CHAPTER ONE - INTRODUCTION

1.0 Background

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis (M Tuberculosis)* or Koch's bacillus. It is spread in infectious droplets through the air that are produced when an infected person sneezes, coughs, or breathes.

With almost 9 million new cases each year, TB remains one of the most feared diseases on the planet (Zager and McNerney 2008)

In 2006, there were 14.4 million individuals worldwide living with TB, including half a million cases of multidrug-resistant (MDR) TB. An additional 9.2 million new TB infections occurred that year. In the same year 1.7 million deaths were attributed to TB (Ammann and Dron 2009).

On March 16, 2004, the World Health Organization (WHO) reported that the largest ever survey of drug-resistant TB has unveiled "worrying" levels of the disease.

At no time in recent history has TB been as widespread a concern as it is today. Despite highly effective drugs, disease and deaths due to *M tuberculosis* are increasing. A most serious aspect of the problem has been the emergence of MDR-TB and extensively drug-resistant (XDR) TB which poses a threat both to the individual patient as well as to communities.

MDR-TB is defined as a strain of *M tuberculosis* that is resistant to at least Isoniazid (INH) and Rifampicin (RMP) whether there is resistance to other drugs or not (Management of MDR-TB in **S**outh Africa 2nd Edition June 1999). These drugs are considered first-line anti-TB drugs (Streptomycin, Isoniazid, Rifampin and Ethambutol) and are used to treat all persons with TB disease. INH and RMP are the two most important first-line TB drugs; their removal (via resistance) from the anti-TB drug armamentarium has serious implications.

XDR-TB is defined as resistance to at least rifampicin, isoniazid, a second line injectable drug (capreomycin, kanamycin or amikacin) and a fluoroquinolone (Zager and McNerney 2008).

Because XDR-TB is resistant to first-line and second-line drugs, patients are left with treatment options that are much less effective.

Without a coordinated control effort, TB will infect an estimated 1 billion more people by 2020, killing 70 million (Evelin Grijalva 2003).

1.1 Geographic Distribution

MDR-TB has been reported in all regions of the world (Zager and McNerney 2008).

China, India and the Russian Federation are thought to carry the largest MDR-TB burden, with China and India accounting for 50 percent of the lobal caseload (WHO).

Five of the top 10 places in the world for MDR-TB include Kazahkstan, Uzbekistan, Lithuania, Ecuador and the Liaoning and Henan provinces in China. Countries of sub-Saharan Africa have amongst the highest rates of transmitted MDR-TB in the world (Zager and McNerney 2008).

WHO estimates that there were 66,700 MDR-TB cases in Africa in 2006. Citing the deadly outbreak of XDR-TB in South Africa's KwaZulu-Natal Province in 2006, which mainly affected HIV-positive patients, WHO warned: "Detection of this outbreak was only possible because of the extensive laboratory infrastructure available in the country. South Africa is one of only two countries on the continent with the equipment to diagnose XDR-TB. According to Dr Paul Nunn, co-ordinator of the WHO's TB/HIV and TB Drug Resistance Unit; “Other countries in Africa have "a very long way to go" before they have similar laboratory capacity.”There are a number of countries in Africa that do not have a single laboratory capable of testing a culture for drug resistance." Africa may have a relatively low incidence of MDR-TB because some of the first-line TB drugs available in Europe and other parts of the world were introduced recently in Africa, meaning that resistance has had less time to develop.

TB has spread to all the nine provinces in Zambia. WHO estimates that Zambia has an incidence of 78,049 cases of TB per year and case detection rate is only 69% (TB Manual MoH 2006). MDR-TB has also been reported in almost every part of the country. In 2005 approximately 50 cases were reported countrywide as having MDR-TB (MoH, TB Annual Report 2006).

1.2 TB, Poverty and HIV/AIDS related

TB is predominantly a disease of poverty with over 80% of cases occurring in Asia and Africa. However the highest incidence of disease is found in the WHO region of Africa. All regions of the world have a stable or falling number of cases of TB except for the African region where the numbers of new cases of TB continue to rise. Driven by increasing poverty, social upheaval and crowded living conditions in developing countries and inner city populations in developed countries, a generalized HIV/AIDS epidemic and compounded by weak health care systems, inadequate laboratories, and conditions that promote transmission of infection, this devastating situation has steadily worsened.

The co-existence of TB with the HIV infection has complicated and made difficult the TB control program. TB has become the leading cause of death among people living with HIV/AIDS, while infection with HIV is the most potent factor for a latent infection to convert to active TB. The mortality rate for HIV-TB co-infection is five-fold higher than that for TB alone. In Zambia about 70% of people with TB are co-infected with HIV (MoH, TB Annual Report 2006)

1.3 Management

Chemotherapy is the most effective weapon against TB, leading to a cure in almost all cases. However, various factors may negatively affect A potentially devastating threat to TB control is the emergence of strains that cannot be cured by standard anti-TB drug regimens. Resistance of *M tuberculosis* to antibiotics is a man-made amplification of spontaneous mutations in the genes of the tubercle bacilli arising from the following: when patients do not complete their full course of treatment; when health-care providers prescribe the wrong treatment, the wrong dose, or length of time for taking the drugs; when the supply of drugs is not always available; or when the drugs are of poor quality. This suppresses the growth of susceptible strains to that drug but permits the multiplication of drug-resistant strains. This phenomenon is called *acquired (or secondary) resistance*. Subsequent transmission of such resistant strains from an

infectious case to other persons leads to disease which is drug-resistant from the outset, a phenomenon known as *primary resistance*.

Most antibiotics are more effective to actively growing organisms than slowly growing ones. Mycobacteria are slowly growing organisms and are therefore relatively resistant to antibiotics. Treatment of MDR-TB requires prolonged and expensive chemotherapy using second line drugs of heightened toxicity. Control of drug resistant TB requires a strong health infrastructure to ensure the delivery of effective therapy coupled with surveillance and monitoring activities to enable timely intervention to limit transmission and spread of the disease. The allocation of resources to detect and treat MDR-TB in poor resource settings remains problematic. With increased international travel, MDR-TB is readily circulating throughout the world.

