A cost-effectiveness analysis of different ways of analyzing sputum for tuberculosis diagnosis: direct smear microscopy, natural sedimentation and centrifugation

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DECLARATION

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ABSTRACT

In Malawi, sputum smear microscopy (Ziehl-Neelsen) is a major diagnostic technique for pulmonary tuberculosis (TB). Though relatively rapid, it tends to be poorly sensitive since it requires a large number of organisms to be present in the specimen before they can be detected. Two approaches that improve sensitivity of direct smear microscopy are sputum liquefaction with chemicals such as sodium hypochlorite (household bleach) and subsequent concentration with gravity (natural) sedimentation and centrifugation. This study estimated the costs and cost-effectiveness of these techniques in processing sputum for detecting new cases of pulmonary tuberculosis in Malawi.

Bleach natural sedimentation and bleach centrifugation methods were compared with direct smear microscopy. Cost and effectiveness data were collected from a randomized controlled trial from one major TB health facility. Effectiveness was determined by number of smear positive TB cases detected by each method. Cost-effectiveness was estimated from a provider's perspective in terms of cost per TB cases diagnosed and cost per smear positive TB case detected.

Cost per positive TB case detected was least in natural (gravity) sedimentation (US \$9.35), compared to centrifugation (US \$11.48) and direct smear microscopy (US \$15.93). The study findings indicate that natural sedimentation can significantly reduce cost of sputum processing. There is a strong economic case supporting the use of natural sedimentation for diagnosing tuberculosis in Malawi. In addition, bleach digests sputum making it less infectious and easy to work with thereby increasing the safety of specimens to clinicians. Therefore, introducing natural sedimentation technique would not only reduce costs but also improve safety to health workers.

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LIST OF ACRONYMS AND ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
BC	Bleach Centrifugation
BS	Bleach Sedimentation
CEA	Cost Effectiveness Analysis
CHAM	Christian Health Association of Malawi
CXR	Chest X-Ray
DALY	Disability Adjusted Life Year
DSM	Direct Smear Microscopy
DOT	Direct Observed Therapy
EHP	Essential Health Package
FM	Fluorescence Microscopy
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
HYE	Health Years Equivalence
ICER	Incremental Cost Effectiveness Ratio
IUATLD	International Union Against Tuberculosis Lung Diseases
MDG	Millennium Development Goals
MK	Malawi Kwacha
MLW	Malawi Liverpool-Welcome Trust
MTD	Mycobacterium Tuberculosis Direct Test
NTCP	National Tuberculosis Control Program
PCR	Polymerase Chain Reactions
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
SP	Smear Positive
TB	Tuberculosis
WB	World Bank
UNDP	United Nations Development Programme
USAID	United States Agency for International Development

US$	United States Dollar
WHO	World Health Organisation
ZN	Ziehl-Neelsen

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB) remains a major global public health challenge. The World Health Organization (WHO) and the World Bank (WB) estimate that globally, 8.8 million cases are detected of which approximately 1.6 million people die annually (World Health Organisation 2007a). The Sub-Saharan Africa is among the worst affected regions with an incident rate of 350 per 100,000 (World Health Organization 2007b). According to the WHO Global TB 2008 Report, there were an estimated 51,172 new cases of TB in Malawi of which 33000 are also HIV positive, but the Malawi's National TB Control Program (NTCP) estimates are around half that (Banda 2009). This indicates that TB case detection in Malawi is about 50%.

Tuberculosis is among the three major killer diseases, behind Malaria and Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS). The disease burden has been exacerbated by TB-HIV co-infection, where HIV positive individuals are prone to developing TB due to weakened immune systems of HIV infected persons. This leads to increased number of tuberculosis cases per year. Worse still, the majority of people with TB or TB/HIV co-infection are in the economic productive age group. This implies that, productivity within this age group decreases and consequently, the economic growth of the country also decreases (Kim *et al.* 2009).

Direct smear microscopy has been a major tool for diagnosing tuberculosis. However, the low sensitivity, which has also been worsened by increasing TB/HIV co-infection, has affected the number of TB cases that can be promptly diagnosed (Bruchfeld *et al.* 2000, Lawson *et al.* 2007). Tuberculosis is not only harder to diagnose in HIV positive patients, but it also tends to progress faster (AVERT 2009). A study by Hargreaves *et al.* (2001), done in an areas of high HIV seroprevalence in Malawi, noted that 22% of the smear negative TB patients were actually confirmed to be smear positive after some weeks of re-examination. The identification of patients who have positive sputum smears is crucial, since these patients are the most infectious especially to close contacts.

In the 1980's, TB cases were much lower in Malawi, with public health facilities having to treat about 5000 patients annually (Banda 2009). The rising number of TB cases has put considerable strain on the public health system (Wandwalo *et al.* 2005, Harries *et al.* 1999). A study conducted by Harries *et al.* (1999) in Malawi, also indicated that, the high incidence of TB has greatly increased risk of infection amongst all categories of health workers, especially clinical officers (Harries *et al.* 1999). With per capita health expenditure of US $19 (The Global Fund 2008) and few health workers, TB epidemic significantly affects the Malawi's health system performance. Consequently, identifying new methods that maintain or improve sensitivity in detecting sputum smear positive TB cases; reducing the risk of transmission among health workers, and at the same time reducing demand on health resources and lowering cost of diagnosis is pertinent. Two promising approaches are sputum liquefaction with chemicals such as sodium hypochlorite (household bleach) and subsequent concentration with gravity (natural) sedimentation and centrifugation. Bleach disinfects sputum specimens rendering them less infectious and thus reducing risk of transmission amongst health workers. In addition, household bleach is universally accessible at an affordable cost.

1.2 Country Setting

Malawi is located in central Africa covering an area of 118,480 sq km (45,745 sq miles), of which 24,400 sq km (9,420 sq miles) consists of water, predominantly Lake Malawi.

The country borders Tanzania, Zambia and Mozambique to the north and west, south, south-west and south-east respectively.

The 2008 national population census estimated the country's population at 13 million people, with 49% of the population being males and 51% being females (National Statistical Office 2008). The total annual population growth rate is estimated at 2.8%. Birth rate is estimated at 41.79 births/1000 and death rate at 17.89/1000 population. Infant mortality rate is at 90.55 deaths/1000 live births. Life expectancy at birth is 43 years.

The Government through a wide network of health centres and hospitals principally provides 60% of health care. The second major provider is a group of mission hospitals commonly known as Christian Health Association of Malawi (CHAM) hospitals (40%). There is also a visible presence of private health facilities mainly within the urban areas of the country. Traditional practitioners such as birth attendants also play a role in providing health care.

The Malawian economy, with gross domestic product (GDP) of US $850 in 2008, has been heavily reliant on agriculture, with tobacco being the main cash crop and major source of foreign earnings. In addition, sugar, tea and coffee provide additional sources of foreign exchange. Recently, the country has ventured into uranium mining in the northern part of the country. This is expected to be the major export commodity that could replace tobacco.

1.3 Rationale of the study

In Malawi, sputum smear microscopy (Ziehl-Neelsen) is a major diagnostic technique for pulmonary tuberculosis. Though relatively rapid, it tends to be poorly sensitive since it requires a large number of organisms (>10^5 orgs/ml) to be present in the specimen before they can be detected (Ramsay *et al*. 2006). A more definite method of detecting tuberculosis is through culture where mycobacterium tuberculosis (MTB) are grown. However, this may take up to 10 weeks before results are available, as such though definitive, it is not ideal for patient management and control of transmission of MTB.

Attempts have been made to improve the sensitivity of tools and different techniques used to detect especially sputum smear positive cases. Factors that improve sensitivity of sputum smear examination include homogenization of sputum with Sodium Hypochlorite (NaOCl); that is household bleach, followed by concentration either by sedimentation or centrifugation (Aderaye *et al*. 2007). Natural sedimentation allows particles to settle down separated by size and density allowing massive components of a liquid to settle at the bottom. Similarly, centrifugation is a method of separating molecules by size or density using centrifugal forces by a spinning rotor. More massive components of the liquid are pressed toward the outside of the centrifuge with more force, so they settle to the bottom of the test tube. While centrifugation requires a centrifuge and electricity, sedimentation can be done locally where such facilities are not present. Both methods increase concentration of the molecules in the specimen, which then improves the diagnostic yield of the specimen. When more patients are detected in the early stages and put on treatment early, transmission rate has been found to decrease significantly.

Late detection of TB imposes a greater challenge on poor outcomes in terms of death rate which is high particularly for HIV infected patients (Mort 2004). Thus, it has become imperative that more cases are detected at a least possible cost, when TB is in its early stages so that patients can be promptly placed on treatment to curtail further transmission of tuberculosis germs. Such an intervention requires improved TB diagnostic techniques for those cases that present at the health facilities over and above encouraging patients to attend health facilities if and when they experience TB symptoms.

In addition, the global report for 2009 indicates that, case detection rate in Malawi has been stagnant at around 40% with treatment success rate at 70% for a period of over 5years (USAID 2009). The low rate of case detection is also a concern for several reasons. Some of these include the delay it imposes on attainment of the TB related Millennium Development Goals (MDGs) which targets reducing TB prevalence by half by 2015 compared with 1990 (World Health Organisation 2007b), diagnosing 70% of new smear positive cases and curing 85% of these cases by 2015 (Baltussen *et al.* 2005). At the current rate of progress, achieving these targets will be an immense challenge. An important question is whether the correct mix of intervention is being used and what strategies should be used to achieve global set targets (Baltussen *et al.*2005). Assessment of cost and cost effectiveness of alternative options can help with such decisions. When such strategies are identified and implemented, it would contribute to attainment of millennium development goals, thus improving population health.

The World Health Organisation (2005) recognizes that some countries, especially those with high HIV prevalence, have already implemented concentration techniques for sputum examination while others are still in the process of implementing them. Taking into account that TB is highly prevalent in poor countries where resources are very scarce, it is crucial that countries determine whether these methods can offer the maximum benefits at the least possible cost before prematurely adopting these methods. To determine which methods will give us maximum benefits, it is essential that economic evaluation be used and as an aid to guide policy makers in decision-making process (Drummond *et al*. 2005).

There seems to be an information gap concerning the cost-effectiveness of smear microscopy, natural sedimentation and centrifugation techniques. Lack of information should drive us to expand our research efforts (Ramsay *et al.* 2006). This study seeks to fill this information gap. To the best of my knowledge, globally, very few published studies have looked at cost-effectiveness of these techniques in analyzing sputum for Tuberculosis diagnosis. Thus, it has become pertinent to estimate cost effectiveness of these techniques with a view to guide policy in prioritization of resource use.

1.4 Aim and objectives of the study

1.4.1 Aim

To investigate the cost-effectiveness of direct smear microscopy, bleach natural sedimentation and bleach centrifugation methods in processing sputum for detecting new cases of pulmonary tuberculosis in Malawi.

1.4.2 Specific objectives

(1) To estimate the provider costs of each of the three methods for analyzing sputum.

(2) To determine the effectiveness of each of the methods in processing sputum.

(3) To estimate and compare the cost effectiveness of these three different approaches for analyzing sputum.

(4) To make policy recommendations on techniques of analyzing sputum for detecting new cases of pulmonary tuberculosis.

1.5 Organization of the thesis

The rest of the thesis has been organized as follows. The second chapter is a literature review. It looks at other economic evaluation studies paying particular attention to effectiveness of the methods used, how they measured effectiveness and calculation of a cost effectiveness ratio. This chapter also describes scope of costs included in the studies. Finally the chapter outlines the conceptual framework, which helps to understand how economic evaluation will be conducted in this study.

Chapter three presents the methodology of the study. The chapter also outlines the types of cost data collected and measures of effectiveness used in the study.

Chapter four presents the study findings in terms of costs and cost-effectiveness. The chapter also presents the measure of effectiveness which is the number of smear positive tuberculosis patients detected. The results of a number of sensitivity analyses then are given.

Chapter five discusses results of the study in relation to provider's costs, cost effectiveness and resource use. Limitations of the study are also highlighted.

Finally, chapter six gives the conclusions of the study and outlines the policy recommendations emanating from the study findings.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

A number of studies have been conducted on the cost-effectiveness analysis of Tuberculosis. Some of these studies have focused on diagnosis, whilst others have focussed on treatment and case management. This chapter reviews some of these studies with particular emphasis on studies that have looked at diagnosis. Firstly, studies that have focussed solely on the effectiveness of different methods of TB diagnosis are discussed. Secondly, studies that have looked at cost-effectiveness analysis of TB diagnosis are reviewed, with critical evaluation of the methodologies used. These methodologies include perspectives of the economic evaluation, data collected, scope of cost data, effectiveness measures, measures of cost effectiveness analyses and how sensitivity analysis were performed. The last section of this literature review focuses mainly on resource allocation requirements. The aim of this latter section is to explain how equity concerns need to be considered when using cost-effectiveness analyses to allocate resources for health interventions.

