then values them to arrive at a cost per test/person treated. The costs included all building, overhead, staff, equipment and consumables, quality control and maintenance, and calibration inputs. Table 3.1. The resource use associated with each test was measured through observations of practice, a review of financial records (budgets, retirements etc.), and interviews with staff in the TB laboratory. Resource use measurement took into account the allocation of fixed resources between Xpert, MODS and many other uses. Estimates of device and test prices, calibration, and training costs were also

obtained. Costs for treatment were estimated using drugs costs from the Global Drug Facility and previous studies. All local costs were converted to US dollars using the average exchange rate as at August 2016. Capital costs such as GeneXpert machine, Inverted microscopes and light microscopes costs were annualized using a standard discount rate of 3%[122]. The building was not considered as capital costs nor was the cost of a safety cabinet included because at this facility (TB lab) all these were already in place prior to starting these techniques. Only renovations/ remodeling was done.

Table 3.1 Cost analysis for GeneXpert implementation at LUTH

Cost	Value	Source	Comments
Capital costs			
GeneXpert Machine	GX-IV with 4 modules and desktop computer at $17 000	GX-IV: Published prices from manufacturer (Cepheid): Negotiated price by FIND for low income countries	Includes international freight, customs and importation, insurance, uninterrupted power supply unit, desktop computer, printer, barcode reader, installation and delivery.
Renovations	Calculated with others inverter/ battery supplied per test)	LUTH Lab use	Includes minor renovations for shelves, air-conditioning, network points, and inverter installation.
Recurrent costs			
Xpert MTB/RIF cartridge	$9.98	Published prices from manufacturer (Cepheid). Discounted for low income countries.	Inclusive of air freight, customs and importation, insurance, and local delivery charges. Varies with cartridge cost
Cartridge procurement	$2.68 ($2.05–$3.23)	Quotation from local supplier	Inclusive of air freight, customs and importation, insurance, and local delivery charges. Varies with cartridge cost
Module calibration	$496/module,	Quotation from local supplier	Module calibration required after every 2000 tests or after 1 year, whichever occurs first. 'Swap pack'calibration method used
Sample consumables	Calculated per test	LUTH Lab use	Includes gloves, disinfectant, and N-95 masks (per day) and sputum collection bottles, request forms, and specimen bags (per test)
Salaries	Lab: Technician at $17.10 /hour; ML Scientist at $21.14/hour	Tertiary Hospital staff cost/hour	Prev. estimated.
Operator staff time per test	Lab: 0.25 h/sample	LUTH Lab use	Allocated at 'hands-on' time per test for GX4 100% effort for GX16 instruments and above
External quality assessment& Training (5 days on-site)	Calculated per test	LUTH Lab use	Three times per year for each module, following calibration. Includes trainer, travel, meals, accommodation, training materials.
Overhead cost	Calculated per test (same overhead as other techniques	LUTH Lab use	Includes electricity, water, medical waste disposal, security services, cleaning services

Table 3.2: Cost analysis for MODS implementation

Cost	Value	Source	Comments
Capital costs			
Inverted Microscope	$4,500	(Euromax 2011)	
Renovations	Calculated with others per test	LUTH Lab use	Includes minor renovations for shelves, air-conditioning, network points, microscope installation.
Recurrent costs			
Reagents (in-house)/ Commercial reagent kits	$3.3 $10.9	Calculated cost per test from in house stock reagents. Commercial kits Hardy Diagnostics	Inclusive of air freight, customs and importation, insurance, and local delivery charges.
Sample consumables	Calculated per test	LUTH Lab use	Includes gloves, disinfectant, and N-95 masks (per day) and sputum collection bottles, request forms, and specimen bags (per test)
Salaries	Lab: Technician at $17.10 /hour; ML Scientist at $21.14/hour	Tertiary Hospital staff cost/hour	Prev. estimated.
Operator staff time per test	Lab: 0.5 h/sample	LUTH Lab use	Allocated at 'hands-on' time per test for GX4 100% effort for GX16 instruments and above
External quality assessment & Training (5 days on-site)	Calculated per test	LUTH Lab use	Includes trainer, travel, meals, accommodation, training materials.
Overhead cost	Calculated per test (same overhead as other techniques	LUTH Lab use	Includes electricity, water, medical waste disposal, security services, cleaning services

3.5 EPIDEMIOLOGICAL INPUT PARAMETERS

Input parameters were obtained from local registries, published data of sensitivity and specificity for MODS assay and GeneXpert, official WHO estimates for TB incidence, mortality and case detection[2]. TB prevalence was defined as all cases of TB diagnosed among persons who are HIV positive undergoing initial evaluation for ART. We assumed that TB treatment was started immediately for those with a diagnosis of TB. The mortality estimate assumes that ART was started during the initiation phase of TB treatment, in accordance with current guidelines.[123] Input parameters are represented in Table 3.3

Table 3.3: Model parameter inputs

Variables	Base value	Range	Reference
Prevalence of TB/HIV	0.19	0.07-0.25	2,6,7,9,29,35
TB treatment success rates in PLHIV	0.6	0.41-0.71	a12,13,14
Screening and Diagnostic tests			
Sensitivity:			
Sputum smear	0.11	0.09-0.38	22,24,33
Chest X-ray	0.71	0.65-0.83	22,24,33
Xpert	0.67	0.62-0.71	222
MODS	0.73	0.66-0.79	222
Specificity:			
Sputum smear	1	0.98-1.00	22,24,33
Chest X-ray	0.77	0.35-0.85	22,24,33
Xpert	0.98	0.97-0.99	222
MODS	0.91	0.89-0.93	222

3.6 COST EFFECTIVENESS ANALYSIS

The primary outcome of the analysis was life years gained. An incremental cost-effectiveness ratio (ICER) was calculated as the difference between total costs for the base case and comparators dividedby the difference in outcomes. The timeframe and analytic horizon for our

analysis was the first 6 months following initiation of ART because mortality risk is concentrated in that period.[4,124]

The model was built in TreeAge Pro 2016 (TreeAge Software Inc., Williamstown, MA).

3.6.1 SENSITIVITY ANALYSIS

Univariate sensitivity analysis was conducted using a tornado diagram of confidence intervals for all parameter inputs. A tornado diagram is a graphical presentation of a 1-way sensitivity analysis and was used to rank the model parameters based on the magnitude of their impact on the ICER. For the parameter with the greatest influence on the model, a univariate threshold analysis to determine the point at which another diagnostic practice would be more effective and conditions under which another diagnostic practice gives equivalent results.