As it is, TB treatment is expensive but MDR-TB is more expensive and mortality due to MDR-TB is very high. The cost of treating a case of MDR-TB in South Africa is 10 to 20 times the cost of treating an uncomplicated drug-susceptible case. The full cost of treating one MDR TB patient is about 30,000 South African Rand. Cure rates are generally below 50% even in the best circumstances. At least 30% of cases are fatal within two years: the remainder are chronic and continue to be infectious, p a threat to communities (Management of MDR-TB in **S**outh Africa 2nd Edition June 1999).

It is against this background that this study intends to determine the prevalence of MDR-TB in adults at UTH in Lusaka, Zambia. The objectives ill be formulated along this line.

1.4 Statement of the problem

TB has continued to be one of the major public health in Zambia and is among the ten top causes of morbidity and mortality. Diagnosed cases of MDR-TB most likely represent a small proportion of the true extent of the problem. The number of persons harbouring latent infections is unknown (and likely unknowable at present). Official statistics also most likely under estimate the true prevalence of MDR-TB.

It should be noted that normally drug resistance can easily be identified after two months of aggressive treatment for TB with first-line drugs if Acid Fast Bacilli (AFB) is still positive. Identification of MDR strains of *M. tuberculosis* can only be established through culture and susceptibility testing of the organism. Routine susceptibility testing should be carried out for patients at risk of harboring MDR strains, i.e. patients qualifying for the retreatment regimen and for whom this regimen has failed. It appears that this routine is not followed which could be one of the reasons for MDR-TB.

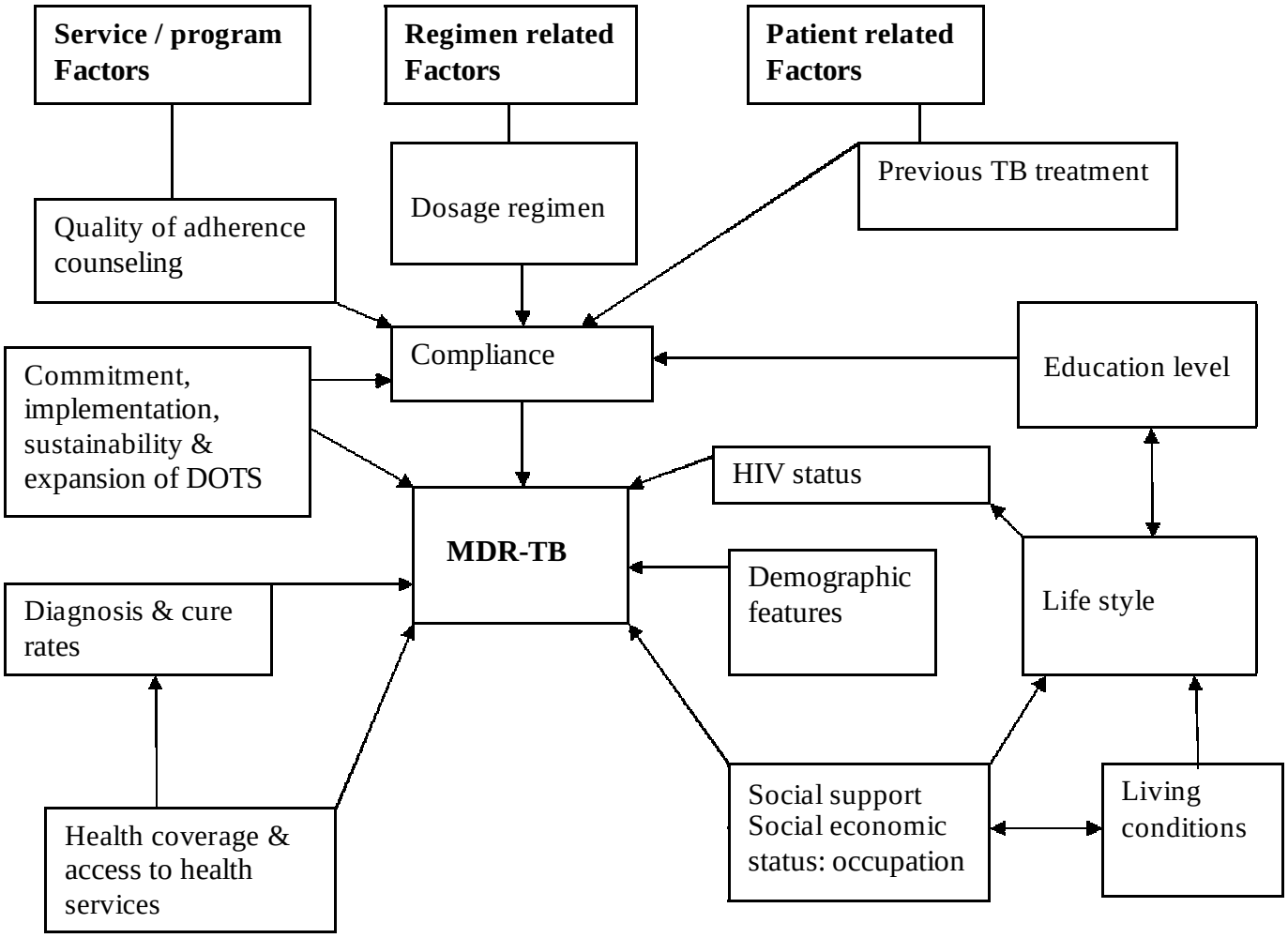
Treatment, diagnosis and management are very costly and lengthy. MDR-TB is very infectious with high mortality rate. If care is not taken this could be a multidrug-resistant epidemic in the country with more people dying of TB.