2.2 Effectiveness analysis

Direct sputum smear microscopy is the basis of TB diagnosis in most low and middle-income countries (Steingart *et al.* 2006). This method is rapid, inexpensive, and highly specific and is also capable of identifying the most infectious cases of TB (Steingart *et al.* 2006). However, problems with its limited sensitivity have prompted investigation of alternative techniques that are more sensitive in detecting the TB bacilli. Some of these methods include Polymerase chain reactions (PCR), fluorescence microscopy (FM), bleach sedimentation (BS) and bleach centrifugation (BC). With respect to PCR, several studies have found that, PCR is a more sensitive and faster method of diagnosing TB, compared to direct smear microscopy (Haldar *et al.* 2007). However, these advantages are partially offset by economic factors as well as technical factors (test is complicated to run in a laboratory), making this method less suitable for use in resource-poor settings.

Regarding fluorescence microscopy (FM), a systematic review by Steingart *et al.* (2006) reported that fluorescence microscopy of auramine-stained smears gave a similar specificity and on average a 10% higher sensitivity than Ziehl-Neelsen staining in 18 studies analysed. Higher sensitivity was observed in 16 of these studies (Steingart *et al.* 2006). In addition, fluorescence microscopy done on one or two specimens was more cost-effective than the Ziehl-Neelsen method used on three sputum specimens. Furthermore, FM has been shown to have an added advantage of reducing the time that is required for examination of smears, with about 15 times as many fields of view being scanned by FM as by conventional microscopy in the same period (Getahun *et al.* 2007). These results indicate that FM could have a major role to play in TB diagnosis in the near future. However, certain factors still threaten the implementation of FM in resource constrained settings. These factors include the high cost of fluorescence bulbs, their short lifetime (typically 200–300 hours) and also the need for expensive power supplies. Irregular power supplies in resource-poor settings are also likely to have an impact on the FM bulb life (WHO 2005).

Despite the general feeling that FM cannot be implemented in resources constrained areas, a recent study in Kenya challenges that fluorescence microscopy (FM) used on one or two specimens for the detection of tuberculosis (TB) was more cost-effective than a Ziehl-Neelsen (ZN) approach, (Kivihya-Ndugga *et al.* 2003). The study suggests that the modern method can be implemented at a lower cost than the conventional direct smear microscopy. Particularly, with high numbers of suspects and high prevalence of HIV, the authors recommended the use of FM on two specimens. Furthermore, the method has an advantage that it shortens diagnostic process thus making it more efficient in obtaining test results and may reduce patient costs such as opportunity costs of waiting time.

Sputum liquefaction with subsequent concentration by centrifugation and gravity (natural) sedimentation are the other 2 methods that are being popularly investigated with regard to the role they could play in optimizing smear microscopy. Liquefaction has been performed using solvents such as sodium hydroxide, sodium hypochlorite (household bleach), N-acetyl-L-cysteine-sodium hydroxide solution, and ammonium sulphate (Getahun 2007). According to a WHO expert consultation meeting that was held in 2005, there is moderate evidence supporting the use of centrifugation with various chemical methods. The 14 studies that have investigated the impact of centrifugation with a chemical (using culture as the reference standard) indicated a mean increase in sensitivity of smear microscopy of about 18%. Out of these 14 studies, 13 showed an increase in sensitivity and one study showed a decrease. The evidence base for the use of bleach with centrifugation is also moderate. The studies that were reviewed by Steingart *et al.* (2006) showed that, there was a mean increase of about 15% in sensitivity, with sensitivity ranging from about +1% to about +38%. Despite this, all the studies showed that sensitivity for processed smears was higher than for direct smears. More recently Ängeby *et al.* (2000) and Merid *et al.* (2009) have also reported similar results.

Based on the studies reviewed above, it can be concluded that the available evidence suggests that processing sputum by use of centrifugation and various chemicals, including bleach, increases the sensitivity of microscopy compared with the direct smear method. However, the evidence base supporting the feasibility of implementing bleach centrifugation in low-income settings is still low. Concerns that have been raised with the use of these methods in resource poor settings include:

1. feasibility of centrifugation in settings with irregular power supply;
2. limited human resources to operate the machinery
3. limited financial resources to meet the recurrent cost of centrifuges and the cost of power required to run the machines
4. inadequate training capacity
5. potential biohazard posed by centrifugation of liquefied infectious sputum

Thus, studies that are conducted in such peripheral settings are imperative so as to determine whether this method has a role to play in such settings.

As highlighted earlier, the other sputum processing technique that is currently being explored as a means of optimizing smear microscopy is liquefaction of sputum with subsequent concentration using natural sedimentation. However, the existing evidence base for processing sputum using natural sedimentation is still weak. A total of 8 studies (four using overnight sedimentation and four using short sedimentation times of 30–45min) investigated the effect of sedimentation with a variety of chemical agents, usually either bleach or ammonium sulphate (Steingart *et al*. 2007). These studies used culture as the reference standard. The findings of these studies indicated that, the mean increase in sensitivity was 23% (median 28%; range 2–34%) in studies using overnight long sedimentation, whilst the studies which used short sedimentation times reported average increases that were more modest at 9% (median 1%; range 0–36%).

The four large studies that investigated natural sedimentation with bleach (using culture as standard), found out that this technique increased the sensitivity of smear by about 33%. However, this result was only specific to the 1 study that had used long sedimentation times. The other 3 studies, that used short sedimentation times reported no or minimal increases in sensitivity (0%, 0%, and 1%). A more recent study by Merid *et al.* (2009) which investigated bleach sedimentation using shorter and longer sedimentation times found out that sensitivity was higher with BS (regardless of sedimentation times) than with direct smear microscopy. Similar to the findings of the other studies, overnight sedimentation increased the sensitivity of the sputum smear compared to short sedimentation time. However, this increase in sensitivity was lower than that reported in the 4 studies, possibly because of the differences in protocols followed.

The problems that can be identified in these studies is lack of standardization of procedures used in the studies. The studies differ in terms of the concentration of bleach or volume of distilled water used. For example, a study by Miorner *et al.* (1996) used 5% of sodium hypochlorite; 8ml of distilled water was added whilst a study by Gebre *et al.* (1995) used 4.4% of sodium hypochlorite, 6ml of distilled water. Such differences in concentration levels have been found to affect smear results. A higher concentration is associated with poor smear outcomes. A study done in Kenya with 232 smear specimen, after adding a step where 3.5% (sodium hypochlorite) was added to specimen and allowed to sediment overnight, Zielhl-Neelsen staining achieved a sensitivity approaching that of culture (27.1% were positive versus 29.3% that were culture positive) (Smart 2007). However adding too high concentration (5% NaOCl) reduced sensitivity (Smart 2007). Thus, it can be observed that lack of standardization could explain inconsistencies in different reported smear results. A recent study by Bonnet *et al* (2008) which used more standardized procedures in fact showed a substantial increase in sensitivity of bleach sedimentation.

The second problem deals with the manner in which smears were allocated to different techniques. In a study by Merid *et al.* (2009), TB suspects were requested to submit three sputum smears from which routine direct smears were prepared. The remaining sputum samples from the first spot, morning and second spot collection were pooled into one cup from which direct smear was prepared. Part of the pooled sample was concentrated using sodium hypochlorite (NaOCl) and the divided into three specimen for short term sedimentation, long term sedimentation and centrifugation technique. On the other hand, a study by Lawson *et al.* (2006) used a different methodology. TB suspects were requested to submit a set of three sputum samples (first on-the-spot, early morning and on-the-spot). A routine diagnostic was performed on each of the specimen. Subsequently, one of three samples was randomised for digestive technique by adding household bleach (NaOCl) for sedimentation procedure. A second randomly selected sample was used for mycobacterium culture. The two studies clearly show differences in allocation of smears to the techniques. Such inconsistent patterns contribute to discrepancies in results.

However, a pattern regarding standardisation that seems to be coming up has had an impact on consistency of results. A study by Bonnet *et al.* (2008a) obtained significantly higher results for bleach treated specimen than direct smear microscopy. The standardised procedure permits a more universal diagnostic procedure for concentrated sputum processing techniques.

Given the current evidence from studies using sedimentation and a variety of chemicals and the specific advantages of avoiding a centrifugation step, the overnight sedimentation approach with bleach and other chemicals seem to be promising processing methods that could be more feasibly implemented in resource poor settings. Also, the fact that bleach is universally accessible at an affordable cost, gives hope that BS could even be more cost-effective than direct smear microscopy. However, evidence on cost-effectiveness analysis (CEA) of BS still needs to be established. Other concerns that merit further investigation include the fact that BS with longer sedimentation times would require that patients come to the health facilities at least twice more on 2 consecutive days (Merid *et al*. 2009). This may result in increased drop-out from the diagnostic process, particularly among those patients who have travelled long distances and/or who have few resources (Merid *et al*. 2009). Such concerns warrant further investigation of use of shorter sedimentation times before prematurely disregarding the applicability of this approach.

The next section presents empirical evidence on the CEA of the different sputum processing techniques. Cost-effectiveness analysis is crucial given the costs and complexity of introducing a new diagnostic method. The latter inevitably prompts Ministries of Health and technical agencies that support them to want solid data illustrating the benefits of new methods (Ramsay *et al*. 2006). Policy makers also need to know if the new methods can be effectively implemented and sustained under certain budgetary constraints.

2.3 Cost-effectiveness analysis

A search in different databases, which included PUBMED, EBSCO HOST, and some direct search from Google scholar, yielded only one cost effectiveness study that was conducted in a peripheral clinic of Kenya; a country in which 50% of individuals with tuberculosis are infected with HIV (Bonnet *et al.* 2008b). This study measured and compared the incremental cost per smear positive (SP) detected case of 10 different approaches; combining direct and/or bleach smear to diagnose TB. Overnight sedimentation was the approach used for the bleach sedimentation. Some of the combinations that were investigated include;

(i) Direct smear on first specimen and direct smear on second specimen if the first specimen was negative. This was the standard.

(ii) Bleach smear on first specimen

(iii) Bleach smear on first specimen and bleach smear on second specimen if first specimen was negative.

A decision analytical model was used to determine the approaches which were more cost-effective. Based on this model, the best and most cost effective approaches were to carry out option (ii) and option (iii) above. Other alternative approaches that were also cost-effective alternatives after excluding option (ii) and (iii) above included using direct smear on first specimen and bleach smear on second specimen if first specimen was negative. However, a major limitation of this alternative was the fact that patients would only receive their results on the third day, thus delaying TB diagnosis. Direct smear on first specimen and bleach smear on first specimen if the first smear was negative, was also another approach that was considered a good alternative. However, this approach requires good specimen collection.

One issue with the study by Bonnet *at al.* (2008) described above was the use of the incremental cost effectiveness ratio (ICER). The ICER represents the additional cost of gaining one unit of outcome by a health care intervention when compared to the next best alternative in mutually exclusive interventions (Shiell *et al*. 2002). However, the ICER tends to be sensitive to small changes in average costs or efficacy. A small change in costs or effectiveness can result into large changes in ICER regardless of there being no statistical differences in costs and efficacy between the study groups (Gan and Lubarsky 1999). In addition, a negative ICER may not provide meaningful values thus interpretation of ICER becomes generally difficult for policy makers to understand. On the other hand, average cost effectiveness ratio is more policy oriented. The format in which results are presented is similar to how budgets are formulated and allocated to various health interventions and as such policy makers find it easier to understand. Average costs are also preferred because of their ability to remain stable over a longer period thus suitable for long term planning. Average, like the marginal costs may only diverge substantially within a short period of time usually one year but also when fixed costs are high (Sinanovic and Kumaranayake 2006).

The correct assessment of effectiveness is also essential. Bonnet *et al.* (2008b) used number of smear positive cases detected. This measure is perhaps the most relevant measure to use for measuring effectiveness of a method used to diagnose pulmonary TB. The importance of examining sputum is to ensure that patients with pulmonary tuberculosis are identified promptly and treated immediately before the disease can spread to close contacts. Since pulmonary tuberculosis is the most infectious type of TB it is critical that the disease be detected in the early stages so that it poses less threat to public health. An intervention that detects more of such cases would be the preferred intervention. An assessment of effectiveness would thus be how well new methods detect number of smear positive cases.

Costs included in an economic evaluation are very critical not only because they affect the cost effectiveness ratio but also the interpretation of the cost effectiveness ratio. Direct costs are the most relevant since they reflect the cost of establishing or running the intervention. In their study, Bonnet *et al.* (2008b) used health service direct costs, which also included labour cost, consumables and some patient's transport cost estimates. A wider view of costs can be achieved by apportioning some of the fixed costs of facilities and administration to the costs of the service (Jamison *et al.* 2006). However, the researchers did not state whether capital costs were included and if they were included how they were apportioned to the intervention. In other studies, researchers have included opportunity costs such as the value of time patients and family members spend accessing health care, which is the loss in productivity. In addition, they also include transport costs to health facility. Jamison *et al.* (2006) argue that when cost-effectiveness analysis includes more costs, the cost per unit of health gain appears to be higher and the intervention will appear to be less cost-effective. On the other hand, when too few costs are included, the cost per unit of health gain will be lower indicating that the intervention is highly cost-effective when actually may not be the case.