Ranges and confidence intervals for prevalence, sensitivity and specificity of tests came from published literature.

3.7 DATA MANAGEMENT AND ANALYSIS

All cost data was collected and entered into Microsoft Excel for Mac 2011. Unit prices of line items were determined and recorded, capital costs annualized at a discount rate of 3%. The cost and epidemiological parameters were entered into TreeAge Pro 2016 (TreeAge Software Inc., Williamstown, MA). This software was used to design the decision tree tree as well as compute the ICER and perform sensitivity analysis.

CHAPTER FOUR

RESULTS

4.1 COST ANALYSIS

The unit cost per patient in the Base arm was $7.78 for a symptomatic smear-positive patient and $12.85 for a symptomatic smear-negative patient. In the algorithm with Xpert arm, the unit cost of diagnostics was $22.69 per patient diagnosed. For the algorithm with MODS, the unit cost per patient diagnosed was $12.28, which was cheaper than for the Expert. (Tables 4.1-4.3)

Table 4.1 Cost per test using GeneXpert

Cost component	**Cost per test**
Capital costs	
GeneXpert machine	$1.66
Other equipment, renovations	$0.15
Recurrent costs	
Xpert MTB/RIF cartridge	$9.98
Cartridge procurement	$2.68
Labor	$4.28
Overhead operating costs	$2.68
Module calibration	$0.60
Consumables	$0.36
Quality assessment and training	$0.30
Total cost per test	$22.69

Table 4.2: Cost of MODS per test

Cost component	**Cost per test**
Capital costs	
Inverted microscope	$0.20
Other equipment, renovations	$0.15
Recurrent costs	
Reagents (inhouse)/Commercial	$3.3/10.9
Labor	$5.29
Overhead operating costs	$2.68
Consumables	$0.36
Quality assessment and training	$0.30
Total cost per test (in house)	$12.28

Table 4.3: Cost of Smear per test

Cost component	**Cost per test**
Capital costs	
Light microscope	$0.20
Recurrent costs	
Reagents (Stains)	$0.62
Labor	$4.28
Overhead operating costs	$2.68
Consumables	$0.09
Total cost per test (in house)	$7.78*

* Cost of Chest ray is added in the Base algorithm

Considering both TB diagnosis and TB treatment, current practice resulted in a cost of $126.39 while the arms with Xpert and MODS were 76.69 and 88.62 respectively. All algorithms seemed to produce an almost equal effectiveness. This means that the same result being produced by the base case WHO 2007 algorithm can be achieved cheaper using either MODS or Xpert. Therefore for the diagnosis of TB in PLHIV with either diagnostic is cheaper than the base algorithm with smear and chest x-ray.

4.1 COST EFFECTIVENESS

The base case algorithm was the most expensive of the three at $126.39. Table 4.4. The algorithm with Xpert was the cheapest at 76.96 per 0.89 life years (LY)gained. It shows that using MODS will result in an additional cost of $11.65 per patient. It is interesting to note that all 3 strategies seem to have equivalent effectiveness in terms of LY gained per TB/HIV patient initiating ART. The incremental effectiveness of MODS over Xpert is barely 0.01 while it is obvious that the base case is the most expensive without adding any extra benefit. It would have been the dominated strategy if it had been less effective. The algorithm with MODS was associated with an incremental cost of $11.65 per patient initiating ART compared with the use of Xpert, the ICER per LY gained was therefore $1703.86. It is therefore not more cost effective than Xpert since the difference in effectiveness is negligible.

Table 4.4: Output of cost effectiveness analysis in order of increasing effectiveness

Strategy	**Cost**	**Incremental Cost**	**Effectiveness**	**Incremental Effectivenes**	**Incremental C/E**	**Average C/E**
With Xpert	76.96	0	0.89	0	0	86.83
With MODS	88.62	11.65	0.89	0.01	1703.86	99.21
Base case (Smear/CXR	126.39	37.78	0.89	0	27845.79	141.29