Results of the Zambia national drug resistance surveil in 1999 indicated the following patterns: MDR to INH + RMP in new cases was 0.9%. The previously treated cases had an MDR to INH +RMP of 2.3% (National TB Strategic Plan 2006-2011).

The economic, social and health security of countries, communities and families with a high prevalence of MDR-TB would be threatened by virtually untreatable disease through transport to get to health facilities, and time lost from work as it strikes people in their most productive years.

This research has uncovered and assessed in detail the magnitude of the problem and suggests the way forward.

1.5 CONCEPTUAL FRAMEWORK



1.6 Justification of Study

MDR-TB is a major public health, social and economic problem and remains one of the most serious challenges to global health and therefore needs to be addressed urgently.
TB is one of the Millennium Development Goals (MDG 6 Target 8) which aims at stopping and beginning to reverse the incidence of TB by 2015.
This study envisioned generating evidence for more effective ways of implementing MDR-TB control interventions without which the attainment of MDGs would not be possible.

1.7 Research objectives

1.7.1 General objective

To determine the prevalence of and factors associated MDR-TB among adults with TB at UTH in Lusaka.

1.7.2 Specific objectives

- To describe the demographic characteristics such as age, gender, and geographical distribution of patients presenting with MDR-TB.

- To determine the proportion of MDR-TB cases among culture-positive TB patients.

- To determine the association between HIV, previous TB treatment and compliance on one hand and MDR-TB on the other.

CHAPTER TWO – LITERATURE REVIEW

2.0 Introduction

This chapter reviewed the literature related to MDR-TB. The review tried to present similar studies conducted in various countries on this topic and provided the reader with an overview of major academic works concerning MDR-TB.

2.1 Global perspective

Sungkanuparph *et al* (2006) presented an abstract of their study in the 27th Annual Congress of the European Society of Mycobacteriology in London, UK.

The researchers were looking at the declining prevalence of Drug-Resistant TB among HIV/TB Co-infected patients receiving antiretroviral therapy (ART). The aim of the study was to determine the impact of ART on the prevalence of MDR-TB among HIV/TB co-infected patients.

The findings were that patients who had received ART increased from 18.5% in 1999 to 92.1% in 2004. The prevalence of MDR-TB in the years 1999 and 2004 were 48% and 7.9%, respectively. The prevalence of MDR-TB significantly declined in 2004 when compared with those in 1999.

Hu (2008) conducted a cross-sectional study to determine the extent of MDR-TB circulating in areas with varied duration of Directly Observed Treatment Short Course (DOTS) implementation in two rural counties in China namely Dequing and Guanyun. Dequing with over 10 years DOTS implementation and Guanyun under its second year of DOTS. The subjects were all culture-positive PTB patients newly diagnosed or re-treated during 12 months of 2004–2005.
Results were that, the rates of MDR-TB in new cases were 3.8% in Deqing and 14.7% in Guanyun, and 16.3% and 34.3% in previously treated cases.

According to the Global MDR-TB & XDR-TB Response Plan 2007–2008 (WHO 2008), Center for Disease Control and Prevention (2005) reported that 7.8% of TB cases in the United States of America (USA) were resistant to isoniazid and that 1.2% were resistant to both isoniazid and rifampicin. Overall, 124 cases of MDR-TB were reported in the USA in 2005, which remained constant from the previous year. Only 27 percent of primary MDR-TB cases were in USA born persons. The percentage of USA born persons with MDR-TB has remained stable at approximately 0.6 percent since 2000. The proportion of MDR-TB cases continued to disproportionately affect foreign-born persons in the USA. Among this group, MDR-TB cases have increased from 26 percent in 1993 to 81.5 percent of cases in 2005.

According to Lumb (2001) the Australian Mycobacterium Reference Laboratory Network collected and analyzed laboratory data on new of disease caused by *Mycobacterium tuberculosis* complex in the year 2001. Findings were that a total of 69 isolates (8.9%), comprising 67 *M. tuberculosis*, one *M. africanum*, and one *M. bovis*, were resistant to at least one of the anti-TB agents. Resistance to at least isoniazid and/or rifampicin was noted for 67 isolates (8.7%), with resistance to both isoniazid and rifampicin observed in 12 (1.6%) isolates. All of the multidrug-resistant isolates were *M. tuberculosis*.

TB Prevention and Control (TBPC), Health Canada (2003) reported that of the 1,379 isolates included for analysis, 173 (12.5%) were resistant to o or more first-line anti-TB drug(s). Resistance to isoniazid was the most common type of drug resistance (9.3%). Twenty isolates (1.5%) were MDR-TB strains, of which seven isolates demonstrated resistance to four or five first-line anti-TB drugs tested.

Cox (2004) reported that in order to determine levels of drug resistance within a DOTS program supported by Médecins Sans Frontières in two regions in Uzbekistan and Turkmenistan, Central Asia, a cross-sectional survey of smear-positive TB patients in selected districts of Karakalpakstan (Uzbekistan) and (Turkmenistan) was conducted. In Karakalpakstan, 14 (13%) of 106 new patients were infected with MDR-TB; 43 (40%) of 107 previously treated patients were similarly infected. The proportions for Dashoguz were 4% (4/105 patients) and 18% (18/98 patients), respectively. Overall, 27% of patients with positive smear results whose infections were treated through the DOTS program in Karakalpakstan and 11% of similar patients in Dashoguz were infected with strains of MDR-TB on admission.

In the state of Tamil Nadu, Paramasivan *et al* (2000) carried out a surveillance of drug resistance in TB at state level. The objective was to determine the proportion of initial and acquired drug resistance in cases of PTB. The results were that out of 400 patients for whom drug susceptibility results were available, 384 ( ) had no history of previous anti-TB treatment. Of these, 312 (81%) were susceptible to all the drugs tested. Resistance to Isoniazid was seen in 15.4% of patients to Rifampicin in 4.4%, including resistance to Isoniazid and Rifampicin in
3.4%.