2.4 Other studies on cost-effectiveness

A study by Dowdy *et al.* (2003) looked at the cost-effectiveness of the Gen-Probe amplified mycobacterium tuberculosis direct test as used routinely on smear-positive respiratory specimens. The study used decision analysis approach to evaluate the cost-effectiveness of programs in which the amplified mycobacterium tuberculosis direct test (MTD) (Gen-Probe) was compared to standard of care (no MTD). To determine validity of MTD test, culture was used as gold standard and number of early TB exclusion measured cost effectiveness, where early TB exclusion referred to number of tests with negative TB results (true negatives). Smear positive results were assumed culture positive for mycobacterium tuberculosis. The marginal cost of MTD test was US $330 per smear positive patient or US $494 per early exclusion of tuberculosis based on negative MTD results. The analysis also included costs of respiratory isolation and cost of drugs. MTD test was found not to be cost effective, however, in centralized laboratory MTD test was regarded as cost saving since large number of patients are treated per day. Like any other test, MTD test is not 100% efficient and this raised issues of false negatives where the test wrongly identifies a patient free of tuberculosis. Regardless of this, the benefits of

MTD test are greater especially considering that culture results may take long to be available.

The study by Dowdy *et al.* (2003) used two effectiveness measures. They assessed effectiveness by number of smear positive case detected and also smear negative specimen. Many studies assess effectiveness by number of smear positive result (Dowdy *et al.* 2008, Walker *et al.* 2000). Conversely, Dowdy *et al.* (2003) used the Amplified Mycobacterium Tuberculosis Direct (MTD) test, which is an enhanced version, approved to be used in smear negative specimen. This permitted use of smear negative as an appropriate measure of effectiveness. In comparison to this study, the methods assessed were mainly designed to test smear positive TB cases; consequently, it was appropriate to measure effectiveness by smear positive TB cases detected.

Another observation is that this study did not take into account HIV status of the patients being tested. HIV status is a major risk factor for TB and effectiveness of tests may be influenced by patient's HIV status where results of HIV positive patients may be statistically different from HIV negative patients. The study used a wider view of costs where capital costs were apportioned to the techniques being investigated (Jamison *et al.* 2006). Costs of drugs were estimated from central unit, which was also a major source of drugs in their country. Sourcing drugs from one major supplier ensures that there is less variability in costs. In addition, major suppliers reflect the true market value of the drugs. Unlike, where there are several suppliers, prices of drugs may vary from one supplier to another, more especially where prices of drugs and diagnostic materials are not regulated. There would be major differences as a result costing may not reflect what really health facilities incur to provide health care.

A related study by van Cleeff *et al.* (2005) compared the cost-effectiveness of the routine diagnostic pathway using Ziehl-Neelsen (ZN) sputum microscopy followed by Chest X-Ray (CXR) if case of negative sputum result (ZN followed by CXR) with an alternative pathway using CXR as a screening tool (CXR followed by ZN). The study enrolled 1389 suspects, among these 998 (72%) were enrolled for smear microscopy, culture and Chest X-Ray. Culture was used as gold standard. The study used laboratory costs and Chest x-rays costs. Effectiveness was determined by the number of correctly diagnosed tests. The study found that the cost per correctly diagnosed case for the routine process was US $8.72, compared to US $9.27 using CXR as screening tool. Chest X-ray followed by Ziehl-Neelsen (ZN) sputum microscopy was more cost effective when costs of treatment were included otherwise excluding cost of treatment it is more cost effective to carry out ZN test followed by chest X-rays. Although chest X-ray has high sensitivity, they cannot distinguish between smear positive and smear negative patients making it difficult to determine infectious patients.

2.5 Economic evaluation studies on TB in Malawi

Malawi has limited record of economic evaluation studies on TB. Most of the studies done focused on equity and access to TB services. This subsequent section reviews one study that focussed on efficacy and another on cost effectiveness of TB interventions.

A study by Hargreaves *et al.* (2001) investigated treatment outcomes of the cohort of smear-negative pulmonary TB (snPTB) patients in an area of high human immunodeficiency virus (HIV) seroprevalence. Patients about to be registered for snPTB treatment underwent further assessment including TB culture and followed up for 8 months. The results showed that of the 352 snPTB patients assessed, 137 patients had bacteriologically confirmed TB. Death rate for non-TB case was 53%. The results suggest two things that can simultaneously be addressed by rigorous diagnosis of TB. Firstly, results suggest that there are more smear negative TB patients who are mistakenly given TB treatment resulting into poor outcomes. Secondly, in HIV positive individuals pulmonary TB is difficult to detect owing to low level of mycobacteria in HIV infected patients. This may enhance the spread of pulmonary TB to close contacts. A report by World Health Organisation (2007b) indicates that one untreated pulmonary TB case can infect 10-15 people per year. Thus, it is increasingly important to explore different ways of improving the diagnostic yield so that more TB patients are identified and put on treatment within shortest possible period. This will then reduce transmission rates and improve treatment outcomes.

Another study done in Malawi by Floyd *et al.* (2003) assessed the cost effectiveness of new treatment strategies for new pulmonary tuberculosis patients introduced in 1997. The first strategy was the strategy used until the end of October 1997 which involved two months of hospitalization at the beginning of treatment. The second strategy was the new decentralized strategy introduced in November 1997 where patients were given the choice of in or out-patient care during the two months of treatment. The two strategies compared were; one that did not require any direct observation of treatment (DOT) and the new community based strategy introduced in November 1997 which required DOT by a guardian who could either be a general community member volunteering to work or health worker. The guardian was needed for the first two months of treatment. Costs were analyzed using three perspectives namely; health services, patients, and the community in 1998 (US$), using standard methods. Cost effectiveness was calculated as the cost per patient cured and the cost per patient completing treatment.

Results indicated that for new smear positive patients, the cost per patient treated was US $456 with the conventional hospital based strategy and US $106 with the new decentralized strategy. The costs fell by 54% for health services and 58% for patients. The cost per patient cured was US $787 for the conventional hospital based strategy, and US $296 for decentralized treatment. The new method was more cost effective than the conventional hospital based. However, the results have a limitation of selection bias since patients were given a choice as to whether to stay in the hospital or be an outpatient. The severity of the disease might have influenced choice of patients; as such, patients recruited for each strategy might have been significantly different between the strategies. Those who are sicker might have chosen to take the hospital option and less sick opting for home based treatment. This would affect the effectiveness of intervention sites in which case home based care may appear to be more effective than hospital based. In addition, given that sicker patients chose a hospital option, such patients are likely to incur more costs due to travelling than home based care and this would make hospital treatment less cost effective. Random allocation would have been the ideal criteria. Perhaps ethical issues associated with patient's rights restricted random allocation of patients to different strategies.

The challenge after identifying cost-effective intervention is to address concerns for an equitable distribution of health and health care. Major issues to consider include target population, people who may benefit from health interventions but also who will bear the costs involved. The next section will look at the resource allocation.

2.6 Resource Allocation

Managers and policy makers usually encounter challenges in making decisions regarding allocation of resources in health care. Resource allocation (human and financial) to health interventions is often faced by multiple criteria such as budget constraints. Financial and human resources are always scarce to meet the demand. With regard to concentration techniques for Tuberculosis, challenges associated with centrifugation may impact heavily on health resources. Assuming the technique has been implemented, it may require that clinical officers and laboratory technicians dedicate more time to the new technique. This might involve shifting their attention from other interventions. In a setting where skilled health workers are very few, it may further strain the health sector resources.

Other than time, the technique may also involve a number of additional financial costs such as cost of reagents. Centrifugation technique requires more diagnostic materials than direct smear microscopy which also increases the volume of materials to be purchased for the health facility. Other costs include; cost of purchase and maintenance of centrifuge;

more especially in Malawi where majority of health facilities do not have centrifuges, cost of training since most of the personnel may not be conversant with the new technique. Notably, most of the costs highlighted are not currently part of the costs in health facilities as such implementing such a method may involve shifting resources from other interventions to the new diagnostic method. Other health interventions may suffer because of such re-allocation.

Similarly, with bleach sedimentation, unlike short sedimentation time, long sedimentation time may require additional time for laboratory technicians thus demanding an extra cost on the available resources. This might be at the expense of other health interventions. With many health interventions against limited resources, improvements in population health require not mere identification of what intervention works but also what works at least possible cost or what is cost effective (McDaid *et al.* 2003). Such useful information can be obtained from a cost effectiveness analysis.

A cost effectiveness analysis also provides budgetary information on resources needed to roll out the program where the program is new. In addition, resource needed to expand the intervention to other districts or areas of the country; it also assesses the likely sustainability of the project/program over time since costs are monitored over time (Jamison *et al.* 2006). Such information is crucial for policy makers and is also more relevant for long term planning.

However, resource allocation may not necessarily involve taking resource from one intervention to the new intervention. It may also involve re-allocating resources within the intervention. This will entail reallocating resources from less productive areas of the intervention. This promotes optimal use and delivery of the health intervention ensuring that there is no waste of resources (Hutubessy *et al*. 2003).

In addition, a cost effectiveness analysis helps to identify ways of reallocating resources to achieve more. It demonstrates not only the utility of allocating more resources from ineffective to effective intervention but also the utility of allocating resources from less to cost effective interventions. For example, National Center for Policy Analysis at Harvard University demonstrated that the number of life years saved could be doubled if resources were allocated to more cost effective interventions (Jamison *et al.* 2006).

Internationally, cost effectiveness information has been used to identify disease control priorities in developing countries and essential health package (EHP) priorities. The EHP comprise of interventions that are feasible, cost effective (based on international data) and affordable (Ministry of Health 2002) but also those that have greater impact to reduce health burden of the population. In some countries, not only has economic evaluation helped to identify diseases priorities but has also become a requirement for public sector funding (Raftery 1998). For example, in Australia, pharmaceutical reimbursements are based on cost effectiveness analysis (IMS 2006). Such requirements ensure that public resources are effectively and efficiently used.

In addition, many countries and organizations have demonstrated that cost effectiveness information can be used alongside other information to aid policy decision making (Hutubessy *et al.* 2003). Notably, when a cost effectiveness analysis has been applied appropriately and broadly to all social conditions and programs that significantly influence health, it may support use of resources that influence determinants of health (Dan and Daniel 2006). These determinants of health largely affect incidence of disease, disability and premature mortality, in which case, determinants of health can be targeted to reduce incidence of disease in the country.

While cost effectiveness approach to resource allocation ensures maximum benefits for the given resources, in real life, rather than allocating all resources to cost effective intervention, equity concerns need to be addressed. This is especially more relevant in developing economies where resources are extremely scarce. Ignoring equity might put other individuals at risk of life threatening health needs. Some authors have argued that allocation of resources using cost effectiveness analysis entails that resources be directed towards interventions that give more health gains. This ascribes a higher priority to those interventions which can cheaply or easily be provided (Dan and Daniel 2006). Those with health needs that require relatively more resources will lose out because their problem requires more resources and providing resources to their health problem will produce less health gains. For example, consider the hypothetical situation whereby 10 tablets are available for treating an ailment. In one case, there are five patients who need two tablets each to be cured. There is also another set of ten patients who need one each of the same tablets to be cured. Following a cost effectiveness analysis of resource allocation implies that maximum benefit will be achieved if only you serve the tablets to those who require one tablet only. However, such allocation will be very unfair to those who require two tablets to be cured. In such a case, a fair treatment would be a random way of giving treatment, which will ensure that patients have equal chances of getting treatment and being cured from the ailment.

Nonetheless, a cost effectiveness analysis helps to identify the most deserving intervention and setting priorities on which interventions should be given more attention especially with budgetary constraints. In a resource-poor setting, it has become pertinent that health economic evaluations become part of the decision-making process for policy-makers (Gold *et al.* 1996; Drummond *et al*. 2005). Medical interventions are not only required to be effective, they also need to maximize efficiency and make a favourable comparison with competing interventions (Drummond *et al.* 2005). There is a knowledge gap on the cost effectiveness of the new approaches to analyzing sputum, particularly relevant to a developing country context where tuberculosis is highly prevalent and resources are constrained. In an environment where resources are scarce it becomes increasingly important to critically evaluate different options.

2.7 Conceptual framework

There are different forms of economic evaluations namely; cost minimization analysis, cost utility analysis, cost benefit analysis, and cost effectiveness analysis. The subsequent sections briefly explain each form of economic evaluation.

Cost minimization analysis

This is the simplest form of economic evaluation. The evaluation assumes that the outcome measure of the two or more comparators is equal; as such comparison is solely based on differences in costs (Shiell *et al.* 2002). The focus is to identify the least cost method.

Cost effectiveness analysis

Cost effectiveness analysis is a measure of economic evaluation that compares costs and outcomes of an intervention. This form of economic evaluation is mainly used where the interventions do not produce the same outcome (Robinson 1993). The method assumes that the interventions being investigated have different effectiveness. Outcomes are measured in single dimensional and measured in natural occurring units. For example, in assessing treatment options for tuberculosis, outcomes would be measured as number of TB patients cured.

A lower cost effectiveness ratio is preferred because the alternative can produce more health benefits at a lower cost than the other. In a situation where an option is more costly and more effective than the current method, the incremental cost effectiveness ratio, a measure of cost per additional gain in outcome measure is used. Assessment is based on value judgment on whether the outcome is worth the additional cost (Shiell *et al.* 2002).

A cost effectiveness analysis requires correct measures of costs and outcomes. Measures of costs include the scope of costs. This varies from one program or intervention to another.