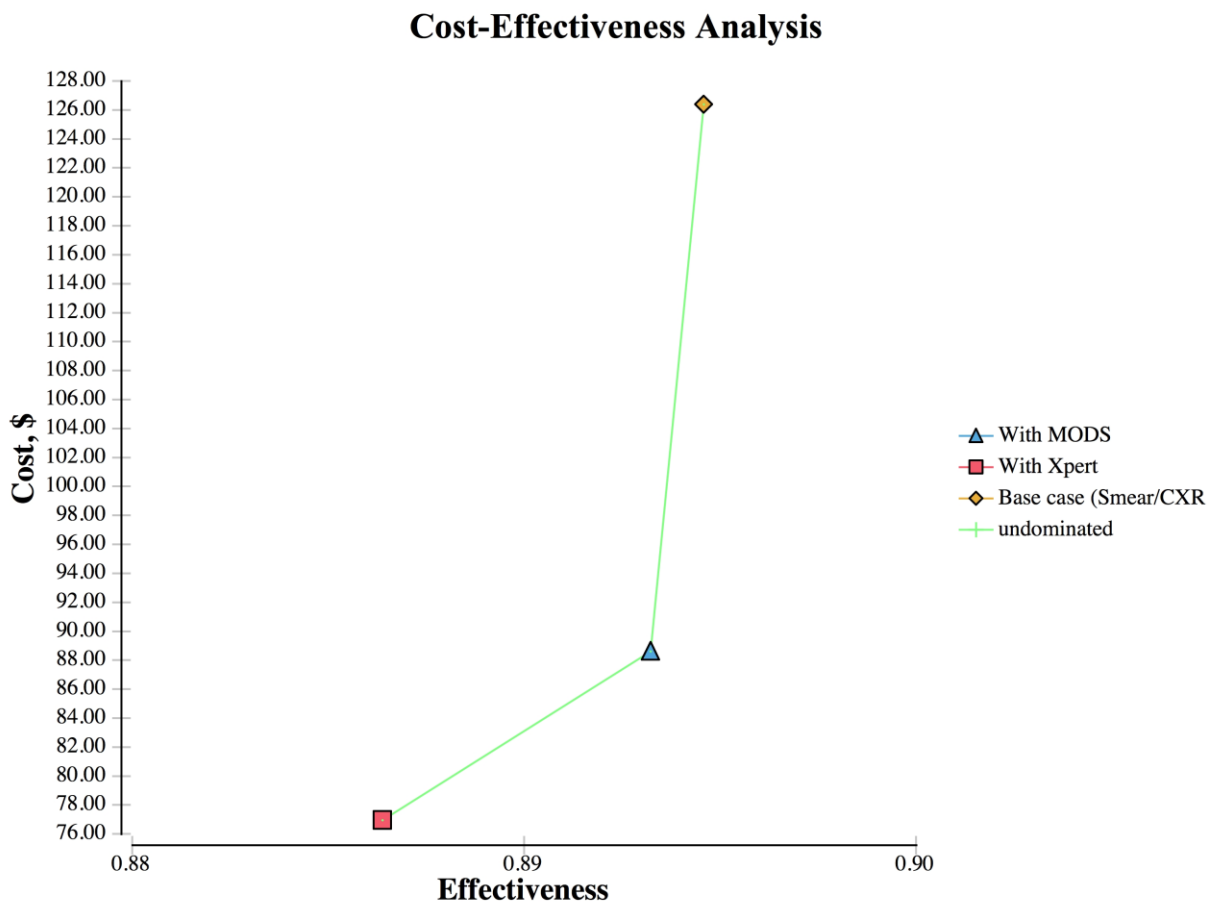

Figure 4.1 Graph showing the Costs VS Effectiveness of the 3 strategies

The graph is a graphical representation of the results of the cost effectiveness analysis showing that the base case scenario is the most expensive with about the same effectiveness as the MODS. The Xpert algorithm though cheapest is only marginally less effective. The MODS therefore though having a marginal superior effectiveness is more expensive. The ICER for MODS compared to GeneXpert is $1703.86 which makes it a cost effective strategy if we consider our cost effectiveness threshold to be Nigera's GDP per capita which was $5638.89 (World Bank 2015). This means that judging by our GDP, it is a strategy that can be implemented to produce (marginal) benefit over GeneXpert. Both Strategies are clearly much

cheaper and would result in significant cost savings (considering the burden of TB/HIV) and therefore constitute a better utilization of scare resources compared to the base algorithm with smear and Chest x-ray.

4.3 SENSITIVITY ANALYSIS

All parameters were varied using a tornado diagram, which aggregates a univariate sensitivity analysis for each parameter. Figure 4.2. This analysis showed that the ICER per LY gained was affected by 7 of the variables in the model. The most significant variable was the prevalence of TB/HIV co-infection. This accounted for significant variation in the model.

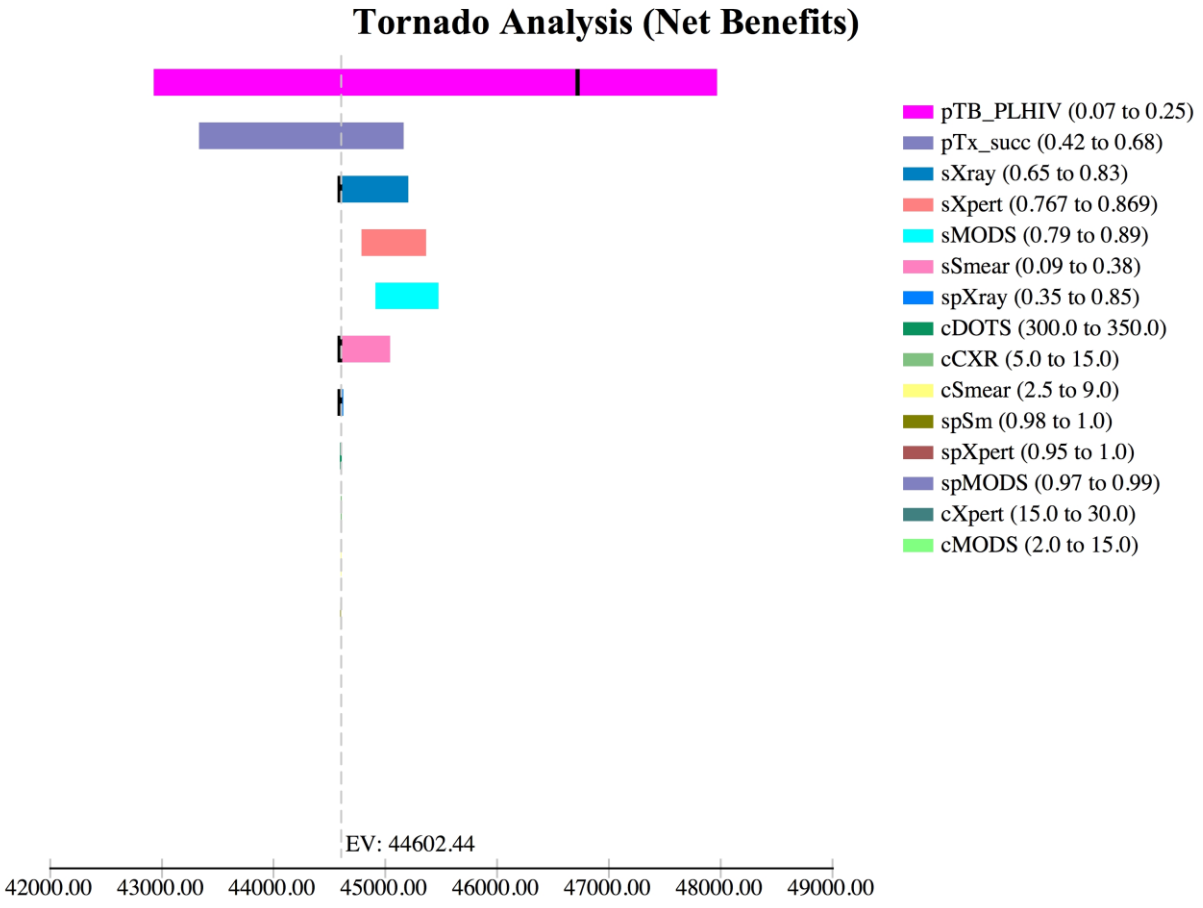

Figure 4.2: Tornado diagram of input parameters

The threshold value for the prevalence of pulmonary T B in HIV positive patients was 0.115. Below this leve as it tends to zero, the net monetary benefits of the three strategies becomes close. At higher values of prevalence the difference between the algorithm with expert and the other is wide. The xpert remains the cheapest even after varying the prevalence. Figure 4.3