2.2 Regional perspective

Studies by the Medical Research Council, National TB Research Programme (1999) in 3 provinces in South Africa indicate a rate of approximately 1% MDR in new TB cases and 4% in previously treated cases. This translates into about 2000 new cases of MDR-TB in South Africa each year.

According to Singh (2007) the World Health Organization announced on 1st September 2006 that XDR-TB had been detected in Tugela Ferry, a rural town in the South African province of KwaZulu-Natal, the epicentre of South Africa's HIV/AIDS epidemic. Of the 544 patients studied in the area in 2005, 221 had MDR-TB. Of these 221 cases, 53 were identified as XDR-TB. This reportedly represents almost one-sixth of all known XDR-TB cases reported worldwide. Of the 53, 44 were tested for HIV and all were HIV infected.

According to Ghandi *(*2006) a cross-sectional study of patients suspected with active TB at a rural district hospital in KwaZulu Natal, South Africa was carried out. The objective was to assess the extent of MDR-TB and XDR-TB and to describe patient and treatment characteristics. The following were the results: out of 1539 patients with isolates sent, 995 (65%) were culture-negative and 544 (35%) culture-positive for *M tuberculosis*. Of the 544 culture-positive, 323 (59%) were not resistant to both isoniazid and rifampicin while 221 (41%) were MDR-TB. 53 (24% of MDR-TB, 10% culture positive) were XDR-TB

According to Adatu (2008) although MDR-TB is present in Uganda, its extent is unknown. A recent survey conducted at Arua Regional Hospital in Uganda's West Nile region found a 2.2% prevalence of MDR-TB, and a 1997 survey by the German Leprosy and TB Relief Association in southwest Uganda found a 1.1% prevalence of the disease.

According to Talbot (2003) Botswana, where in 2000 the prevalence of HIV infection among adults was 38% and the TB rate, was 591/100000. A 1995–1996 survey demonstrated low levels of anti-TB drug resistance. The objective was that, because TB drug resistance may increase rapidly in HIV-infected populations, a second survey was undertaken in 1999 to determine any increase in anti-TB drug resistance. The following were the results: 783 patients were consecutively enrolled from all districts. Of these, 483 (61.7%) were male, the median age was 33 years, and 82% were new patients. Drug resistance occurred in 6.3% of new patients and 22.8% of retreatment patients. Resistance to at least isoniazid and rifampicin was found in 0.5% of new and 9.0% of retreatment patients.

According to Urassa (2008) a total of 280 *M tuberculosis* isolates were obtained from consenting adult TB patients involved in a placebo-controlled study to evaluate the efficacy of multivitamin supplements on response to anti-TB treatment in Dar-es-Salaam, Tanzania. Fourteen (5.0%) isolates were resistant to any of the anti-TB drugs. The prevalence of primary resistance was 5.0%, 0.7%, 0.4% 0% for streptomycin, isoniazid, rifampicin and ethambutol respectively. One isolate (0.4%) was MDR, with resistance to isoniazid, streptomycin and rifampicin.

2.3 Local perspective

Very scanty literature has been found on the prevalence of MDR-TB in Zambia. According to National TB Strategic Plan 2006-2011, results of the Zambia national drug resistance surveillance in 1999 indicated the following patterns: MDR: INH + RMP was 0.9%. The previously treated cases had an MDR to INH +RMP of 2.3%. The study did not articulate the variables under investigation in a lear perspective.

From the literature reviewed, it is evident that MDR-TB is a global burden. New rapid methods of detecting drug resistance are helpful but too costly to be used in developing countries like Zambia. MDR-TB poses an enormous threat to Zambia's health and its medical resources.

CHAPTER THREE - METHODOLOGY

3.0 Introduction

A cross-sectional study was conducted among culture-positive TB patients. Facility TB records and databases for *M tuberculosis* isolates which were cultured and had drug-sensitivity testing performed against four first-line anti-TB drugs using the Mycobacteria Growth Indicator Tube (MGIT) 960 machine were studied retrospectively. These drugs include streptomycin, isoniazid, rifampicin and ethambutol. All the records and databases available between 2003 and 2008 were reviewed. Study cases were selected on the basis of the results of susceptibility tests, using the proportion method. The proportion method is commonly used for determining drug susceptibility of *M. tuberculosis* isolates in the laboratory. The results of this method are reported as the percentage of the total bacterial population resistant to a specific drug, which is defined as the amount of growth on a drug-containing medium as compared with growth on a drug-free control medium.

The sensitivity of the BACTEC MGIT 960 system for testing of *M tuberculosis susceptibility* to four first-line anti-TB drugs has been found to be 100% for all four drugs and specificity ranged from 89.8% for streptomycin to 100% for rifampicin.

These data demonstrate that the fully automated and nonradiometric BACTEC MGIT 960 system is an accurate method for rapid susceptibil of *M. tuberculosis*.
The necessary information that was collected was entered in the data collection sheet.

3.1 Study site

The study was conducted at the University Teaching Hospital, TB Laboratory, Lusaka, Zambia.

3.2 Inclusion criteria

- Adults aged 15 years and above.
- Culture-positive TB patients.

3.3 Exclusion criteria

- Individuals below 15 years old
- Culture-negative TB patients

3.4 Sample size

The sample size was calculated using computer software, **EPI-INFO** version 6 as shown below.

Population Survey or Descriptive Study Using Random Sampling

Population size	:	538
Expected frequency	:	50.00%
Worst Acceptance	:	45.00%

Confidence Level	Sample size
80%	126
90%	180
95%	**224**
99%	297
99.9%	359
99.99%	397

The cut-off point for statistical significance was set at 5% level (Confidence Level 95%), and therefore, the calculated sample size was **224** as shown above.

The number of records reviewed was **538**. This is the total number of culture-positive TB patients from which MDR-TB cases are expected. This study population was readily available and manageable and therefore all records were reviewed.