Cost utility analysis

This method enables broader comparison than cost minimization and cost effectiveness analysis. This method measures costs in monetary terms and outcomes in generic terms. These generic measurements include quality adjusted life year (QALYs), disability adjusted life years (DALYs) or health years equivalents (HYEs). Cost per unit output is derived as cost per QALY gained or cost per DALY lost. It allows assessment of both mortality and morbidity for a given intervention.

Cost-benefit analysis

This is an economic evaluation that enables broader comparison between alternative claims on societal resources (Shiell *et al*. 2002). It primarily addresses issues of allocative efficiency. The method values both costs and outcomes in monetary terms. It is rarely used because of the difficulty associated with valuation in monetary terms of intangible costs and benefits. Nevertheless, a cost benefit framework analysis is still useful because the impacts on costs and benefits can be presented in a balance sheet to highlight where trade-offs can be made.

2.7.1 Types of costs

Type and scope of costs depends on the perspective that a cost effectiveness analysis is taking. A provider perspective will only consider costs that are borne by the provider or the health facility. A wider view of costs takes into account a societal cost in which case the analysis values all costs incurred by patients, provider and the society. In particular societal perspective considers the following costs;

Cost incurred by health facility.

These include the time personnel spent in diagnosing TB which is valued by their monthly package; Maintenance cost of equipments, rent or cost of building; Operating costs such as costs of electricity, water and telephone.

Costs incurred by patient

These include transport costs to the health facility, food costs, opportunity cost of time lost due to illness, cost of user fees such as consultation, diagnostic, hospitalization and any other fee a patient pays to access health care.

2.7.2 Measurement of costs

Perspective of economic evaluation informs the scope of costs that have to be measured for an intervention. The most relevant are direct costs. These costs are valued at market prices. Essentially, valuing costs at market prices reflects the opportunity cost of using the input (Drummond *et al.* 2005). For example, laboratory personnel time can be measured by their remuneration package. Other direct costs such as diagnostic materials can be obtained from the major supplier.

On the other hand, capital costs are valued slightly different. Capital costs do not only reflect opportunity cost of tying resources to equipment but also returns for the investment. As such, the measurement incorporates interest rates reflecting returns from an investment. In addition, as the capital item is being used the value decreases since the capital item wears off, thus the cost measurement also includes depreciation. To capture this, the capital item is annualized at a given interest rate and an annual cost of equipment is determined.

2.7.3 Allocation of shared costs

Shared costs refer to those costs used by different programs in an organization. A staff member may be engaged in different interventions. For example, a lab technician may be involved in carrying out malaria tests, TB tests and HIV tests. In such cases, it becomes necessary to measure their time for the particular intervention under investigation, which in this study would be tuberculosis. The best criterion to assess time dedicated to an intervention is to actually record time personnel spend working on TB tests and determine the percentage of time dedicated to the intervention. Interviews with staff members involved also provide a reliable estimate.

Shared costs also include capital items, which are used for other methods. Some capital items are allocated directly to cost centres while others use percentage of staff time dedicated to the intervention.

2.7.4 Determining effectiveness

Effectiveness is the measure of how well the method works. In TB management, several effectiveness measures have been used. Some studies have used conventional measures such as QALYs or DALYs while other studies have used natural units. For example, interventions aimed at measuring treatment outcomes have used number of TB cases cured. There are other interventions aimed at improving diagnostic yield. These also use natural units such as number of cases detected by each method.

2.7.5 Source of effectiveness data

Source of effectiveness data is critical for economic evaluations. The best source of effectiveness data for economic evaluation is a randomized control trial (RCT) (Drummond *et al.* 2005). Other than RCTs, effectiveness data can also be sourced from non-randomized studies, cohort studies, case control studies and in extreme cases expert opinion. RCTs are preferred because they are less prone to selection bias since subjects are assigned randomly to intervention methods.

2.7.6 Sensitivity Analysis

Sensitivity analysis is a method of assessing uncertainty in economic evaluations. The analysis assesses robustness of the results by varying values of key variables across possible range. There are three major types of sensitivity analyses.

Simple sensitivity analysis

This varies one or more component of the evaluation across a possible range. The analysis can be one –way where one variable is changed at a time and the effects of varying the variable on the outcome observed. The sensitivity analysis can also be multi-way where more than two variables are changed simultaneously and effects of the change are observed.

Monte Carlo Simulation

This allows analysts to specify multiple ranges of values using computer-modelling software. Values are randomly selected by computer software from a specified distribution of variables. The method has an advantage of being able to deal with a large number of variables but also creates confidence intervals around the mean based on the selected range.

Threshold sensitivity analysis

A form of sensitivity analysis which uses the best case and the worst case approach. If two methods are being compared, the comparison is based on two extreme estimates; the lowest cost and highest benefits (best case) are compared to highest cost and lowest benefit (worse case).

Using sensitivity analysis, results of economic evaluation can be reported with certainty. Results are robust if changes in major epidemiological or economic variables do not significantly change mean cost effectiveness ratio.

2.8 Summary of literature review

This chapter reviewed literature that is relevant for this study. Literature on the effectiveness of different methods for diagnosing tuberculosis, compared with direct smear microscopy (DSM) was reviewed. These methods include: Polymerase Chain Reaction (PCR), Fluorescence Microscopy (FM) and sputum liquefaction followed by bleach sedimentation (BS) and bleach centrifugation (BS). Polymerase Chain Reaction and FM, though more specific than DSM, tend to be more expensive and hence less suitable for use in resource constrained settings. However, recent evidence on FM challenges this, and suggests that FM could have a role to play in resource poor settings. Nonetheless, the evidence base supporting this finding is still low.

Several studies have supported effectiveness of natural sedimentation and centrifugation techniques with bleach. With regard to natural sedimentation, the majority of studies have supported longer sedimentation time than shorter ones. Still more, some studies have found that there is no significant difference in effectiveness when short or longer (overnight) sedimentation time is used. The fact that household bleach is readily available at an affordable cost also implies that bleach processing methods could be implemented successfully in resource poor settings. Nonetheless, certain concerns such as the limited financial resources to meet the recurrent cost of centrifuges and the cost of power required to run the machines still remain challenges that could hinder effective implementation of bleach centrifugation methods in resource poor settings. In addition, there seems to be very limited research on the cost-effectiveness analysis of these methods. However, one cost effectiveness analysis study that compared natural sedimentation and direct smear microscopy concluded that there is economic gain in using natural sedimentation than direct smear microscopy. This study therefore indicates that bleach sedimentation is a promising approach of diagnosing TB in resource constrained settings.

In a world of scarce resources, priorities have to be set on how resources should be allocated. The ideal situation is to allocate resources to interventions that give maximum benefits at least cost. An economic evaluation technique helps to inform this process. Even so, equity concerns still need to be considered when economic evaluation is being used as a resource allocation tool.

This chapter concluded with a review of the principles of economic evaluation, different forms of economic evaluation and types of costs that are included in CEA and how they are measured. The different sources of effectiveness data as well as the different ways of measuring effectiveness in economic evaluation studies were also discussed.

CHAPTER 3

METHODOLOGY

3.1 Introduction

The chapter presents the methods used in the study. These include the study setting, type of data utilized in the study, the perspective of economic evaluation, the measure of cost effectiveness, and sensitivity analysis used in the study.

3.2 Study site

The study sites include Bwaila Hospital and Malawi-Liverpool Welcome Trust. Bwaila is a tertiary hospital, situated in the capital city of Malawi-Lilongwe. It is primarily a TB hospital. It has bed capacity of 220 and serves a population of approximately 200 000. On the other hand, Malawi-Liverpool Welcome trust is a research centre situated in Blantyre, which is approximately 400 km away from Bwaila hospital.

3.3 Choice of study sites

Bwaila hospital was chosen as recruitment centre because it registers highest number of TB patients and is the main TB referral hospitals in Lilongwe-Malawi. Due to inadequacy of diagnostic equipment especially centrifuge for centrifugation technique, actual process of specimen for this study was done at Malawi-Liverpool Welcome Trust (MLW).

3.4 Perspective of the study

This study adopted a provider's perspective. Costs were estimated in 2008 Malawi Kwacha (MK) and then converted to United States dollars (US$) using the exchange rate of 2008. Outcomes were measured in terms of number of patients treated for TB and number of smear positive patients.

Tuberculosis suspects (people who cough for at least 3 weeks) submit three specimen of sputum as recommended by Malawi National Tuberculosis Control Program (MoH 2007). The three specimens from one patient were randomized to the three arms under investigation. To determine the validity of the test, culture was used as a gold standard.

3.5 Description of alternatives

Initially, sputum was analyzed using direct smear microscopy and, after smear positives and negatives were identified, samples, both smear positives and negatives, were randomly selected and tested using each of the three competing techniques. Laboratory technicians involved in the study were blinded on which specimens were smear negatives or smear positive. These techniques used in the study are described below;

3.5.1 Bleach centrifugation

Part of the specimen remaining from the direct smear microscopy was transferred from a wide mouth collection container into a sterile, 30ml universal container. An equal volume of freshly prepared (prepared same day) 3.5 % sodium hypochlorite solution was used to rinse out the wide mouthed container and added to the sputum in the sterile, 30ml universal container. The mixture was shaken by hand for 30 minutes during which it was shaken for approximately 7 times (at the start, after approximately every 5 minutes, and at the end of incubation). Up to an equal volume of sterile distilled water was added to the mixture. The mixture was then mixed by inversion several times and spun using a centrifuge at 3000 revolutions for 15 minutes. The supernatant was decanted and 2 smears, each containing 10ul of deposit, were made using sterile plastic calibrated loops. Slides were marked with a diamond marker to delineate the site of the material for microscopy. One smear was heat-fixed, stained using ZN (as described above) and examined for AFB using light microscopy. Positive smears were graded in accordance with the International Union Against Tuberculosis and Lung Diseases (IUATLD) system and all smear results were recorded. The other smear was heat-fixed and archived under appropriate conditions.

3.5.2 Bleach natural sedimentation

An equal amount of freshly prepared 3.5% sodium hypochlorite (NaOCl) solution was added to the remainder of the specimen in the wide-mouthed collection container. The mixture was then shaken by hand for 20 seconds then placed at 45^o to allow sedimentation into the dependent corner of the container and incubated at room temperature for 30-45 minutes. At the end of this time, 2 drops of the sedimentation deposit were transferred from the digested sediment using a 2ml Pastette onto clean glass slides and allowed to air dry. As in centrifugation, slides were marked with a diamond marker to delineate the site of the material for microscopy. One smear was heat-fixed, stained using ZN and examined for AFB using light microscopy. Positive smears were graded in accordance with the International Union Against Tuberculosis and Lung Diseases (IUATLD) system and all smear results were recorded. The other smear was heat-fixed and archived under appropriate conditions.

3.5.3 Culture

To determine the validity of the test, the remaining specimen was tested using culture method, which was the gold standard. A culture positive result is a definite TB case.

The remainder of the specimen was transferred from the wide-mouthed collection container into a sterile, 30ml universal container. An equal volume of freshly prepared 4% sodium hydroxide solution was used to rinse out the wide-mouthed container and added to the sputum in the sterile, 30ml universal container. The mixture was mixed and centrifuged in accordance with the decontamination part of the Malawi Liverpool Welcome-trust TB culture protocol. Two smears, containing 10ul of the deposit were made using a sterile plastic calibrated loop. Slides were marked with a diamond marker to delineate the site of the material for microscopy. One smear was heat-fixed, stained using ZN and examined for AFB using light microscopy. Positive smears were graded in accordance with the International Union Against Tuberculosis and Lung Diseases (IUATLD) system and all smear results recorded. The remaining smear was heat-fixed and archived under appropriate conditions.

3.6 Data required and source of cost data

3.6.1 Provider cost

The analysis required data on annual cost of the personnel which included laboratory technicians, laboratory managers, administrative staff and cleaners, taken from payroll/pay scales based on their time. Other type of data required included cost of diagnostic materials, annual cost of building, annual equipment cost, operating and maintenance costs. This information was collected using two research tools, cost sheet and questionnaire (appendix C and D). A questionnaire was administered to personnel working directly on the intervention while cost sheet was used to record various cost items and determining usage of materials.

Data sources included financial reporting systems, expenditure and procurements records, central medical stores for diagnostic materials, equipment data was obtained from suppliers, cost of building obtained from building contractors and interviews with staff members.

3.7 Costing

Costing was undertaken retrospectively from a provider's perspective. Costs were divided into recurrent and capital. An ingredient-based costing methodology was used where quantities of resources were multiplied by their respective prices to obtain total costs (Sinanovic and Kumaranayake 2006). Table 3.1 gives a summary of methods that were used to identify, measure and value costs.