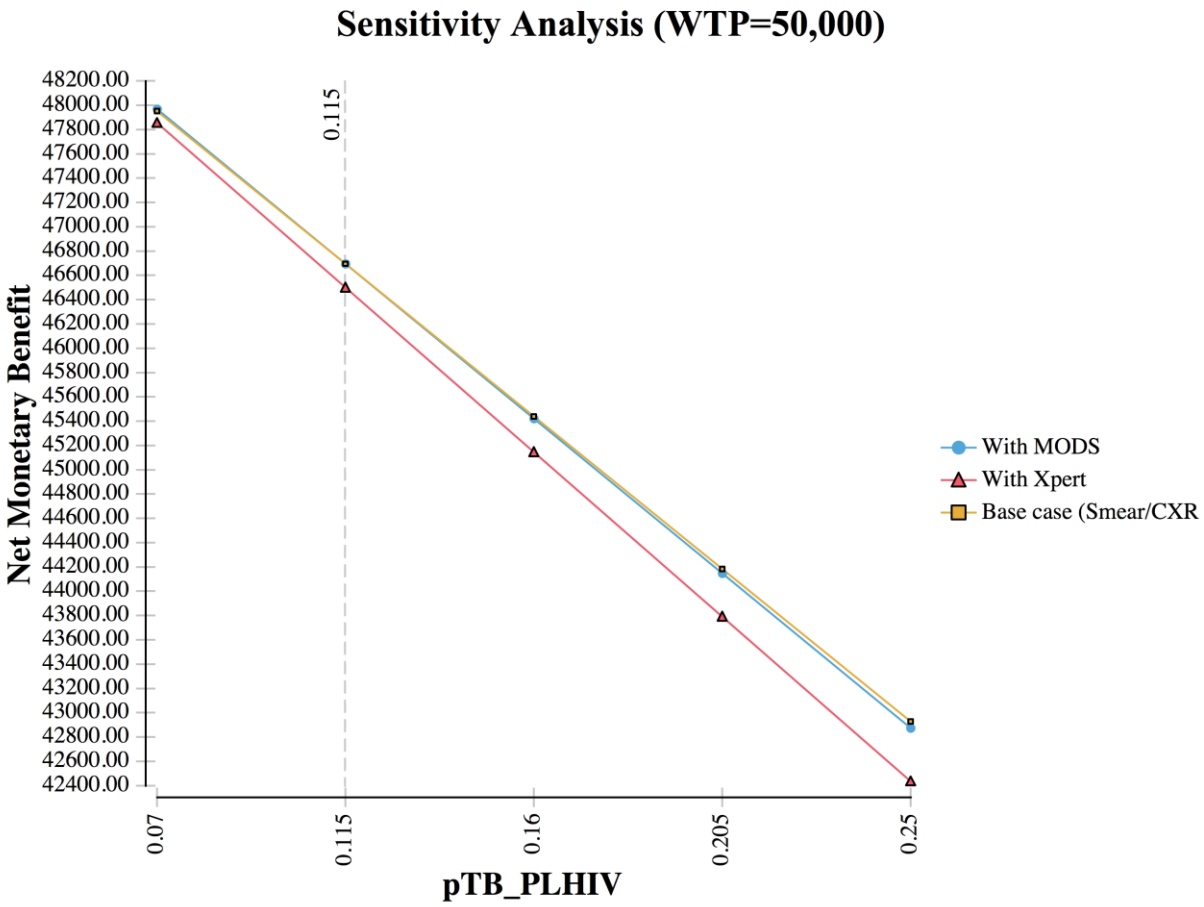

Figure 4.3: Sensitivity analysis for prevalence of TB/HIV showing the threshold.

CHAPTER FIVE

DISCUSSION

The cost analysis study found the cost per unit test to be highest for geneXpert. This was as a result of the high cost of procurement of the catridges for the test. The cost of one diagnosis of TB in this HIV positive cohort to the TB programme however was cheapest for Genexpert, followed closely by MODS. The base algorithm had the highest cost per diagnosis of the three. Though the cost of individual test was highest for Xpert, the algorithm was cheaper because MODS has a significant labour and overhead cost compared to Xpert. The base algorithm is expensive and does not offer value for money.

The results demonstrate that a diagnostic approach that uses geneXpert is the most cost effective for diagnosing TB in PLHIV compared to the base algorithm.Other studies have also shown Xpert to be cost effective compared to algorithms based on smear microscopy and the WHO 2007 algorithm.[97–99,102,114] Some south African studies have gone ahead to determine the best strategy for placement, comparing the roll out of Xpert machines to district laboratories (laboratory based) to placement at Clinics i.e. at point of care where patients are receiving care (Clinic based).[121,125]The clinic based strategy was considered to enable same day treatment as results may also get lost/ not get to health personnel/patients in due time to ensure treatment is commenced. In Nigeria, this would be the next step; to investigate which roll out modality would yield the maximum result now that we know that it is the cheapest. It also offers the advantage of being portable and does not require as much technical expertise as culture based methods to implement. The analysis also showed that the algorithm with MODS was more expensive but was marginally more effective compared to Xpert. There are studies that show that MODS is cheap, as cheap as $2 per test in Peru.[23]MODS was developed for high burden resource

constrained settings.[22,126]It is also cheaper to implement than our base algorithm. It is also cost effective compared to GeneXpert though the effectiveness is only marginal over Xpert. This is therefore also a viable option for Nigeria as this technique also offers an advantage of testing for resistance to both Rifampicin and Isoniazid at the same time compared to the mono-resistance testing of Rifampicin alone by Xpert. The result of resistance testing with Xpert (if positive), then requires conventional drug susceptibility testing (DST) as a follow up. This study only considered these two novel TB diagnostic methods for diagnosis in HIV positive patients and did not factor in resistance testing and the high prevalence of MDR TB in Nigeria[2] into the decision tree. Therefore the results should only be considered in response to the question which is the most cost effective for diagnosis, i.e which will improve case detection, ensure more patients are put on treatment and so reduce mortality in this cohort of patients. Utility for diagnosis of drug resistant TB can be considered in a subsequent study, which would look at both HIV positive and HIV negative patients.