3.5 Sampling method:

- Convenience sampling

3.6 Data collection:

A data collection sheet was used to collect information from facility TB records and databases which were reviewed at the TB Laboratory at UTH. Data collection took three months from the time ethics committee gave approval. The data was based on clinical specimens that were culture-positive for *M tuberculosis*.

The following information was collected:

- Demography: age, sex, HIV status, and occupation;
- Specimen: type, date of collection
- Isolate: species of mycobacterium and results of drug susceptibility testing; and
- If the isolate was drug resistant: history of previous B treatment to determine whether resistance was initial or acquired.

3.7 Data processing and analysis:

Information obtained was checked and verified. Quantitative data was entered and analyzed using computer software, **EPI-INFO**. The chi-square test was used to determine the associations of independent variables on one hand MDR-TB on the other. The cut-off point for statistical significance was set at 5% level. Results were edited and presented in graphical and tabular form.

3.8 Ethical considerations:

Approval was sought from the Research Ethics Committee of the Unive ity of Zambia. Permission was also obtained from UTH management. Confidentiality was maintained by use of codes and no names were indicated in the data collection sheet.

Since it was a record based retrospective study and did not involve human subjects, a waiver for consent was requested.

3.9 Budget:

The researcher spent about K 12,000,000.00 towards the research project. This catered for stationery, printing costs, allowances for research assistants and travel costs. The expenses were met partly by Ministry of Health and the researcher. Detailed budget is in appendix I.

3.10 Operationalisation of variables

The key variables of study were: Age, sex, occupation, previous TB treatment, HIV/AIDS and compliance.

In this study, variables were operationalised as follows:

Age: Age as a measure of lived life was measured on interval scale.

Sex: Gender classified as male and female.

Occupation: Employed or not employed.

Previous TB treatment: Presence of resistant isolates of *M.tuberculosis* in patients who, in response to direct questioning, admit having been treated for TB for one month or more or, where adequate documentation is available, in a patient for whom there is evidence of such a history (Anti-TB Drug Resistance in the world Report No. 3).

HIV/AIDS: Having been tested for HIV and found to be positive.

Compliance: Here, compliance refers to how well patients manage to complete the full course of prescribed medication by taking more than 80% of medicine during treatment. This often depends on adequate counseling, accessibility of the service, the attitudes and ongoing support of health care staff (WHO standard).

CHAPTER FOUR - RESULTS

4.0 Introduction

With the use of the data collection sheet and retrospective review of patient records to extract baseline data, it was found that 559 records of culture-positive TB patients had drug sensitivity testing performed on them between 2003 and 2008. After going through the data collection sheet, 21 (3 from those who had MDR-TB and 18 from those who did not) were rejected, leaving us with 538. The reasons for the rejection were that some sheets were incompletely filled and others had some pages missing.

The mean age for respondents at the time records were reviewed was 34.4 years (standard deviation of 8.2). Out of the 538 respondents 298 (55.4%) were females. The average age for females was 32.9 years (standard deviation of 7.9) and 35.9 years for males (standard deviation of 8.5).

The proportion of MDR-TB among the TB culture-positive patients was **10.9%**

Figure 1: Age and MDR-TB

N = 538

Figure 1 shows MDR-TB distribution by age. The majority of those with MDR-TB were in the 30 – 44 years age group.

Table 1: Sex and MDR-TB

SEX	MDR-TB		TOTAL
	POSITIVE	NEGATIVE	
FEMALES	43 (72.9%)	255 (53.2%)	298
MALES	16 (27.1%)	224 (46.8%)	240
TOTAL	59 (100%)	479 (100%)	538

Of all the MDR-TB positives, 72.9% were females and 53.2% were females among MDR-TB negative. The observed proportions of females between positive and negative were statistically different ($X^2 = 8.2$, $p = 0.004$) as shown in table 1.

Table 2: Occupation and MDR-TB

EMPLOYMENT STATUS	MDR-TB		TOTAL
	POSITIVES	NEGATIVE	
EMPLOYED	20 (33.9%)	201 (41.9%)	221
NOT EMPLOYED	39 (66.1%)	278 (58.1%)	317
TOTAL	59 (100%)	479 (100%)	538

The results of the test of significance indicated that there was no significant association between employment status and MDR-TB ($X^2 = 1.41$, $p = 0.234$) as shown in table 2.

Table 3: Previous TB treatment and MDR-TB

PREVIOUS TB TREATMENT	MDR-TB		TOTAL
	POSITIVE	NEGATIVE	
YES	48 (81.4%)	207 (43.2%)	255
NO	11 (18.6%)	272 (56.8%)	283
TOTAL	59 (100%)	479 (100%)	538

Of all the MDR-TB positives, 81.4% of respondents had previously been treated for TB compared to 43.2% of no previous TB treatment. A test of significance (X^2 =30.7, $p < 0.001$) indicated that these observed proportions were statistically different as shown in table 3.

Table 4: HIV and MDR-TB

HIV	MDR-TB		TOTAL
	YES	NO	
POSITIVE	41(69.5%)	231(48.2%)	272
NEGATIVE	18 (30.5%)	248 (51.8%)	266
TOTAL	59 (100%)	479 (100%)	538

Of all the MDR-TB positives, 69.5% of the respondents were HIV positive compared to 48.2% among the MDR-TB negative respondents. A significant association was observed between HIV and MDR-TB ($X^2 = 9.5$, $p = 0.002$) as shown in table 4.

Table 5: Compliance and MDR-TB

COMPLIANCE	MDR-TB		TOTAL
	POSITIVE	NEGATIVE	
YES	18 (30.9%)	273 (56.9%)	291
NO	41(69.1%)	206 (43.1%)	247
TOTAL	59 (100%)	479 (100%)	538

We were also interested in determining whether there was an association between compliance and MDR-TB. Of all the positives, 30.9% of the respondents complied with treatment and 56.9% of respondents who complied were MDR-TB negative. A test of significant ($X^2 = 14.84$, $p < 0.001$) indicated that these observed proportions were statistically different as shown in table 5.