Table 3.1: Costing Template

Type of Cost	Identification	Measurement		Valuation	
	Categories	***Costing method***	***Source of data***	***Valuation method***	***Source of data***
Recurrent costs					
Personnel	-Administration and laboratory staff (Lab technicians, assistants and managers)	-Documented Staff time on these activities. -Total remuneration package costs. -Other external costs.	-Record reviews - Interviews	Total remuneration package	Provider expenditure reports
Supplies	Stationary, Calibrated loops, universal container, diagnostic materials.	Quantity consumed	Procurement records	Actual costs	Central medical stores/ provider expenditure reports
Building operating and maintenance costs	-Overheads (electricity water and other utilities.). Telephone.-stationary, computer photocopier.	-Actual costs from facility records.	Facility records	Time taken by each of the methods used	Time sheet facility records/ interviews
Capital Costs					
Building	-Laboratory space. -Office space	-Current replacement costs (building cost per m x square meterage of facility -30years life span -3% discount rate for annuitization	Lab technicians/ managers	-Replacement prices -Laboratory space used	-Building and construction contractors.
Equipment	-Furniture, medical equipment (centrifuge and microscope)	Actual replacement costs. -10years life span -3% discount rate for annuitization	Laboratory technicians	-Actual replacement prices. -Time usage.	Central medical stores/local suppliers

3.7.1 Recurrent costs

Recurrent costs included cost of volume of materials used in the study. Recurrent costs in this study include:

a) Personnel (administration and laboratory staff time)

b) Building and equipment operating and maintenance costs (e.g. maintenance of centrifuge, refrigeration costs, etc)

c) Overheads such as water and electricity.

d) Supplies (30ml universal container, sterile plastic calibrated loops, stationary such as diamond marker, pens, paper and storage boxes, and diagnostic materials (sticks, slides, preparation agents, bleach, vikon)

Personnel costs were assessed based on the cost of the full benefits package for the personnel involved. The benefit package included salary, bonus payments, gratuity payments or employer pension contributions, medical aid and any other direct costs of employment.

3.7.2 Capital costs

Capital costs refer to inputs or resources that usually last for more than one year such as buildings and equipment. Capital costs in this study included:

a) Building (laboratory space)

b) Equipment (microscope, centrifuges, bio-safety cabinets, fridge, autoclaving waste and slide drier)

c) Furniture

The study used 30 years as useful life years for laboratory space, 10 years for centrifuge, 5 years for furniture and 10 years for microscope. The study used a discount rate of 3% to annualize capital cost. These capital items were annualized to allow differential timing.

3.7.3 Allocating shared costs

The study had a number of shared costs such as cost of electricity, water, telephone, building furniture and equipment. Allocation to different techniques was based on staff time for a particular technique. The rationale was that we expected equipment to be used for the period during which the personnel involved in the study were working. For example, microscope was in use when laboratory technicians were conducting tests. Similarly, electricity was being used laboratory technicians were working on the specimens.

Initially, number of hours spent by laboratory technicians for each method was estimated. Shared costs were allocated basing on the percentage time spent on the method. For example, if laboratory technicians spent 20% of their time on direct smear microscopy, then 20% of the total cost of electricity was allocated to direct smear microscopy. Similarly, same criteria were applied for natural sedimentation and centrifugation. The staff time used was based on the time of personnel who was actually using the equipment. For example, cost of furniture used by laboratory manager was based on the laboratory manager’s time dedicated to each method.

Costs of some equipment were allocated directly to the relevant method. For example, annual and maintenance costs of a centrifuge were directly allocated to centrifugation technique. Supplies were directly allocated to different techniques.

3.8 Effectiveness

Effectiveness data was obtained from a Randomised controlled trial (RCT) that took place at Bwaila hospital and Liverpool-Welcome Trust in Lilongwe and Blantyre respectively, and the researcher was granted access to the raw data (Chirambo *et al* 2008). Sputum samples for the RCT were selected from the laboratory register of patients who had already submitted sputum as part of the routine diagnosis at Bwaila hospital. A total number of 912 patients' samples sputum samples (spot, early morning and spot) were selected for TB examination. Half of the recruited patients (456) were smear positive patients and were matched with 456 smear negative patients. The selected samples were then transported to Liverpool-Welcome Trust in Blantyre.

The selected samples were then initially examined using direct smear microscopy. The remainder of the specimen (a set of three) from each patient was randomized to centrifugation, natural sedimentation and culture. Smear positive TB patients were validated by culture which was the gold standard. A culture positive result was regarded as a definite tuberculosis case.

Although 912 patients submitted sputum, some samples were lost due to leakage and contamination in transporting specimen to study area. As a result, only 807 patients' samples were analyzed using natural sedimentation, 772 patient's samples using direct smear microscopy and 771 patients' samples were analyzed using centrifugation technique. Furthermore, a complete set of comparable specimen could only be obtained from 652 patient samples. As such, effectiveness analysis could only be performed from the complete set of comparable samples.

Effectiveness was determined by number of smear positive TB cases detected. As discussed in the literature above, the approaches that were used in the RCT are designed to improve diagnostic outcomes for pulmonary TB and it was necessary to use number of smear positive cases detected as a measure of effectiveness.

Based on this data, sensitivity, specificity, and positive and negative predictive values were calculated. Table 3.2 below is a dummy variable indicating presentation of effectiveness results.

Table 3.2: A dummy table for presentation of effectiveness data

	Total number of patients screened for TB	**Smear positive TB patients**	**Sensitivity**	**Specificity**	**Positive predictive values**	**Negative predictive**
Direct Smear microscopy						
Natural Sedimentation						
Centrifugation						

3.9 Cost effectiveness analysis

Cost effectiveness analysis is an economic tool where inputs are measured in monetary terms and outcomes in natural units (Drummond *et al.* 2005). It addresses issues of technical efficiency by evaluating alternative ways of achieving the same objective. The study assessed cost effectiveness using average cost effectiveness ratio where total cost for each method was divided by effectiveness measure. The major outcome measure was the number of smear positive TB patients diagnosed for each method. But the study also calculated average cost per method so in essence two ratios were calculated, firstly, total cost were divided by total number of patients screened for each method. This was basically an average cost. Secondly, total costs were divided by number of smear positive TB patients determined by each method. Unlike marginal costs, the average costs were preferred because of their relevance for national policy (Sinanovic and Kumaranayake 2006).

The study assessed the cost effectiveness by comparing average cost effectiveness ratios as given below.

Average cost effectiveness ratio = Total costs of method A_i/Total number of smear positive detected by A_i

Where A_i is a method of analyzing sputum and í can be direct smear microscopy, natural sedimentation or centrifugation technique.

3.10 Sensitivity Analysis

Sensitivity analysis helps to assess robustness of the findings to changes in key epidemiologic and economic variables (Walker 2001). The study performed two one-way sensitivity analyses. First, varying a percentage of staff time spent on each intervention method. The least possible time spent was assumed to be 25% less of the average staff time spent while longest possible time was assumed to be 50% more of average staff time spent on each method. Secondly, discount rate for annuitization of capital costs was also varied. A discount rate of 3% was used for the study and for purposes of sensitivity analysis, the discount rate was varied between 1% -5% and effects of variations were recorded.

CHAPTER 4

STUDY FINDINGS

4.1 Introduction

This chapter presents study findings. Taking a provider perspective, the chapter gives a summary of the economic costs for each of the methods used for analyzing sputum, namely direct smear microscopy, natural sedimentation and centrifugation techniques. The chapter also gives effectiveness and average cost-effectiveness results. The findings of the sensitivity analyses are presented in the last section.

4.2 Total provider cost

Provider costs were grouped into recurrent costs and capital costs. Recurrent costs include personnel time, supplies (diagnostic materials used), building operating and maintenance costs. Capital costs include building, equipment and furniture. There were no training costs involved in this study. Costs were calculated in Malawi Kwacha (MK) and converted to 2008 United States Dollars (US$).

Total provider costs (table 4.1) ranged from US $7,544 for natural sedimentation, US $12,279 for direct smear microscopy while centrifugation technique had total cost of US $8,859. Total capital costs for natural sedimentation amounted to US $338 while direct smear microscopy incurred US $576 and centrifugation had total capital costs amounting to US $404.

Within methods, the greatest range was recorded for direct smear microscopy at US $6,622 followed by centrifugation technique at US $4,211 and least range being natural sedimentation at US $3,674. Natural sedimentation recorded the least total cost at US $7,544.

Table 4.1: Total provider costs per method (in 2008 US$)

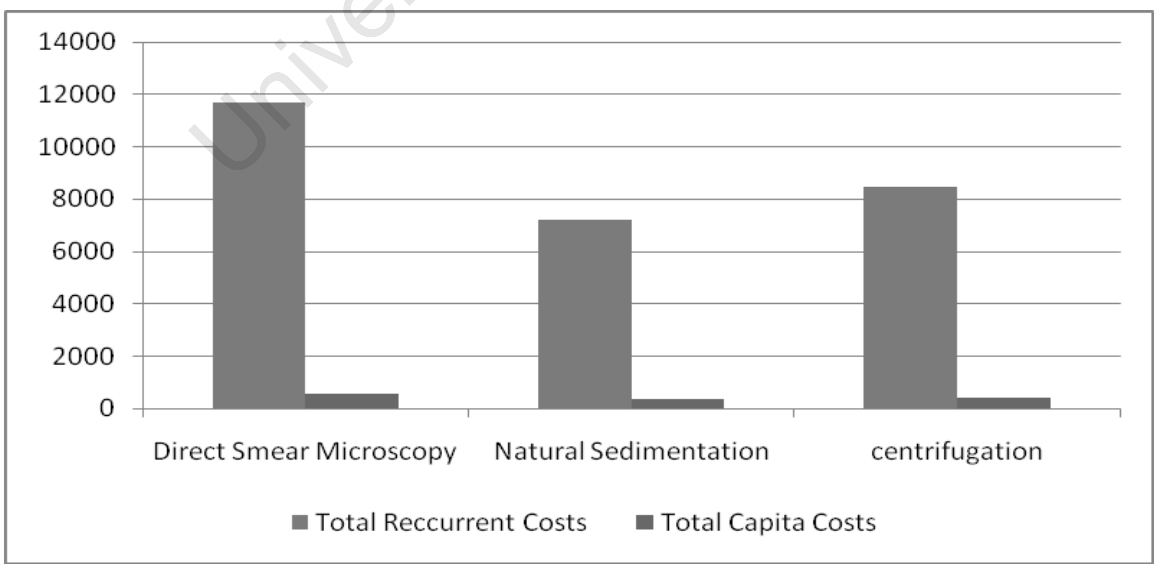
	Direct Smear Microscopy (US$)	**Natural Sedimentation (US$)**	**Centrifugation (US$)**
Recurrent Costs			
Personnel	4,212.94	3,689.80	3,689.80
Supplies (Diagnostic materials)	6,647.90	2,995.23	4,227.70
Building operating and maintenance costs	841.75	520.30	536.67
Total Recurrent Costs	**11,702.58**	**7,205.33**	**8,454.17**
Capita Costs			
Building	25.00	15.71	15.71
Equipment and Furniture	551.78	323.18	389.15
Total Capital Costs	**576.78**	**338.89**	**404.86**
Total Costs	**12,279.37**	**7,544.22**	**8,859.17**

The highest total costs were incurred through direct smear microscopy method at US $12,279. Total cost for centrifugation method was US $8,859 which was 14.84% higher than natural sedimentation. A similar trend in costs was also observed in total recurrent costs; direct smear microscopy incurred highest cost (US $11,702) followed by centrifugation (US $8,454) and finally natural sedimentation with total cost of US $7,205.

Higher costs for direct smear microscopy were constantly observed for each of the cost category (figure 4.1). Highest costs were incurred in supplies and diagnostic materials. Supplies accounted for highest costs in centrifugation and direct smear microscopy while for natural sedimentation, personnel accounted for highest costs. Overall, personnel cost accounted for the second largest cost. Lowest costs were incurred in capital costs with building recording the least costs. Same amount of building costs were observed in natural sedimentation and centrifugation owing to equal time spent in carrying out tests.

The higher cost in supplies for direct smear microscopy reflects the relatively more diagnostic materials required to determine patient's TB status. While natural sedimentation and centrifugation with bleach is equally effective with single specimen from a patient direct smear requires three specimens from a patient (Lawson *et al* 2007). The more specimen needed for diagnosing TB translates to more staff time especially laboratory technician's time, more reagents required and occupying more building space, thus the higher costs for direct smear microscopy.

Figure 4.1 Total recurrent and capital costs (in 2008 US$)



Capital costs were relatively same for all the methods but recurrent costs exhibit a higher variability between the methods. The relatively same capital costs for the methods suggest that the provider cannot make significant savings by using either natural sedimentation or centrifugation. On the other hand, the wide range in recurrent costs suggests a potential target for reducing total costs.

Table 4.2 Percentage of total provider costs of TB diagnosis for each method.

	Direct Smear Microscopy	**Natural Sedimentation**	**Centrifugation**
Recurrent costs			
Personnel	34.31	48.91	41.65
Supplies (diagnostic materials)	54.14	39.70	47.72
Building operating and maintenance costs	6.85	6.90	6.06
Total recurrent costs	**95.30**	**95.51**	**95.43**
Capital Costs			
Building	0.20	0.21	0.18
Equipment and furniture	4.49	4.28	4.39
Total capital costs	**4.70**	**4.49**	**4.57**
Total costs	**100.00**	**100.00**	**100.00**

Results from table 4.2 display a significant variation in proportion of costs across methods. In each of the methods investigated, personnel and supplies accounted for the highest proportion (over 90% of total cost) for TB diagnosis. The high cost of personnel and supplies in direct smear microscopy is attributed to more specimens needed to diagnose TB patients which also translate to more time for laboratory personnel. On the other hand, natural sedimentation and centrifugation require a single specimen; though they require more diagnostic materials such as bleach, virkon disinfectants, carbol fuschin Stain, methlene blue stain, filter paper; these materials are relatively cheap such that their contribution to total cost for a single specimen is relatively lower thus lower proportion to total costs. The major contributors to supplies were costs for Calibrated loop, autoclaving bags, applicator sticks, gloves and pipettes, which were used by all the three methods studied as such for single specimen methods, costs of such materials, were much lower.