The base algorithm was the most expensive. Unfortunately this is still the most common algorithm in use especially as most treatment units have neither access to GeneXpert nor MODS facilities. In Nigeria, there are only ninety-six centres with Xpert machines[2] and two tertiary health centres with capacity for MODS. This is grossly inadequate considering the size and disease burden in Nigeria. The logistics involved in moving samples to and from these centres is herculean and so results are not received in a timely manner to ensure treatment is started on time. This ultimately results in the significant morbidity and increased mortality of TB associated HIV infection. There are therefore significant cost savings to be made and efficient use of resources to achieve the desired outcome of decreasing the mortality in this cohort of patients if this algorithm is replaced with the algorithm with Xpert.

Our analysis is subject to several limitations, which may have affected the outcome. The TB program perspective was used which meant we didn't consider the costs of other treatments (ART, hospitalization, healthcare utilization costs) as done in other studies. Also, it might have been useful to stratify PLHIV according to the severity of the disease as at initiation as this may affect outcome by increasing probability of dying during therapy. Also further analysis could be done to ascertain the percentage of patients who may have presented with resistance at initiation.
It should be noted that these costs were conservative as the setting, Lagos University Teaching Hospital had a TB lab that could perform TB cultures and only required remodeling and a few new equipment.

Also, patients who were treated based on a clinical suspicion of TB despite having negative tests were not accounted for. The impact of improved TB diagnosis would be reduced to the degree that this clinical suspicion correctly identifies patients with TB. However, the high sensitivity and specificity of the improved TB diagnostic algorithms that were assessed will lead to more effective identification of TB compared with clinical suspicion, thereby increasing the number of TB cases treated.

Precise data on the mortality associated with undiagnosed TB is unavailable as reporting is still problematic.
This study does however provide support for ongoing efforts to expand TB diagnostic capacity. It concurs with other studies that Xpert is a cost effective strategy for diagnosis of TB in PLHIV. Wide- spread implementation will involve operational and logistical challenges; so these issues must be considered in a systematic and coordinated way to ensure that limited resources are put to optimal use.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSION

The study shows that though the unit cost of GeneXpert is higher than that of MODS, using a GeneXpert-based algorithm was more cost-effective compared to using a MODS-based algorithm for diagnosis of HIV-associated PTB. The high cost of the GeneXpert was as a result of the cost of catridges while the most significant expense contributing to the cost of MODS was the wages. Both strategies were cheaper than the WHO 2007 algorithm of Smear followed by Chest X-ray.

Effectiveness in terms of LY gained was similar for all 3 strategies. The cost effectiveness of using GeneXpert in a resource limited setting is often questioned because of affordability and sustainability concerns. On the other hand, MODS test was specifically developed for resource limited settings and has superior diagnostic accuracy to GeneXpert.

GeneXpert has advantages of being portable so can be used in clinics rather than central laboratories, and the turnaround time of 2 hours may be useful to ensure treatment is started same day. This could increase TB detection and access to drug-susceptibility testing which is important for early diagnosis and treatment of drug-resistant TB.

Cost-effectiveness analysis is one of the major considerations for decision making to adopt a new technology or diagnostic strategy. Other factors to take into account include human resource and training requirements, impact of the new technology on the health system as a whole, the infrastructure required, quality assurance, procurement and maintenance issues among others.

6.2 RECOMMENDATION

1. The National TB programme should continue the role out of GeneXpert machines to more facilities especially in states with high burden of TB/HIV. It is bound to improve case detection leading to early treatment and the resultant gains in quality of life.Also, getting as many machines as possible in the community will also reduce the dependence on the Smear with x-ray algorithm leading to significant cost savings for the health system.
2. The National TB programme in collaboration with the state governments, should set-up MODS laboratories in each state. This will supplement the efforts of the regional labs by proving laboratories with culture facilities around the country that can go further than the mono resistance testing of Xpert to carry out resistance testing for both Rifampicin and Isoniazid at the time of diagnosis. Another advantage is its use for drug susceptibility testing.
3. The Regional reference laboratories should be supported to continue their current functions.
4. Public health laboratories/ Public health Institutes should engage in and commission more cost effectiveness studies. This will ensure that decisions on strategies or methods adopted are thoroughly scrutinized and made based on scientific evidence. This will ensure efficient use of our scarce resources.