CHAPTER FIVE – DISCUSSION OF RESULTS

5.0 Introduction

This study has shown high rates of MDR-TB at UTH in Lusaka (10.9%) as compared to Ministry of Health statistics for Zambia which currently stand at 2%. These findings along with similar data from other regions, suggest that Zambia is one hot spot for MDR-TB. However we have no reason to suspect that the prevalence of MDR-TB is different in other Towns / Provinces of Zambia.

Although MDR-TB has been encountered in Zambia and its presence known, there is no comprehensive report mainly due to limited facilities ilable for culture and susceptibility tests in certain parts of the country.

5.1 Discussion on Age and MDR-TB

According to this study, there was no strong difference in the proportion of MDR-TB in the age groups (15-59 years). This is almost similar to a study done by Talboit *et al* (2003) in Botswana, in which the median age where drug resistance occurred was 33 years. A similar study done by Helen *et al* (2002) in Central Asia found that a valid culture for *M. tuberculosis* with MDR-TB was obtained with a median of 31 years.

5.2 Discussion on sex and MDR-TB

A strong difference emerged between females and males. We found that there were more females than males with MDR-TB. A study done by Helen *et al* (2002) in Central Asia found that a valid culture for *M. tuberculosis* was obtained and a higher proportion of female gender remained significant predictors of MDR-TB. The finding of a greater risk for MDR-TB among women is important and confirms similar findings in other countries. In Zambia, females usually take care of the sick and ailing members of the family with little or no knowledge about home based care and thus more prone to infection.

5.3 Discussion on occupation and MDR-TB

In this study, there was no significant association between occupation and MDR-TB Tommie Victor (Faculty of health Sciences, Stellenbosch University, South Africa), however reported that there was a significant association between occupation and MDR-TB with MDR-TB cases being more prevalent in the employed. This is due to constant interaction and thereby facilitates the transmission of TB from infectious patients. However Patient cooperation and adherence is most often a problem when the patient is unemployed or when looking for a job as access to healthcare becomes almost difficult. The poor nutritional status weakens their immune system and makes them more vulnerable to developing TB (Harrier and Maher 1996).

5.4 Discussion on previous TB treatment and MDR-TB

From our results, of all the MDR-TB positives, 81.4% of respondents had previously been treated for TB compared to 43.2% of no previous TB treatment. A test of significant indicated that the observed proportions of respondents was statistically different.

Previous TB treatment is among the factors associated with MDR-TB. The proportion of previous TB treatment of all TB cases is an indicator of program performance. Previously treated cases, worldwide, are not only more likely to be drug-resistant, but also to have resistance to more drugs than untreated patients. According to a study done by Talbot *et al* (2003) Botswana, 9.0% of retreatment patients were MDR-TB. Cox *et al* (2004) conducted a cross-sectional survey in selected districts of Karakalpakstan (Uzbekistan) and Dashoguz (Turkmenistan) and reported that in Karakalpakstan,43 (40%) of 107 previously treated patients were infected with MDR-TB with Dashoguz having 18 (18%) of 98 previously treated patients were infected with strains of MDR-TB.

We also compared studies by the Medical Research Council, National TB Research Programme (1999) in 3 provinces in South Africa which indicated a rate of approximately 4% in previously treated cases.

5.5 Discussion on HIV/AIDS and MDR-TB

We were also interested in determining whether there was an association between HIV/AIDS and MDR-TB. A significant association was observed between HIV/AIDS and MDR-TB.

The co-existence of TB with the HIV infection has complicated and made difficult the TB control program. TB has become the leading cause of death among people living with HIV/AIDS, while infection with HIV is the most potent factor for a latent infection to convert to active TB. The mortality rate for HIV-TB co-infection is five-fold higher than that for TB alone. In Zambia about 70% of people with TB are co-infected with HIV (MoH, TB Annual Report 2006). According to Singh *et al* (2007), of the 544 patients studied in Tugela Ferry, a rural town in the South African province of KwaZulu-Natal area in 2005, 221 (40.6%) had MDR-TB. Of these 221 cases, 53 (24%) were identified as XDR-TB. Of the 53, 44 (83%) were tested for HIV and all were HIV infected.

5.6 Discussion on compliance and MDR-TB

We were also interested in determining whether there was an association between compliance and MDR-TB. A test of significant indicated that the observed proportion of respondents who complied to treatment among those with MDR-TB (30.9%) was statistically different to that of respondents with MDR-TB who did not comply (69.1%).

When the supply of drugs is not always available, MDR-TB may increase as patients are increasingly able to purchase drugs privately and use them irrationally. Additionally, patients are often requested to purchase drugs themselves after they leave the hospital for continuation phase at home. Many patients cannot afford all drugs and therefore purchase what they can, resulting again in treatment interruptions.

This synthesis indicates that patients often take their TB medication under difficult circumstances and experience significant challenges, many of which are outside of their direct control. Taking a lengthy course of medication is not easy and frequently involves difficult decisions, sometimes at substantial personal and social cost to the patient. Compliance is a complex, dynamic phenomenon; a wide range of interacting factors impact on treatment-taking behaviour, and patient behaviour may change during the

course of treatment. More patient-centered interventions, and far greater attention to structural barriers, are needed to improve treatment a and reduce the global disease burden attributable to TB. DOTS treatment on its own may well stop the production of more MDR-TB, but it is unlikely to reduce high levels of existing drug resistance. Effective treatment of all cases of TB is equired to prevent transmission. MDR-TB treatment is lengthy and expensive, and the pool of those with expertise treating MDR-TB is limited. A simpler, more affordable and more effective treatment strategy is required; however, until this exists, patients require treatment with existing strategies. Some patients receive adherence counseling, while others do not. Polypharmacy in this situation might lead to non-compliance and ultimately to treatment interruptions.

