# Assessing the challenges of MDRTB control in Kenya


## Moses Muli Kitheka
## Kenya



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**Assessing the challenges of MDRTB control in Kenya**

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**Master of Public Health**

By

**Moses Muli Kitheka**

**Kenya**

Declaration:
Where other people's work has been used (either from a printed source, internet or any other source) this has been carefully acknowledged and referenced in accordance with departmental requirements.
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**Dedication**

This thesis is dedicated to my dear wife Ann, and our lovely daughter Faith; the two of you are the source of my power and strength.

To my mother, Nancy and all members of the Mitaa family for your unequivocal support throughout my life. I love you all.

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## List of abbreviations

| | |
|---|---|
| AMPATH | Academic Model for Prevention and Treatment of HIV |
| ART | Anti retroviral therapy |
| CDR | Case detection rate |
| CNR | Case notification rate |
| CPT | Cotrimoxazole preventive therapy |
| CRL | Central Reference Laboratory |
| DLTLD | Division of Leprosy, Tuberculosis and Lung Disease |
| DOTS | Directly Observed Treatment Short course |
| DRS | Drug resistance survey |
| DST | Drug Susceptibility Testing |
| DTLC | District Tuberculosis and Leprosy Coordinator |
| E | Ethambutol, a first line TB drug |
| EPTB | Extra pulmonary TB cases |
| GFATM | Global Fund to Fight Aids, TB and Malaria |
| GLC | Green Light Committee |
| GDP | Gross domestic product |
| H | Isoniazid, a first line TB drug |
| HIV | Human Immunodeficiency Virus |
| HLA | Human leukocyte antigen |
| IPT | Isoniazid preventive therapy |
| IUATLD | International Union against Tuberculosis and Lung Disease |
| KNH | Kenyatta National Hospital |
| TB | Tuberculosis |
| MOH | Ministry of Health |
| MSF | Medecins Sans Frontieres |
| MTRH | Moi Teaching and Referral Hospital |
| MDRTB | Multi-Drug Resistant Tuberculosis |
| NGO | Non Governmental organization |
| NASCOP | National AIDS and STI Control Program in Kenya |
| PTLC | Provincial Tuberculosis and Leprosy coordinator |
| R | Rifampicin, a first line TB drug |
| RAD | Return after Defaulting treatment |
| S | Streptomycin, a first line TB drug |
| SCC | Short Course Chemotherapy |
| SS+ | Sputum Smear Positive TB cases |
| SS- | Sputum Smear Negative TB cases |
| UNITAID | International facility for the purchase of drugs to treat HIV/AIDS, Malaria and Tuberculosis |
| WHO | World Health Organization |
| XDRTB | Extensively Drug Resistant Tuberculosis |
| Z | Pyrazinamide, a first line TB drug |

## ABSTRACT

***Background***: The WHO has acknowledged MDRTB as a threat to global TB control. MDRTB is difficult and challenging to treat, with access to diagnosis and treatment being major constraints especially in developing countries like Kenya

***Study objective***: To assess the progress and challenges of MDRTB control in Kenya and propose informed recommendations to improve the quality of MDRTB control for the country.

***Methodology***: To better understand MDRTB, this study will examine the factors influencing the development of TB drug resistance, and how these eventually lead to MDRTB. In exploring MDRTB control, this study looks at documented best practices as found in the literature and from reputable global organizations in TB control like the WHO and the IUATLD. These main areas identified include knowledge of local TB drug resistance patterns by use of DRS, quality DOTS expansion and enhancement, enhanced case detection for MDRTB, infection control, socioeconomic incentives and research. The study then looks at each of these areas in Kenya so as to assess the current progress and generate specific recommendations for better MDRTB control.

***Findings***: This study found that MDRTB control is a big challenge in Kenya and needs more attention. DOTS expansion for TB control has been progressing well, but access to diagnosis and treatment of MDRTB is still very poor. The major constraints to this are lack of technical capacity and financing for MDRTB control activities.

***Conclusion***: MDRTB is a big threat to TB control in Kenya and the DLTLD needs to invest in all the components identified in this study to better control MDRTB.

**Key words**
MDRTB, tuberculosis, drug-resistant tuberculosis, Kenya, epidemiology

**Word count**: 13,813

## DEFINITIONS OF TERMS USED

**6 months SCC**: The treatment given to new TB cases for a total duration of 6 months. This regime only offers a total of 6 months of Rifampicin during the entire course of treatment

**8 months SCC**: The treatment given to new TB patients for a total duration of 8 months. This regime offers Rifampicin for only 2 months during the entire course of treatment.