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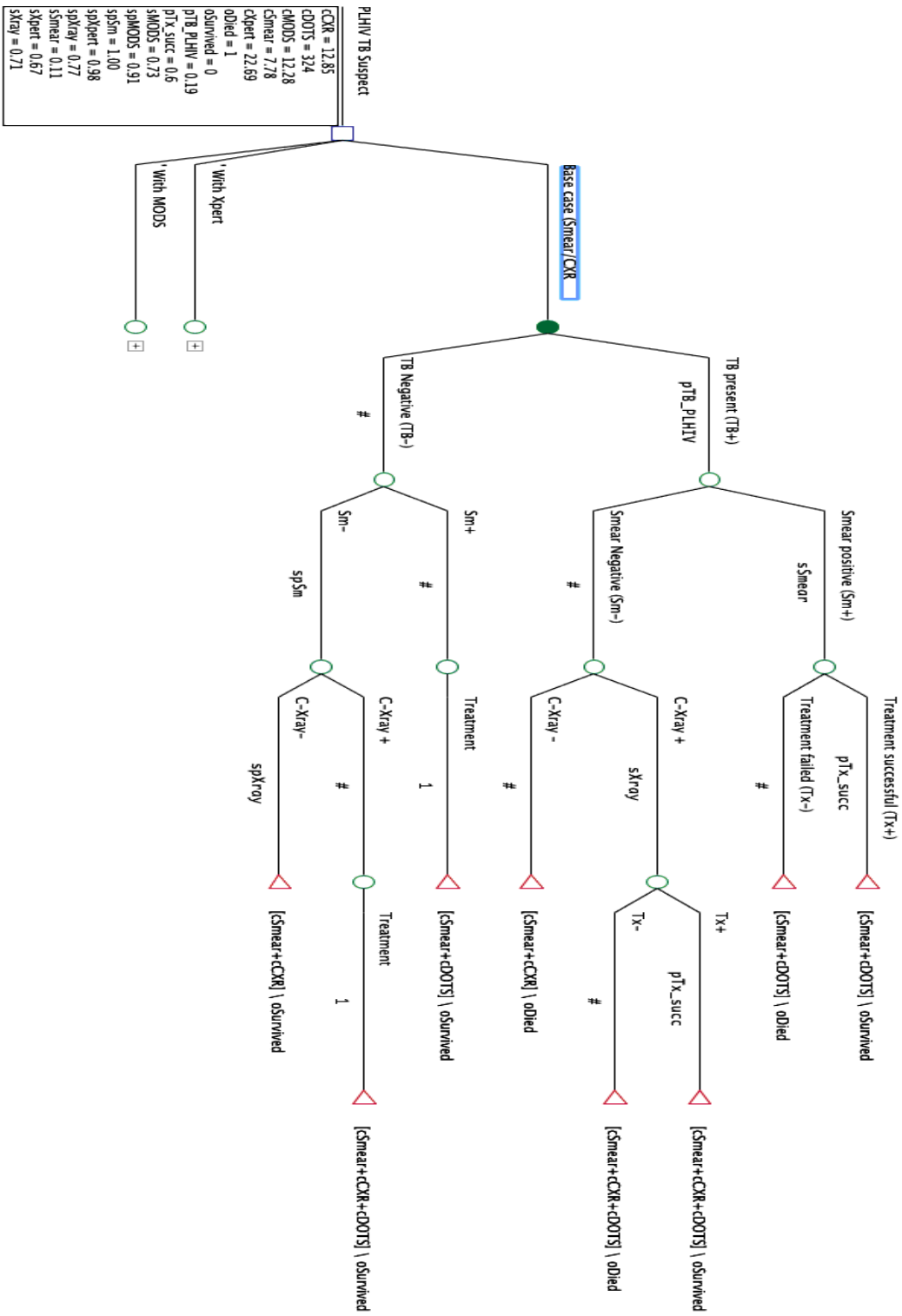
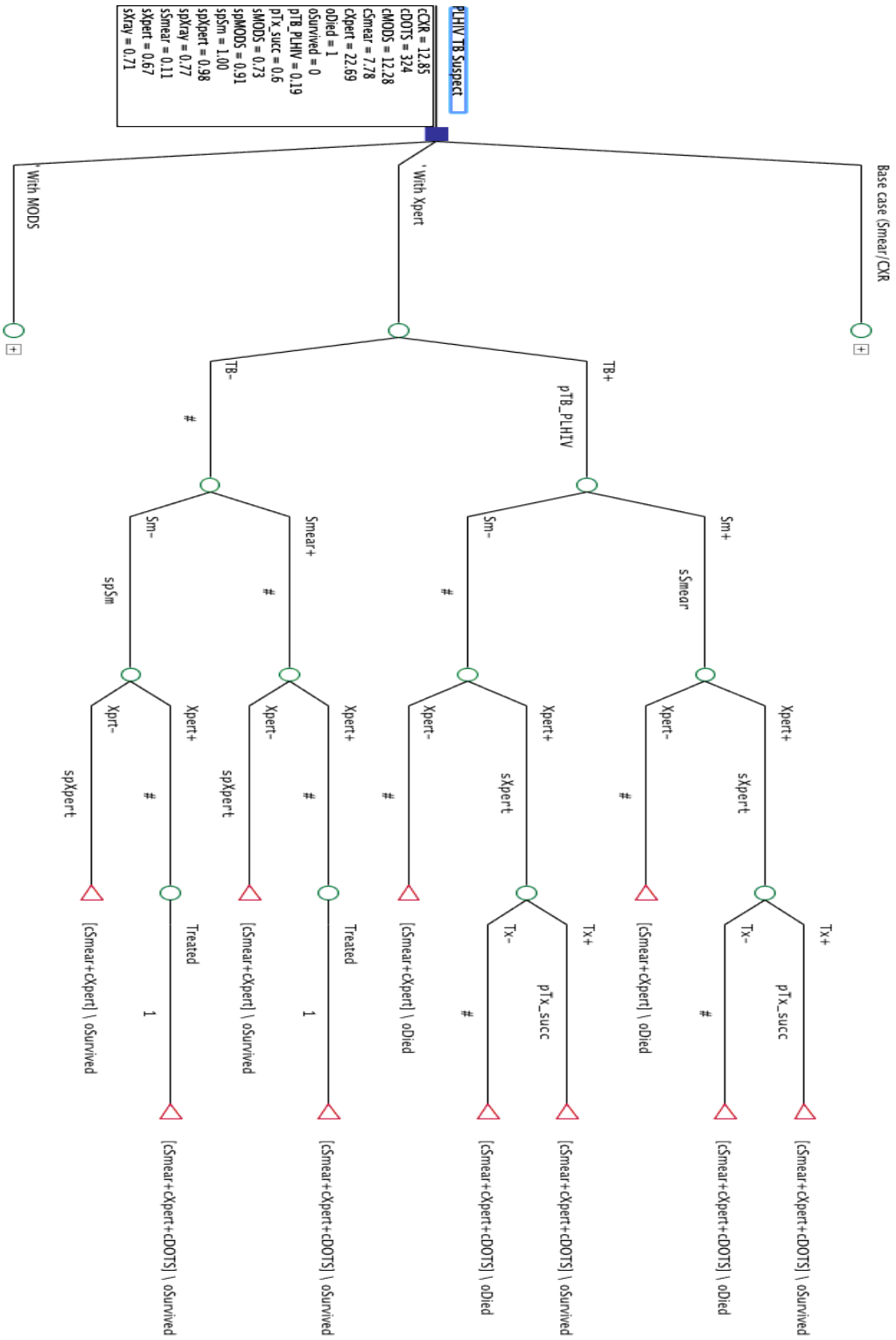
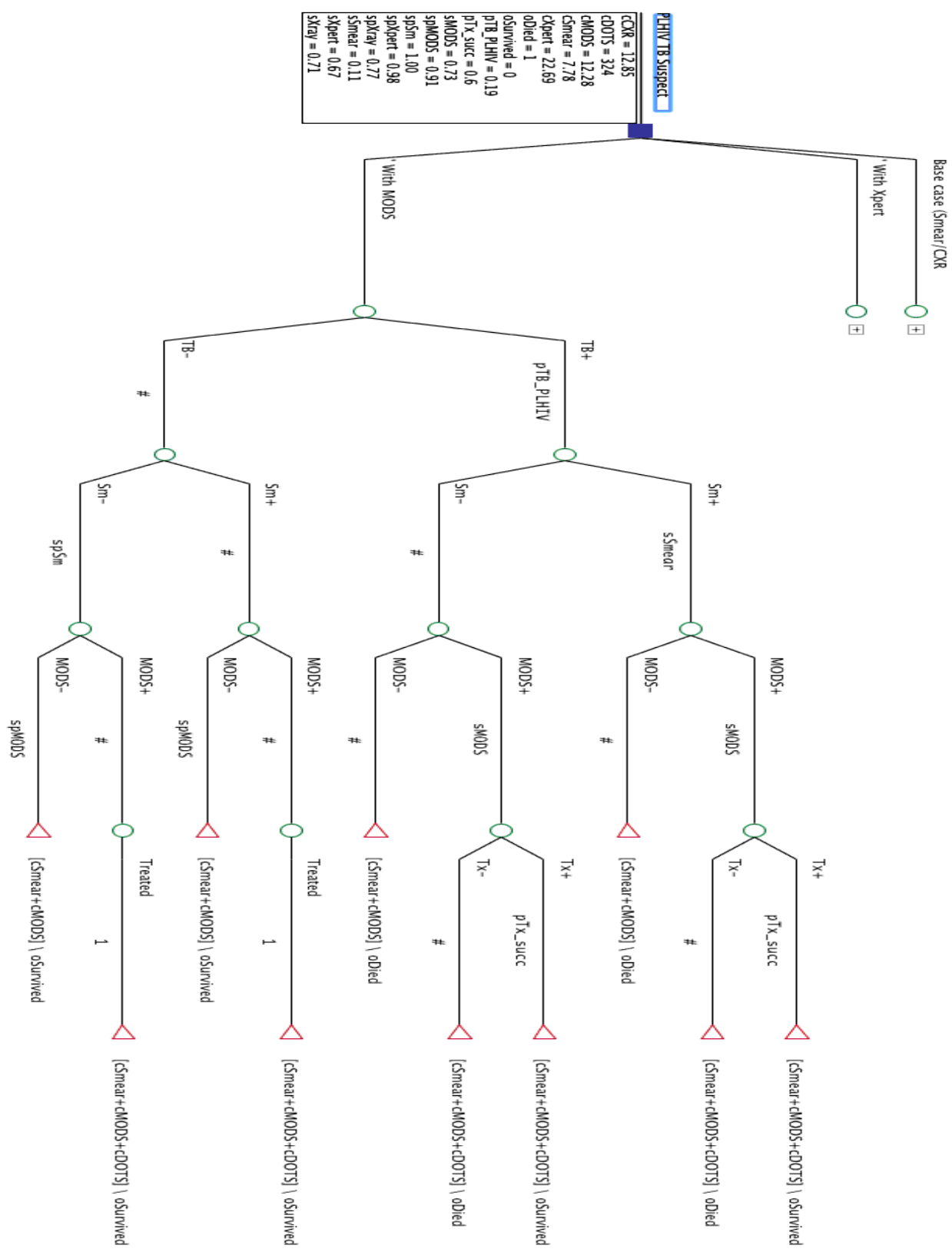
APPENDIX 1: Base case scenario model