Capital costs have least proportion across the methods suggesting low usage of equipment of materials and relatively lower costs of space used. The TB laboratory for this study was relatively small and one major office was used for personnel, which really reduced capital costs. Besides that, specimens were sent in a package once a week to Welcome Trust (study site) which meant two days of week's working days utmost three were mostly utilized for the study.

4.3 Average provider costs per patient diagnosed for pulmonary tuberculosis

Average provider cost, exhibit a high variability between methods (table 4.3), with direct smear microscopy indicating the highest average cost (US $16). The high average cost reflects the higher cost for diagnostic materials and more personnel time need to carry out the tests. Least average cost was incurred in natural sedimentation (US $9) while centrifugation technique (US $12).

The cost for supplies in natural sedimentation was far much lower than half of the cost of supplies for direct smear microscopy (US $4 vs. US $9), reflecting the lower cost of additional materials used in natural sedimentation, such as bleach. Bleach is locally found and very cheap. There is a smaller difference in personnel average cost for direct smear microscopy and natural sedimentation owed to ¾ of an hour as sedimentation period for specimen before they are examined for presence of tuberculosis bacteria. Direct smear microscopy indicates a higher average cost for equipment and furniture than natural sedimentation. The high equipment costs in direct smear microscopy emanates from the longer diagnostic time suggesting that equipments were used for longer time hence higher cost. In addition to that direct smear microscopy requires more specimens which implies more time for equipment which results into higher equipment costs

Table 4.3: Average provider costs of analyzing sputum from recruitment to results recording per patient diagnosed.

	Direct Smear Microscopy	**Natural Sedimentation**	**Centrifugation**
Recurrent costs			
Personnel	5.46	4.57	4.78
Supplies (diagnostic materials)	8.62	3.71	5.48
Building operating and maintenance costs	1.09	0.64	0.70
Total average recurrent costs	**15.18**	**8.93**	**10.95**
Capital costs			
Building	0.03	0.02	0.02
Equipment and furniture	0.72	0.40	0.50
Total average capital costs	**0.75**	**0.42**	**0.52**
Total average costs	**15.93**	**9.35**	**11.48**

The denominator for average costs was based on number of sputum test that were performed by each method. Due to leakage in some specimen, natural sedimentation method was performed on 807 patients while direct smear microscopy had 771 patients and centrifugation technique was performed on 772 patients.

Comparing natural sedimentation and centrifugation technique, table 4.3 indicates that natural sedimentation had lower cost almost in all cost categories. Notably, total personnel costs for both methods were equal, however, natural sedimentation has lower average cost due to slightly more specimen analyzed (807 vs. 771) than centrifugation. There is also a significant difference in average cost for supplies, reflecting slightly more diagnostic materials used (filter paper and Virkon disinfectants) for centrifugation than natural sedimentation. Average cost for equipment is also higher for centrifugation. Unlike natural sedimentation, centrifugation requires use of additional equipment, centrifuge, which rotates at various speeds about a central point and separates liquids of different densities by centrifugal forces. As a result the method has greater costs for equipment than direct smear microscopy.

Table 4.4: Percentage average provider costs of analyzing sputum from submission of specimen to reporting of results, 2008 US$ (% of total).

	Direct Smear Microscopy	Natural Sedimentation	Centrifugation
Recurrent costs			
Personnel	34.27	48.88	41.64
Supplies (diagnostic materials)	54.11	39.68	47.74
Building operating and maintenance costs	6.84	6.84	6.10
Total average recurrent costs	**95.29**	**95.51**	**95.38**
Capital costs			
Building	0.19	0.21	0.17
Equipment and furniture	4.52	4.28	4.36
Total average capital costs	**4.71**	**4.49**	**4.53**
Total average costs	**100.00**	**100.00**	**100.00**

Results from table 4.4 indicate similar trend in output to results in table 4.2 with total recurrent costs accounting for over 95% of total cost across the methods. Building and maintenance costs have similar proportion across the methods, reflecting similar cost for building, operating and maintenance costs of materials. Capital costs also exhibit similar trend and almost same percentage contribution to total average costs within each method.

4.4 Effectiveness

This section presents results of the effectiveness analysis. As indicated in the methodology, data for effectiveness was obtained from a Randomized Controlled trial (RCT). Sensitivity and specificity were obtained from the analysis of the RCT (Chirambo *et al.* 2008). Total number of smear positive cases detected by each method was quantified by a simple descriptive analysis in STATA version 10.

The results (table 4.5) indicate that direct smear microscopy detected 325 smear positive TB patients while natural sedimentation detected the least number of smear positive patients (293) and centrifugation method detected 314 smear positive TB patients. Direct smear microscopy was the most effective than natural sedimentation and centrifugation as indicated by total number of smear positive patients detected. Other studies have reported higher sensitivity and more smear positive cases detected. One possible reason could have been the transferring of specimen from recruitment centre (Lilongwe) to study area in Blantyre. It was observed that during courier of samples almost one third of specimen were contaminated which were not tested. Contamination might have been reduced by carrying out the tests within the same health facility. Nevertheless, the report from the RCT indicates that concentration techniques were more sensitive than direct smear microscopy (Chirambo *et al.* 2008). Natural sedimentation appears to have higher sensitivity (80.90% vs. 74.60%) than centrifugation. However, specificity was higher for centrifugation.

Table 4.5: A summary of patients' outcomes, sensitivity, specificity and total smear positive patients.

Method	Sensitivity	Specificity	Total patients tested	Smear positive patients
Direct Smear Microscopy	-	-	652	325
Natural Sedimentation	80.90%	67.60%	652	293
Centrifugation	74.60%	69.70%	652	314

In addition the report (Chirambo *et al*.2008) indicate that most of the specimens achieved a more positive grade that is from scanty to 2+ and 3+ which confirms that concentration techniques were more sensitive than direct smear microscopy.

4.5 Cost-effectiveness

Taking a provider perspective, results show that the most cost effective method of analyzing sputum is natural sedimentation with average cost effectiveness ratio of US $26 per smear positive patient detected (table 4.6). Natural sedimentation has also reflected higher sensitivity than centrifugation and direct smear microscopy. The least cost effective was direct smear microscopy where the provider incurred the highest cost (US $18). However, this method also identified highest number of smear positive TB cases suggesting that it has highest effectiveness compared to other methods.

Table 4.6: A summary of costs, effectiveness and average cost- effectiveness ratios (Cost in 2008 US$).

	Total Cost (US$)	**Total number of patients**	**Total number of smear positive patients**	**Average cost per patient diagnosed (column 2/column 3)**	**Cost per smear positive patient (column 2/column 4)**
Direct Smear Microscopy	12,279.37	771	325	15.93	37.78
Natural Sedimentation	7,544.22	807	293	9.35	25.75
Centrifugation	8,859.03	772	314	11.48	28.21

4.6 Sensitivity Analysis

Sensitivity analysis shows robust results with cost and cost effectiveness assumptions not sensitive to variation of discount rate (table 4.7). However, these assumptions were sensitive to changes in staff time. For example, natural sedimentation had highest (26.88%) percentage divegence from base case. Despite of the changes in staff time, cost-effectiveness ranking remained the same. Natural sedimentaion technique still remained the most cost effective method, followed by centrifugation.

Table 4.6: A summary of sensitivity analysis.

	Direct Smear Microscopy	Natural Sedimentation	Centrifugation
Alternative estimates of provider costs (Staff time)			
Lower limit 25%less staff time			
% Divergence from base case provider cost estimate	-10.25	-13.34	-11.47
% Divergence from base case provider cost effectiveness estimate	-10.25	-13.40	-11.55
% Divergence from base case provider cost effectiveness estimate per smear +ve patient	-10.24	-13.36	-11.41
Upper limit 50% more staff time			
% Divergence from base case provider cost estimate	18.58	26.84	20.65
% Divergence from base case provider cost effectiveness estimate	18.59	26.88	20.6
% Divergence from base case provider cost effectiveness estimate per smear +ve patient	18.57	26.83	20.67
Discount rate			
Lower limit 1% discount rate			
% Divergence from base case provider cost estimate	-0.69	-0.66	-0.55
% Divergence from base case provider cost effectiveness estimate	-0.69	-0.69	-0.59
% Divergence from base case provider cost effectiveness estimate per smear +ve patient	-0.69	-0.66	-0.53
Upper limit 5% discount rate			
% Divergence from base case provider cost estimate	0.76	0.72	0.81
% Divergence from base case provider cost effectiveness estimate	0.74	0.69	0.81
% Divergence from base case provider cost effectiveness estimate per smear +ve patient	0.74	0.7	0.82

4.7 Summary

The chapter presented costs, effectiveness and cost-effectiveness of direct smear microscopy, natural sedimentation and centrifugation techniques. Natural sedimentation was found to be the most cost effective with least cost though with least number of TB patients detected. It was followed by centrifugation, which is also highly effective. Direct smear microscopy was the least cost effective method owed to large number of specimen needed to diagnose a patient, which increased cost of diagnostic material and the cost of time laboratory technician spend to carry out TB tests. The new methods have shown higher sensitivity.

CHAPTER 5

DISCUSSION

5.1 Introduction

This chapter discusses the main study findings. The chapter highlights merits and demerits of the methods used. It also draws some lessons presented in literature and compares results with some similar studies done in Malawi and other countries.

5.2 Brief summary of study findings.

The cost effectiveness analysis showed that natural sedimentation is the most cost effective method of analyzing sputum and direct smear microscopy the least cost-effective technique of the three techniques evaluated in the study. The total cost of direct smear microscopy is almost twice the total cost of natural sedimentation. Though least cost, natural sedimentation was also the least effective method. The results also indicated that centrifugation technique is more effective than direct smear microscopy.

5.3 Discussion of results

Annually, about 27,500 patients are diagnosed for tuberculosis in Malawi. Based on our findings, this would cost approximately US $438,075 for direct smear microscopy. The same number of patients would approximately cost US $257,125 for natural sedimentation. Comparing total annual cost for direct smear microscopy and natural sedimentation, the method would save about US $180,950 per year reducing the total expenditure for TB diagnosis by almost 41%. Similarly, centrifugation technique would cost US $315,700 saving US $122,375 (28% of cost for direct smear microscopy) per year.

Looking at the macro budget for 2008 and taking an exchange rate of K140.53 to US $1, the annual budget for health sector was about US $224,285,714 (Goodall 2008). The savings made from natural sedimentation would be 0.08% of the total health sector budget. This is a significant amount especially in a country highly dependent on donor funding. Implementing cost effective methods would help reduce budget deficits and reliance on donor funding. Recently, it has been observed that donor funding is dependent on political situation of the country and where the donors are not impressed with government's financial management; they pull out their financial support as evidenced by several African countries which have suffered freezing of donor funding (Linskkey 2009). For example, in Malawi between 2001 and 2003, the government was regarded as highly corrupt and this prompted donor countries to pull out their resources (Tenthani 2002). Another example is the recent situation in Zimbabwe where donors pulled out due to political intolerance and human rights violation. This resulted into a collapse of the health care in public facilities (Linskey 2009). Similar situation has been witnessed in Zambia; Kongo Times of 20th June 2009 reported that health funding was frozen after alleged financial mismanagement. All these examples suggest the disadvantage of heavy reliance on donor funding. In an event where government can effectively use resources within the economy by implementing cost effective methods, reliance on donor funding would be reduced. Besides reducing budget deficits, saved resources would be used to finance other health intervention and further improve population health.

The results of this study are similar to those of a study done in Kenya where a simple decision analytical model was used to look at the cost effectiveness of added value of bleach sedimentation microscopy for TB diagnosis (Bonnet *et al* 2008b). However, their study looked at incremental cost-effectiveness of bleach sedimentation whilst this study focused on average cost effectiveness. Besides that, this study also looked at bleach centrifugation technique. Study results showed that bleach sedimentation on 1st specimen was the most cost effective strategy (US $2 per smear positive case detection rate) followed by bleach smear on 1st specimen and 2nd specimen than direct smear microscopy technique (Bonnet *et al.* 2008b). The findings are similar to this study finding though the cost effectiveness ratio was considerably lower than the cost effectiveness ratio in this study. Their study showed that the best alternative was to carry out direct smear on 1st specimen and bleach smear on second if 1st specimen is negative. But the problem would be that patients would only get the results on a third day which will then increases transportation costs for the patient and delay initiation of treatment assuming the patient is sputum smear positive.

Notably, the highest burden of TB is found in poor countries and within countries the prevalence of TB is higher among the poor (Kemp *et al.* 2007). In Malawi, though TB treatment is free of charge at point of delivery, the poor reported spending 244% of their total monthly income on TB diagnosis, compared with 129% of the non poor (Kemp *et al.* 2007). Most of these expenditures were a result of transport and food while accessing health care as such reducing number of hospital visits through improved diagnosis can reduce economic burden of TB diagnosis for the poorest.