5.7 Limitation of the study

The following were the limitations of the study:

- Poor record keeping and data from some records were incomplete which resulted in rejection of some respondents.
- The study was done at UTH which is a referral hospital and this could have attracted a biased population as most people are more ikely to come for confirmation or to make sure of an MDR-TB which they could have been told to have from somewhere.
- Expressing the prevalence in a geographic setting as a proportion may not adequately reflect the burden of MDR-TB in the country.
- We were unable to trace the geographical location of individual patients as MDR-TB is a notifiable disease which requires follow-ups.

CHAPTER SIX – CONCLUSION AND RECOMMENDATIONS

6.0 The key concluding remarks are as follows:

1. The proportion of MDR-TB among culture positive samples was high (10.9%).
2. The prevalence of MDR-TB was highest among respondents aged between 30 and 44.
3. There were more females with MDR-TB than males.
4. There was no significant association between occupation and MDR-TB.
5. The prevalence of MDR-TB was highest among respondents who had previously been treated for TB.
6. A significant association was observed between HIV/AIDS and MDR-TB.
7. A significant association was observed between compliance and MDR-TB.

With growing worldwide concern regarding MDR-TB, this study is vital in providing necessary data timely to monitor trends in MDR-TB that has been reviewed at UTH. The data collected indicate that the prevalence of MDR-TB in this country is similar to that in the overall global situation. There has been a gradual increase in MDR-TB over the years in the world according to WHO. According to WHO, increase in prevalence of any resistance may reflect an environment that favours the acquisition of additional resistance and lead to future increases in MDR-TB and possibly XDR-TB. Therefore, there is need for continuous monitoring of MDR-TB and XDR-TB.

6.1 This study recommends the following

- Strengthen TB control by expanding DOTS in order to improve treatment compliance and avoid treatment interruptions and consequently prevents the emergence of further MDR-TB cases. Full adoption of DOTS is vital if the creation of MDR-TB cases is to be halted.
- Standardized annual recording and reporting on all categories of previous treated cases namely relapse, failure and return after non-compliance should be mandatory.
- National and International initiatives should aim at preventing drug resistance, weeding out irrational prescribing practices and forming guidelines for standardizing treatment in order to curb HIV infection and MDR-TB.
- There should be continuous drug resistance surveillance, culture and drug susceptibility testing of every TB patient.
- In order to expand drug resistance surveillance, the government should invest in laboratories so that we are able to culture and do drug susceptibility testing for TB.

References

Adatu F, Bretzel G, Aziz M, Wendl-Richter U, Aisu T, Van Wijnen A, Sticht-Groh V (2008). ***Anti-tuberculosis Drug Resistance Surveillance***. Int J Tub and Lung Dis. 3(9):810-815

Ammann A and Dron HA (2009). ***International meeting on emerging diseases and Surveillance***. Geneva, Switzerland

Amor YB, Nemser B, Singh A, Sankin A, and Schluger N (2008). ***Underreported Threat of Multidrug-Resistant Tuberculosis in Africa.*** 14(9):

Ansari NA, Kombe AH, Kenyon TA, et al. (2002). ***Pathology and causes of death in a group of 128 predominantly HIV-positive patients in Botswana***. Int J Tuberc Lung Dis.6:55-63.

Anthony D H, Dermot M. (1996). ***TB/HIV A clinical manual.*** World Health Organisation publication.

Breathrach AS, de Reiter A. (1998). ***An outbreak of multi-drug resistant tuberculosis in a London teaching hospital.*** J. Hosp Infect 2239:111-117.

Chapman and Hall (1998). ***Clinical tuberculosis***. 2nd Edition. Editor Davies PDO London.

Chintu C, Mudenda V, Lucas S, et al (2002). ***Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study***. Lancet. 360:985-990.

Cox HS, Orozco JD, Male R, Ruesch-Gerdes S, Falzon D, Small I, Doshetov D, Kebede Y and Aziz M (2004). ***Multidrug-resistant Tuberculosis in Central Asia. Emerging Infectious Diseases.*** Int J Tuberc Lung Dis. 10 (5):865-871

Dowdy DW, Chaisson RE, Moulton LH, Dorman SE (2006). ***The potential impact of enhanced diagnostic techniques for tuberculosis driven by HIV: a mathematic model.*** Lancet 20:751-762.

Elizabeth CB, Rosa M, Salani M, Ferreira P, Creusa LC, Jorge LN, (2004). ***Occurrence of active tuberculosis in households inhabited by patients with susceptible and multidrug-resistant tuberculosis.*** J. bras. Pneumol.30 (4): 456-467

Enarson DA (2000). ***Controlling tuberculosis—is it really feasible?*** *Tuber Lung Dis*: 80:57–9.

Evelin Grijalva (2003). ***TB Advocacy Report - The Human Face of TB.*** 416 Available from: http://www.who.int/gtb/publications/Colors_report/

Gandhi NR, Moll A, Pawinski R, Lalloo U, Sturm AW, Zeller K, Andrews J, Friedland G. (2006). ***High Prevalence and Mortality from Extensively Drug-Resistant (XDR) TB in TB/HIV Co infected Patients in Rural South Africa.*** IAS Toronto abstract #MOPE0181

Harriers AD and Maher D (1996): ***TB/HIV: a clinical Manual.*** Geneva: WHO /TB/96.200.

Health Canada (2003). ***Reported susceptibility results of the Canadian Tuberculosis Laboratory Surveillance System***. Ottawa, Canada.

Hu Y, Mathema B,Wang W, Hoffner S, Kreiswirth B, Xu B (2008). ***Microbial Drug Resistance.*** 14(3): 227-232.

Irish C, Herbert J, Bennet D et al (1999). ***Database study of antibiotic resistant tuberculosis in the United Kingdom.*** Brit Med J. 318:497-8.

Janeiro R (2007). ***The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in, Brazil.*** 21:1441-1

John C, Norman H, Fred M (1999). ***Clinical tuberculosis***. London, Macmillan Publishers.