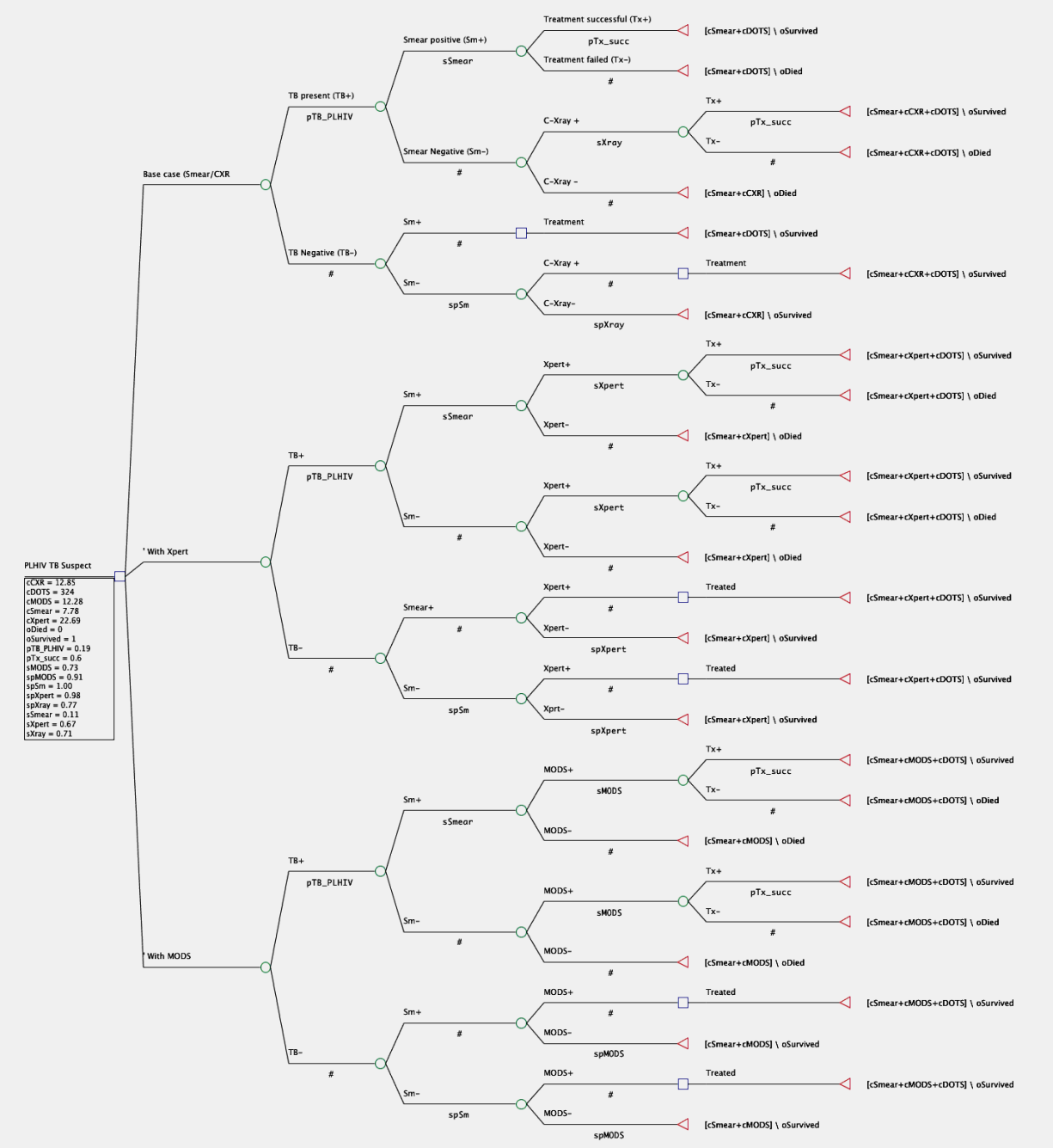
APPENDIX 2: Algorithm with geneXpert model