There would also be a decrease in opportunity cost. Most of the TB patients go to health facilities with guardians which means both patient and guardian are not productive at that particular time. If you have more visits there is a greater loss of productivity as is the case with direct smear microscopy. As such, reducing number of visits will fundamentally reduce costs thus making current method more costly over these new techniques.

Bonnet *et al.* (2008b) observed that a second best alternative was to carry out a direct smear on 1st specimen and bleach smear if 1st specimen was negative but this would require collecting a good specimen. A good specimen is regarded as the early morning specimen (van Deun *et al.* 2002). Getting a good morning sputum specimen is essential for AFB test since they are likely to contain bacilli because secretions tend to build up in the airways overnight (Smart 2007) making it a highly efficient specimen for TB diagnosis (van Deun *et al.* 2002). Even in normal TB diagnosis, where three specimens are tested for presence of AFB, a good specimen is still essential for improved sensitivity of the specimen.

Like this study, Bonnet *et al.* (2008b) did not take into account patient's perspective. However, they estimated transport cost that captured some of the patients' costs. In comparison, this study did not take into account patient's costs. Nevertheless, the use of single sputum specimen for same-day result would mean that patients would incur fewer costs in obtaining diagnosis. Normally, patients submit sputum on spot specimen, another evening and morning, which means it takes two days to submit specimen then a third day for collection of results. Such multiple visits would be minimized in centrifugation and sedimentation techniques since a single specimen would be required to determine whether a patient has tuberculosis or not.

This study also suggests that patient's costs would also be the same for bleach sedimentation and techniques since patients will have almost same waiting time and will not need to come back to collect results. Diagnostic time for sedimentation and centrifugation techniques were almost the same so we do not expect to have differences in patient costs between the two methods. Other studies used longer sedimentation time. For example, Bonnet *et al.* (2008b) used overnight sedimentation in which case, we would expect bleach sedimentation technique to have more patient costs than centrifugation due to multiple visits. Longer sedimentation time would also result into more workload for laboratory technicians.

Much as the calculation of cost effectiveness seems to be easy, choices about units of measurements and scope of the costs included alter the numerical results (Jamison *et al.* 2006). This also affects the interpretation of results. This study results show higher cost effectiveness ratio for direct smear microscopy compared to study results of van Cleeff *et* *al.* (2005). They reported a much higher cost effectiveness ratio of US $8.72 compared to this study's US $38.98 for direct smear microscope. Regardless that these studies were done in different settings but the scope of costs used could explain the large difference in cost effectiveness ratios. They used laboratory costs only while in our study we included direct administrative costs. This could have increased the costs in our method hence increasing the cost effectiveness ratio.

5.4 Benefits and constraints of the methods

5.4.1 Natural sedimentation.

Bleach sedimentation could be the most realistic choice to aid the expansion of TB microscopy to the community (Dacombe *et al.* 2006). Besides being cheap, its widely available chemical which makes it suitable to be used in rural health facilities. In addition, it does not require additional equipment to perform a test. Unlike the centrifugation technique, though highly effective, cannot be operational in most of the health facilities. Firstly, because of the need for electricity since most of the rural health facilities do not have reliable electricity which makes centrifugation a nightmare to implement in peripheral laboratory circumstances in Malawi. Secondly, centrifugation also needs special expertise and the risk of infection for using improperly maintained centrifuges may also be a major concern with current shortage of health workers it may not be realistic to implement the method. The Malawi Ministry of Health (2008) reports that in 90 microscopic centers there are 191 laboratory technicians and most of these personnel are concentrated in facilities with huge workload such as central and district hospitals. This suggests that some health facilities have no laboratory technicians as such expanding microscopic centers should commensurate with an increase in health worker, without which may not be realistic.

Although the bleach sedimentation slightly increased sensitivity than direct smear microscopy, it has the intrinsic advantage of disinfecting (Dacombe *et al*. 2006); once sample has been processed it becomes mucoid rendering it less infectious, thus safer, and easier to work with. Making the work safer may remove some of the concerns about employing less skilled workers, which has lately been common in Malawi especially with shortage of health workers. There has been a shift of tasks in such a way that some of the work supposed to be done by doctors was shifted to nurses, some of the work for nurses was shifted to clinicians and finally down the line, work was also shifted to guardians. Though it has lessened the shortage of health worker but the risk of infection involved would be the greatest concern as such strategies that improve safety of worker will increase work morale among the health workers. The results of this study also exhibited a shift of smear results in terms of grading system. It was observed that after adding bleach, both methods showed more specimens shifting from scanty to attaining higher positive grade confirming the assertion by microscopists that adding bleach renders the specimen easier to read (Dacombe *et al.* 2006). Thus reducing time taken to read slides and in the process improving efficiency.

5.4.2 Bleach Centrifugation

Bleach centrifugation is more effective method than direct smear microscopy. It is highly sensitive as evidenced by the number of smear positive patients detected. The ability to determine larger number with a single specimen can be attributed to clearer microscopic field with reduced debris. Like bleach sedimentation, bleach centrifugation has protective effect of disinfecting the specimen thus rendering it less infectious and easy to work with in the laboratory. However, bleach centrifugation is capital intensive. It requires well skilled workers to operate the centrifuge. In addition, cost of purchasing and maintaining the machine may strain the resources for the health sector. The machine also requires steady supply of electricity which makes it suitable to be effectively used in major hospitals such as central, district and Christian Health Association of Malawi (CHAM) hospitals. Implementing centrifugation technique may not be realistic in Malawi’s health sector especially with the current shortage of health workers. Although there are some job shifts as highlighted above, less skilled workers may not easily handle this technique or may compromise quality of work.

The new methods discussed have the potential of not only reducing workload but also improving diagnosis of TB. The WHO 2008 global report estimates that Malawi has approximately 50,000 TB cases annually (WHO 2008). However, only 50% of these cases are identified and treated (Banda 2009). This implies that the remaining 50% potentially transmit the disease to the general population. The consequences of such undiagnosed TB cases include high rates of transmission since TB has a long period of infectiousness. The disease could be passed on to several people. The World Health Organization 2005 fact sheet estimates that one active TB case that is left undetected can potentially infect about 15 people per year (WHO 2005). This means that every year there would be more TB cases in the country which would put pressure on the health sector's human and financial resources. As a result it may be very difficult to control the disease.

5.5 Reliability of the study findings

5.5.1 Use of micro and ingredient based costing

Micro costing is a valuation method in health economics that attempts to measure costs and benefits of the service as accurately as possible (Smith *et al.* 2005). Accurate estimation of costs and effectiveness of the health intervention is the major strength of cost effectiveness analysis (Smith *et al.* 2005). The main focus is high level of precision regarding the delivery of service from which highly specific policies can be drawn. There are three approaches of doing micro costing namely; direct measurement where inputs such as staff time and supply are directly measured to develop a precise cost estimate. The second approach is use of pseudo-bill and finally regression analysis. Pseudo-bill use stored data from government department while regression analysis uses regression technique to estimate cost of services. This study used direct measurement approach and tried to accurately measure cost of materials used so that results are reported with certainty. Micro costing also allows for making interesting extrapolations, which may trigger debates on areas of health care provision. The sampled costs can be extrapolated to national. For example, the expected total expenditure in the health sector could be estimated.

The study analysis also used ingredient costing which works on the same principle of micro costing. Materials used in delivering health care are valued such as time workers spend and actual materials used per patient. The cost of each material per patient is estimated and multiplied by quantity to get the cost of materials used per patient. These approaches support reliability of study results.

5.5.2 Use of data from a randomized controlled trial

Randomized controlled trials are rated the best source of effectiveness data for economic evaluation. Their intrinsic feature of random allocation of specimen to intervention group (Sibbald and Roland 1998) minimized selection bias. Analysis was based on groups as allocated thereby ensuring that differences between groups were by chance alone. Secondly, its ability to deal with ascertainment bias and minimize co-intervention bias by blinding the trialists/ laboratory technician as to which treatment was given to what method until the end of the study (Prescott *et al.* 1999). Bias was also minimized by employing clearly described treatment policies for each method that were followed consistently.

5.6 Limitations of the study

5.6.1 Variability of bleach quality.

Bleach is easily accessible and locally found at a very low cost. However, there are several issues surrounding its use. The optimal storage temperature has not yet been determined which might be a major concern because if the concentration levels change due to temperature, higher concentrated bleach has been associated with poor outcomes. As such, a standardized bleach concentration has to be maintained at all times. Inconsistency in concentration of bleach may result in poor outcomes.

5.6.2 Absence of patient's cost perspective

The study did not take into account patient's perspective. However, with the new sputum processing methods analysis, patients are likely to incur less costs since they will obtain on spot results as such they will not make multiple visits which increases transport, food and opportunity costs patients incur. The new methods will still be more cost effective than currently used direct smear microscopy method. Looking at the diagnostic time between centrifugation and natural sedimentation technique, patients are expected to get results within same time as such we would still expect in overall, natural sedimentation to be more cost effective over centrifugation.

CHAPTER 6

CONCLUSIONS AND POLICY RECOMMENDATIONS

6.1 Study conclusions

Natural sedimentation method is more cost effective than centrifugation and the direct smear microscopy. Diagnosing TB suspects using natural sedimentation would save about 41% of TB diagnosis related costs in form of staff time and diagnostic materials. The saved staff time would be redirected to other interventions. At the same time the shortage of health workers especially laboratory technicians would be lessened. The major concern is the lower effectiveness though the method had the highest sensitivity than centrifugation. This might reduce number of patients detected for TB though lowering costs by almost 41% of diagnosing TB. Regardless of the lower effectiveness, bleach has the potential to reduce transmission especially to those who directly process sputum.

Centrifugation with bleach is more cost effective than direct smear microscopy. It is a best alternative to direct smear microscopy since it detected almost same number of tuberculosis patients. Implying that it is equally effective than the current method but also cost saving. The disadvantage is that it requires special expertise in using centrifuge that makes it not suitable in the Malawi context. In addition, most of the rural hospitals do not have a reliable source of electricity as a result it may not be implemented in most of the peripheral hospitals and health facilities.

Direct smear microscopy was the least effective method. However it detected the highest number of tuberculosis cases. This could be attributed to the use of three specimens in detecting tuberculosis in which case if a morning specimen produced a negative result, the spot might be positive thereby increasing chances of capturing all TB patients.

6.2 Recommendations

There is an urgent need for policy change in implementing cost effective case finding methods for pulmonary tuberculosis in Malawi. Currently, directly smear microscopy is the major case finding for pulmonary tuberculosis where patients submit three sputum specimens to examine presence of mycobacterium for detecting tuberculosis. However, the associated low sensitivity has been a major concern for tuberculosis control. Thus improvements with concentration technique such as centrifugation and sedimentation would be timely and desirable especially now with the high prevalence of HIV/AIDS where case finding for tuberculosis with direct smears microscopy tends to be even difficult.

Tuberculosis related millennium development goals target detection rate of 70% and cure rate of 85% by 2015 (Baltussen *et al*. 2005). Currently there have been some considerable improvements in working towards attaining TB related millennium development goals. With such improvements incorporating strategies that reduce costs such as diagnosing TB by natural sedimentation with bleach may be cost saving and could substantially reduce expenditure on TB diagnosis.

The improved sensitivity reflected in results section imply that the natural sedimentation detect TB in people with lower number of mycobacterium, especially those who are HIV positive. In such patients, TB could be detected promptly and patients put on treatment in their early stages. An improvement in case finding is desirable towards attaining tuberculosis related millennium development goals. Implementing these techniques would improve not only case detection but also cure rates since patients will be diagnosed early and put on treatment in early as such they could be able to respond well to treatment. It would also reduce transmission rates to close relatives and the public. TB infection among health worker has also been a major concern in Malawi (Harries *et al.* 1999). However, with bleach concentration techniques, such concerns will be implicitly addressed since bleach digests sputum making it less infectious and easy to work with thereby increase safety of specimen to clinicians (Dacombe *et al.* 2006).

Malawi, like many other Sub-Saharan countries face shortage of health workers. While government trains few health workers, of the few, some have migrated to European countries for greener pastures. Natural sedimentation method could potentially reduce laboratory workload significantly. Reducing workload for the few available health workers would positively increase their work morale. There could be less time devoted to diagnosis but at the same time not compromising quality of diagnosis.

Natural sedimentation with bleach is similar to the current method (direct smear microscopy) with an exception that bleach has to be added to specimen and allow it to sediment for 45minutes. It does not require special expertise and could be implemented throughout the country in peripheral health facilities. Furthermore, the method has an advantage of same day results for patients. This could reduce patient costs for transport because of few or reduced visits to the health facilities. Patients could have same day results and, once found with smear positive TB, could start treatment the same day instead of waiting for three to four days, and in some cases even one week.

Bleach concentration techniques could potentially help reduce dropout rates which account for 15% in Malawi (Reid and Shah 2009). Such dropouts' occur between the diagnostic pathway that is between time of submitting sputum for examination and collection of results. Perhaps costs involved in care seeking pathways also contribute to such a high dropout rate (Kemp *et al.* 2007). Reducing the diagnostic pathway would ensure all patients get results in time and put on treatment within shortest possible time.