John C, Pierre C, Dermot M (1997). ***Guidelines for the management of drug resistant tuberculosis*** World Health Organization publication.

Joint Tuberculosis Committee of the British Thoracic Society (1998). ***Chemotherapy and Management of tuberculosis in the United Kingdom: recommendations.*** Thorax. 53:536-548.

Lumb R, Bastian I, Dawson D, Gilpin C, Frank H, Greg J, Aina S (2001). ***Tuberculosis in Australia: bacteriologically confirmed cases and drug resistance.*** 27(2):173-179

Pablos-Mendez A, Raviglione MC, Laszlo A et al (1998). ***Global surveillance for antituberculosis drug resistance,*** N Eng J Med. 338:1641-9.

Paramasivan CN, Bhaskarair K, Venkataraman P, Chandrasekara V and Narayanan PR (2000). ***surveillance of drug resistance in tuberculosis in the state of tamil nadu.*** Ind. J. Tub. 47: 27-33.

Raviglione MC, Snider DE Jr, Kochi A (1995). ***Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic***. *JAMA*. 273:220–6.

Sharma.S.K and Mohan A (2004). ***MDR-TB***. Indian J Med Res (120): 354-376

Singh JA, Upshur R, Padayatchi N (2007). ***XDR-TB in South Africa: No Time for Denial or Complacency***. journal.pmed. 4(1): 10.1371

Springer L (2006). ***MDR-TB***,Springer US. (2): 245-293

Sungkanuparph S, Boonchuay E, Suthat C, Supeda T, Weerawat M (2007)**. *Declining Prevalence of Drug-Resistant Tuberculosis among HIV/Tuberculosis Co-Infected Patients Receiving Antiretroviral Therapy***. J Med Assoc Thai. 90 (5): 884-8

Talbot EA, Kenyon TA, Mwasekaga MJ, Moeti TL, Mallon V, Binkin NJ (2003). ***Control of anti-tuberculosis drug resistance in Botswana.*** The International Journal of TB and Lung Disease. 7(1): 72-77(6) T

TB Handbook (2006). Lusaka. Ministry of Health

The Zambia National TB and Leprosy Control Programme (2006). Lusaka. Ministry of Health

Urassa W, Mugusi F, Villamor E, Msamanga G, Moshiro C, Bosch R, Saathoff E and Wafaie Fawzi (2008) ***Primary antimicrobial resistance among Mycobacterium tuberculosis isolates from HIV seropositive and HIV seronegative patients in Dar es Salaam Tanzania***; *BMC Research Notes*, **1:**58doi:10.1186/1756-0500-1-58

Weyer K, Blumberg L, Cameron N, Calver A, Churchyard G, Fourie B, Girdler-Brown B, Matji R and Wilcox P (1999). ***Management of MDR-TB in South Africa***.Journal of Southern Africa Infection Control (1)2:6-9

WHO report (2007).***Global tuberculosis control: surveillance, planning, financing.*** Geneva: (WHO/HTM/TB/2007.376.)

Zager EM and McNerney R (2008). ***MDR-TB,*** BMC Infectious Diseases, London. 8:10

APPENDICES:

APPENDIX I: BUDGET

BUDGET CATEGORY	UNIT COST (ZMK)	QUANTITY	TOTAL
1. STATIONARY			
a) Flash Disc	150,000.00	*2	300,000.00
b) Bond paper	30,000.00	*10	300,000.00
c)Pens	1,000.00	*10	10,000.00
d) Pencils	500.00	*10	5,000.00
e) Rubbers	1,000.00	*10	10,000.00
f) Note book	10,000.00	*1	10,000.00
g) Stapler	50,000.00	*I	50,000.00
h) Staples	10,000.00	*1Box	10,000.00
i) Scientific Calculator	70,000.00	*1	70,000.00
SUBTOTAL			765,000.00
2. SERVICES			
a)Ethics Committee	450,000.00	1	450,000.00
b)Data entry	600,000.00	1	600,000.00
c)Data analysis	1,000,000.00	1	1,000,000.00
d)Typing proposal	3,000.00	70 pages	210,000.00
e)Photocopying proposal	200.00	280 pages	56,000.00

f)Typing Data collection sheet	3,000.00	1 page	3,000.00
g)Photocopying Data collection sheet	300.00	1page *60	18,000.00
h) Typing report		90 pages	270,000.00
I) photocopying report		360 pages	72,000.00
j) Binding		5 copies	250,000.00
SUBTOTAL			2,929,000.00
3. PERSONNEL			
a) Lunch allowance			
Principal investigator	50,000.00	1* 40 days	2,000,000.00
Research assistant	30,000.00	2* 40 days	2,400,000.00
b) Transport allowance			
Principal investigator	30,000.00	1* 40 days	1,200.000.00
Research assistant	20,000.00	2* 40 days	1,600,000.00
SUBTOTAL			7,200,000.00
TOTAL			10,129,000.00
CONTIGENCY 10%			1,012,900.00
GRAND TOTAL			11,141,900.00

APPENDIX II: GANNT CHART

			2009			2010										
No	**Task to be performed**	**Responsible person**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sept**	**Oct**	**Nov**
1	Literature review	Researcher	→													
2	Proposal Development	Researcher	→	→												
3	Presentation to Graduate Forum	Researcher	→	→												
4	Approval by UNZAREC	Researcher		→	→	→	→									
5	Data collection	Researcher				→	→	→								
6	Data analysis	Researcher				→	→	→								
7	Report writing	Researcher						→	→							
8	Submission of draft report	Researcher						→	→							
9	Submission of final report	Researcher									→	→				
10	Dissemination	Researcher						→	→	→	→	→	→	→	→	→

APPENDIX III: DATA COLLECTION SHEET

Date	Serial #	Age	Sex	Occupation	Previous TB treatment	HIV/AIDS Status	Compliance