APPENDIX 3: DECISION TREE OF DIAGNOSTIC SCENARIOS



APPENDIX 4: DECISION TREE OF DIAGNOSTIC SCENARIOS



APPENDIX 6: MODS INGREDIENTS COSTS

Consumables	Quantity	Unit price ₦	Total Cost ₦
Hardy MODS kit	2x1x100	88,000	176,000
Freight and custom clearance			155,000
Middlebrook7H9 broth(Difco)	1 tin	35,000	35,000
Casitone (pancreatic digest casein)	1 tin	15,000	15,000
*Isoniazid powder (sigma)	5g	5,000	1,000
*Rifampicin powder (sigma)	5g	5,000	1,000
*Dimethyl sulphoxide (DMSO)	1 Ltr	10,000	10,000
*0.22um filters (aqueous solvents) blue	1x50/case	10,000	10,000
*0.22um filters (organic solvents)yellow	1x50/case	10,000	10,000
*PANTA (Antibiotic mixture lyophilized BD	2x6bottles/pack	26,000	52,000
*OADC (Middlebrook OADC enrichment BD)	2x10X20ml/pack	30,000	60,000
*24 well plates (Multiwell 24 well BD Falcon 35-3047)	2X50/pack	30,000	60,000
*McCartney bottles	100	200	20,000
*Sealable polythene bags 6x6 (ziplock)	2x100/pack	1,000	2,000
15 ml glass tubes	200	200	40,000
Glycerol(glycerin)	1 Ltr	5,000	5,000
Ethyl alcohol (absolute)	1Ltr	10,000	10,000
15 ml polypropylene conical tubes	2x50	5,000	10,000
50 ml polyprolene conical tubes	2x25	5,000	10,000
2ml polyprolene crio vials	1x500	5,000	5,000
Tween 80	1 Ltr	5,000	5,000
Sodium hydroxide(pellets)	200g	4,500	4,500
N-acetyl-L-cysteine	5g	5,000	5,000
Sodium citrate (trisodium salt dihydrate)	200g	4,500	5,500
Potassium Phosphate Monobasic crystal. (KH_2PO4)	I tinx500g	10,000	10,000
Sodium Phosphate Dibasic anhydrous (Na_2HPO4)	I tinx500g	10,000	10,000
2 ml test tubes rack	5	4,000	20,000
Aerosol barrier 100-1300ul (blue)	5x100/ pack	2,000	10,000
Aerosol barrier 1-200ul (yellow tips)	1x1000	2,000	10,000
Aerosol barrier 100-1300 blue tips	1x1000	10,000	10,000
Pasteur pipettes	1x200	10,000	10,000
Pasteur pipette teats (fillers)	10	50	500
Multi-channel automatic pipette(8Chanell)	2	90,000	180,000
Automatic pipette (100-1000ul)	2	35,000	70,000
Automatic pipette (0-20ul)	2	35,000	70,000

Automatic pipette (20-200ul)	2	35,000	70,000
Glass manual pipette (10ml)	10	200	2,000
Pi pipette filler	2	2000	4000
Cotton wool	1x500g	1,500	1,500
Glass slides (frosted end)	4x100	500	2000
N95 face mask	10x1x10	10,000	100,000
Laboratory aprons and caps	4	8,000	32,000
Laboratory coats	4	6,000	24,000
Disposable latex hand gloves (size7.5)	10x1x100	800	8,000
Na Hypochlorite (bleach)	10x1 Litre	500	5,000
Detergent	10x500g	1,000	10,000
Liquid hand washing soap	10x200ml	1,000	10,000
Autoclave bags	1 x100/pack	20,000	20,000
Autoclave tape	1 roll	2,000	2,000
Kitchen wipes	5x2/pack	1000	5,000
Aluminium foil	1	1,500	1,500
Brown wrapping paper	100	50	5,000
Masking tape	2rolls	500	1,000
pencils	10	20	200

*Not necessary if Hardy MODS kit® is used

APPENDIX 7: GENEXPERT INGREDIENTS

Consumables	Quantity	Unit price ₦	Total Cost ₦
GeneXpert Catridge	10x1x100	3,350	3,3500,00
15 ml sputum cups	100	200	20,000
Glycerol(glycerin)	1 Ltr	5,000	5,000
Ethyl alcohol (absolute)	1Ltr	10,000	10,000
15 ml polypropylene conical tubes	2x50	5,000	10,000
2ml polyprolene crio vials	1x500	5,000	5,000
Pasteur pipettes	1x200	10,000	10,000
Cotton wool	1x500g	1,500	1,500
Glass slides (frosted end)	4x100	500	2000
N95 face mask	10x1x10	10,000	100,000
Laboratory aprons and caps	4	8,000	32,000
Laboratory coats	4	6,000	24,000
Disposable latex hand gloves (size7.5)	10x1x100	800	8,000
Na Hypochlorite (bleach)	10x1 Litre	500	5,000
Detergent	10x500g	1,000	10,000
Liquid hand washing soap	10x200ml	1,000	10,000
Autoclave bags	1 x100/pack	20,000	20,000
Autoclave tape	1 roll	2,000	2,000
Kitchen wipes	5x2/pack	1000	5,000
Aluminium foil	1	1,500	1,500
Brown wrapping paper	100	50	5,000
Masking tape	2rolls	500	1,000
Markers	10	100	1,000