Bleach centrifugation technique is more effective than natural sedimentation. However, country wide implementation would be capital intensive and would also increase maintenance costs for most health facilities. Besides that less skilled workers may not be able to carry out the tests which will restrict usage in most rural health centres as such implementing this method may not be realistic in Malawi. The need for electricity makes it also difficult to implement centrifugation technique. Alternatively, bleach centrifugation could be used in main health facilities such as central hospitals and district hospital where there is much more workload and usually have well trained staff. However, the obstacle with implementing different strategies would be public response. People could tend to discredit rural health facilities if they know that more effective diagnosis in offered in main hospitals and this may even increase workload in central and district health facilities as such universal implementation of tuberculosis diagnostic technique would be the most ideal situation.

6.3 Conclusion

Natural sedimentation is the most cost effective method of analyzing sputum. The method can potentially save about 41% of TB diagnostic costs. These saved resources could be redirected to other interventions. Natural sedimentation technique is the most realistic method of analyzing sputum for tuberculosis diagnosis in Malawi that can improve pulmonary tuberculosis case finding. Its intrinsic feature of rendering specimen less infectious and easy to use makes it suitable for use in peripheral health facilities.

Centrifugation is more cost effective than direct smear microscopy. The method is highly effective, and could also be an alternative to direct smear microscopy. However, implementation faces a lot of challenges as such it may not be realistic to implement in the Malawi health sector. Direct smear microscopy was the least cost effective method but also the most effective in terms of number of smear positive cases detected.

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APPENDICES

APPENDIX A: PARTICIPANT CONSENT FORM

Consent form for participating in the study: A cost-effectiveness analysis of different ways of analyzing sputum for tuberculosis diagnosis: direct smear microscopy, natural sedimentation and centrifugation

What is the purpose of the study?

My name is………………… I work for Research for Equity and Community Health (REACH) Trust. We are carrying out a study aimed to assess the cost effectiveness of different techniques of analysing sputum for pulmonary tuberculosis, namely direct smear, bleach natural sedimentation and bleach centrifugation. This will involve asking for information from management, laboratory technicians and officers from central medical stores. The study will collect the cost and effectiveness data (e.g. costs for diagnostic test, laboratory, transport, building, equipment, staff time and overheads).

What are the possible benefits of participating?

There will be no immediate benefits to you. However the information we obtain from this study will help policy makers and healthcare providers' in resource allocation decisions in the public sector. The information you provide will play an important role in determining costs involved in diagnosis of tuberculosis.

What are the possible drawbacks or discomforts in participating?

The study poses no risk, pain, physical hazards or discomfort to any participant. The study will use financial records and other information on materials used in diagnostic tests for tuberculosis.

Do I have to participate?

Your participation in this study is voluntary. Should you agree to participate you are required to sign this form. You are free to withdraw from the study at any stage and this will in no way affect your job.

Will the information be treated confidentially?

Yes, should you agree to participate in the study, all information collected for this study will be kept strictly confidential. Individual responses or any other recorded information you provide will never be made public, and no information which could identify you will ever be released.

Contact details

If you have any questions about this interview contact…*Mafayo Phiri*… Tel…002659051514/ 0027788797400..Fax: 002651751247 or e-mail…ciscophiri@yahoo.com…

I,……………………………. (Name of respondent in block letters) have read and understood all the information given to me about my participation in this study and I was given the opportunity to discuss it and ask questions. I volunteer to take part in this study. I have received a copy of this consent form.

______________________ ______________

Signature of respondent **Date**

Interviewer/ fieldworker: I have:

Explained the nature and purpose of the study to the respondent	N	Y
Handed over a copy of the consent form	N	Y

____ _______________

Signature of the interviewer/fieldworker **Date**

APPENDIX B: LETTER OF REQUEST TO COLLECT DATA AT HEALTH FACILITY IN MALAWI

Date: ………………………………….

Address: REACH Trust, P.O. Box 1597, Lilongwe.

Dear Sir/Madam

RE: Request to conduct a study Bwaila Hospital/ Malawi Liverpool Welcome Trust (MLW)

I am *Mafayo Phiri*, a student at University of Cape Town (UCT), South Africa, currently doing a masters degree program in Public Health specialising in Health Economics. I would like to undertake a study at Bwaila hospital. The study aim is to assess the cost effectiveness of different techniques of analysing sputum. This will involve asking for information from management and laboratory technicians. The study will collect cost and outcome data (e.g. costs for diagnostic test, laboratory, transport, building, equipment, staff time and overheads).

It is hoped that results from this study will help in prioritization of resource use.

Ethical approval has already been sought from the University of Cape Town Ethics Committee, National Health Research Ethics Committee in Malawi. Issues concerning consent and full confidentiality will be strictly adhered to at all times. A favourable approval to carry out this study would be appreciated.

Thanks for your anticipated cooperation.

Yours faithfully,

Mafayo Phiri

Principal investigator

APPENDIX C: COST SHEET

Cost effectiveness analysis of ways of analyzing sputum for TB diagnosis; smear microscopy, natural sedimentation and Centrifugation.

A. PERSONNEL

PERSONNEL						
Laboratory Staff		**Annual Cost**				
Type of staff working on TB	**Number of Hrs on TB diagnosis**	**2006**	**2007**	**2008**	**Proportion of time spent on average working on TB**	**Total annual Cost on TB diagnosis**
(E.g. Lab Technicians and laboratory Managers)						
Total Annual Cost of Support Staff						

Support Staff;

B. OFFICE AND LABORATORY SPACE

Support Staff						
		Annual Cost				
Type of staff working on TB	**Number of Hrs on TB**	**2006**	**2007**	**2008**	**Proportion of time spent on Average working on TB**	**Total annual Cost on TB diagnosis**
(Eg.Administration Cleaners)						
Total Annual Cost of Support Staff						

Building Costs		
Space used (Square Metres)	**Cost of building space used**	**Annualised Cost**
Laboratory		
Office		
Total		

C. OPERATING COSTS

Operating and maintenance costs			
	2006	**2007**	**2008**
Water			
Electricity			
Telephone			
Microscope			
Biosafety Cabinet			
Autoclaving waste			
Centrifuge			

D. EQUIPMENT

Laboratory Equipment		
Equipment	**Purchasing cost**	**Annualised Cost**
Furniture		
Centrifuge		
Microscope		
Biosafety Cabinets…		
Autoclaving waste		
……….		

E. DIAGNOSTIC MATERIAL USAGE

Material Usage		
	Quantity used	**Amount used per test**
A. Smear Microscopy		
Calibrated loop		
30ml Universal Container		
Daimond marker		
Storage boxes		
Amplicator sticks		
Slides		
Preparation agents		
Carbol fuschin stain		
Methylene blue stain		
Acid alcohol		

Material Usage		
	Quantity used	**Amount used per test**
B. Natural Sedimentation		
Calibrated loop		
30ml Universal Container		
Daimond marker		
Storage boxes		
Amplicator sticks		
Slides		
Preparation agents		
Carbol fuschin stain		
Methylene blue stain		
Acid alcohol		
Bleach		
Pipettes		

Materials used		
	Quantity used	**Amount used per test**
C. Centrifugation		
Calibrated loop		
30ml Universal Container		
Diamond marker		
Storage boxes		
Amplicator sticks		
Slides		
Preparation agents		
Carbol fuschin stain		
Methylene blue stain		
Acid alcohol		
LJ slope with pyruvate		
LJ slope non pyruvate		
Filter papers		
Virkon (disinfetctant)		
Pipettes		
Phosphate buffered saline		
Sodium hydroxide		

F. DIAGNOSTIC TIME

Time Spent on Sputum tests		
Method	**Number of specimen analyzed per week**	**Number of hours spent per week**
Smear microscopy		
Natural Sedimentation		
Centrifugation		

G. OVERAL COSTS

Time spent							
People involved	**Salary paid by**	**Number of working days in 2006**	**Number of working days in 2007**	**Number of working days in 2008**	**Days allocated to TB Diagnosis 2006**	**Days allocated to TB diagnosis 2007**	**Days Allocated to Tb Diagnosis 2008**

1. A working day is assumed to have 8 hours
2. Number of working days excludes public holidays and weekends

APPENDIX D: COSTING SHEET QUESTIONNAIRE

Name of Facility:

District:

Respondent:

Interviewer:

Informed Consent:

My name is……………….. I work for Research for Equity and Community Health (REACH) Trust. We are carrying out a study aimed to assess the cost effectiveness of different techniques of analysing sputum for pulmonary tuberculosis, namely direct smear, bleach natural sedimentation and bleach centrifugation. I will be asking you for information on amount of materials used in the study and their costs (e.g. costs for diagnostic test, laboratory, transport, building, equipment, staff time and overheads).

Your participation in this study is voluntary. Should you agree to participate you are required to sign a consent form which is on a separate sheet. You are free to withdraw from the study at any stage and this will in no way affect your job.

______________________ ______________

Signature of respondent **Date**

Interviewer/ fieldworker: I have:

Explained the nature and purpose of the study to the respondent	N	Y
Handed over a copy of the consent form	N	Y

________________________________ ______________

Signature of the interviewer/fieldworker **Date**

Recurrent Costs

1. In this section I would like to know about the staff working on each method of analyzing sputum, the time they dedicate to their tasks and their remuneration packages.**(List of laboratory and Support Staff involved)**
(To ask staff)

	Q1.1	Q1.2	Q1.3	Q1.4	Q1.5
Laboratory Staff (lab technicians, managers)	Who are the people involved in TB Diagnosis using smear microscopy in this facility?	What is their role in this procedure?	How many hours per week does (name) dedicate to this procedure	How many hours per week does (name) work at this facility	What is the total annual Salary that (name) Receives
Support Staff (e.g. administration, cleaners)					

	Q2.1	Q2.2	Q2.3	Q2.4	Q2.5
Laboratory Staff (lab technicians, managers)	Who are the people involved in TB Diagnosis using Natural Sedimentation in this facility?	What is their role in this procedure?	How many hours per week does (name) dedicate	How many hours per week does (name) work at this facility	What is the total annual Salary that (name) Receive
Support Staff (e.g. administration, cleaners)					

	Q3.1	Q3.2	Q3.3	Q3.4	Q3.5
Laboratory Staff (lab technicians, managers)	Who are the people involved in TB Diagnosis using **Centrifugation** in this facility?	What is their role in this procedure?	How many hours per week does (name) dedicate	How many hours per week does (name) work at this facility	What is the total annual Salary that (name) Receive
Support Staff (e.g. administration, cleaners)					

Usage and Cost of Diagnostic Materials

4. In this section I will ask questions on quantities of diagnostic materials that were used for each of the methods. Below is the list of the materials used. *(Cost of Materials to check on procurement records or central medical stores)*

4.1 Smear Microscopy

Materials	**Per week**		**Per month**		**Total used**	
	Quantity	**Cost**	**Quantity**	**Cost**	**Quantity**	**Cost**
Calibrated loop						
30ml universal container						
Diamond marker						
Storage boxes						
Applicator Sticks						
Slides						
Preparation agents						
Carbol fuschin stain						
Methylene blue stain						
Acid alcohol						

4.2 Natural Sedimentation

Materials	**Per week**		**Per month**		**Total used**	
	Quantity	**Cost**	**Quantity**	**Cost**	**Quantity**	**Cost**
Calibrated loop						
30ml universal container						
Diamond marker						
Storage boxes						
Applicator Sticks						
Slides						
Preparation agents						
Carbol fuschin stain						
Methylene blue stain						
Bleach						
Pipettes						

4.3 Centrifugation

Materials	Per week		Per month		Total used	
	Quantity	Cost	Quantity	Cost	Quantity	Cost
Calibrated loop						
30ml universal container						
Diamond marker						
Storage boxes						
Applicator Sticks						
Slides						
Preparation agents						
Carbol fuschin stain						
Methylene blue stain						
Acid alcohol						
LJ slope with pyruvate						
Lj slope non pyruvate						
Filter papers						
Virkon (disinfectants)						
Pipettes						
Phosphate buffered saline						
Sodium hydroxide						

5.0 Time for carrying out tests *(laboratory technicians to respond verified through records)*

This section has questions about time you take to analyze sputum for each of the methods used from the time specimen is taken to the time results are reported to the patient.

Time spent on Sputum tests				
Method	**Number of Specimen Analyzed per week**	**Number of hours spent per week**	**Number of specimen analyzed per month**	**Number of hours spent per month**
Smear Microscopy				
Natural Sedimentation				
Centrifugation				

6.0 Capital Costs
(To take actual measurements of laboratory and office space, Cost of building sourced from Contractors)

Building costs	Space Used (square meterage)	Cost of building space used	Annualized cost
Laboratory Space			
Office space			

6.1. Laboratory Equipment *(Physical observation of equipments used costs to check through procurement records)*

6.2. Cost of the following equipment used for analyzing sputum. ***(To verify cost with facility records)***

Laboratory Equipment		
	Purchasing Cost	**Annualized Costs**
Centrifuge		
Microscope		
Autoclaving waste		
Biosafety Cabinet		
Slide dryer		

7.0. Operating and Maintenance costs *(record reviews)*

I would like to know the costs incurred for overheads during the entire period of the study;

Overheads				
	Costs in 2006	**Costs in 2007**	**Costs in 2008**	**Total Costs**
Water				
Electricity				
Telephone				
Other utilities				