**MDRTB control**: the term "control" as applied to TB is used here as defined by Brewer and Heymann (2004) to mean all measures aimed at ensuring "progressive decline of the incidence and prevalence of a disease (in this case MDRTB) in a population ultimately leading to its elimination"

**Treatment success rate**: This is a measure used to assess TB outcome. It is the sum total of cure rate and treatment completed

## INTRODUCTION

Multi-drug resistant tuberculosis (MDRTB) is a global threat to Tuberculosis (TB) control, with half a million new cases notified to the world health organization (WHO) in the year 2007 (WHO 2009a). The recent onset of extensively drug resistant Tuberculosis (XDRTB), first defined in 2006, has additionally worsened the situation. Globally, much of the MDRTB has been reported in china and India with both bearing almost half of the total global burden of MDRTB and the former Soviet Union states (WHO 2008a). The WHO estimate that there are half a million incident cases of MDRTB annually, this represents around 4-6% the total TB burden globally (Chan & Iseman 2008). The prevalence of MDRTB in sub Saharan Africa is described as low but this is equally challengeable.

Kenya has reported cases MDRTB and this bears serious implications for TB control. MDRTB is a new phenomenon in the country, and the control of MDRTB is technically demanding and may pose a threat to the successes gained in TB control over years. Having worked as a PTLC in central province, my experience is that MDRTB control activities have not been optimised and a lot needs to be done. The country faces numerous challenges in MDRTB control needs to move fast to address some of the issues which are easily manageable. This thesis is aimed at helping the DLTLD improve on MDRTB control.

This study examines the progress of MDRTB control as compared to documented best practices. The aim is to generate specific informed recommendations for the DLTLD as it strives to control MDRTB.

## CHAPTER 1: BACKGROUND INFORMATION ON KENYA

### 1.1 Geography and Demography

Kenya is located in east Africa and covers an area of 582,646 square kilometres. It is bordered to the north by Sudan and Ethiopia, to the east by Somalia, to the south by Tanzania and to the west by Uganda. It has a coastline in the south east at the Indian Ocean (CBS 2004).The country has eight administrative provinces each headed by a provincial commissioner. Kenya population grew from 10.9 million in 1969 (CBS 2004) to the current estimated population of 37.5 million in 2007 (World Bank 2009). The population is expected to double by the year 2040 and reach 74 million if unchecked (UNDP 2009).The population is predominantly young, with over half (53.7%) of the population being below 19 years old (CBS 2008)

**Table 1: Basic demographic indicators**

| Indicator | 1969 | 1979 | 1989 | 1999 | 2007 |
|---|---|---|---|---|---|
| **Population (millions)** | 10.9 | 16.2 | 23.2 | 28.7 | 37.5 |
| **Population growth rate** | 3.3 | 3.8 | 3.4 | 2.9 | 2.6 |
| **Life expectancy at birth** | 50 | 54 | 60 | 56.6 | 54 |

Source: CBS (2004); World Bank (2009)

### 1.2 Socio-economic situation and health indicators

The economy is largely reliant on agriculture which contributes 25% of the country's gross domestic product (GDP). The majority of Kenyans also are poor, with 56% living below the poverty line (CBS 2004). This was due to the poor economic growth recorded in the nineties, but after 2002 there was a significant economic rebound with GDP growth rates improving from 0.6% in 2002 to 7.0% in 2007 (CBS 2006;CBS 2008).

**Table 2: Socio-economic and health indicators for Kenya**

| Indicator | Value | Year |
|---|---|---|
| **Fertility rate** | 4.9 | 2003 |
| **Under 5 mortality rate** | 115 per 1000 | 2003 |
| **Infant mortality rate** | 77 per 1000 | 2003 |
| **Maternal mortality ratio** | 414 per 100,000 | 2003 |
| **GDP** | 24.2 Billion US dollars | 2007 |
| **Government expenditure on health as a percentage of total Government expenditure** | 6.1% | 2007 |

Sources: CBS (2004); WHO (2009c)

### 1.3 Health system organization

The government of Kenya, through the ministries of medical services and public health is the main provider of health services in Kenya. The roles of purchasing and provision of medical services in the public sector is done by the government which provides much inefficiency. There is however a vibrant private health sector which has thrived because of poor service provision in the public health facilities over the years. There is general shortage of healthcare workers across all cadres, and the current estimates are shown in table 3.

**Table 3: Number of health personnel per 100,000 population in Kenya**

| Cadre | 2005 | 2006 | 2007 |
|---|---|---|---|
| **Doctors** | 15 | 16 | 17 |
| **Pharmacists** | 7 | 7 | 7 |
| **Registered nurses** | 30 | 30 | 33 |
| **Graduate Nurses** | 1 | 1 | 2 |

Source: Kenya bureau of statistics (CBS 2008)

### 1.4 Tuberculosis program in Kenya

The national TB program in Kenya was established in 1956. This was later merged with the leprosy control project in 1980 to form the national leprosy and tuberculosis control Program. In July 2007, the program was elevated to a fully fledged division, the Division of leprosy, tuberculosis and lung diseases (DLTLD) within the ministry of public health and sanitation (DLTLD 2009). TB treatment is distributed all over the country, with a total of 2,280 facilities offering treatment for TB, of which 930 are also diagnostic as shown in table 4.

**Table 4: Distribution of TB treatment and diagnostic centres in 2008**

| Type of facility | Treatment centres | Treatment centres which have diagnostic capacity |
|---|---|---|
| **Ministry of Health** | 1666 | 653 |
| **NGO** | 382 | 172 |
| **Private** | 232 | 105 |
| **Total** | 2280 | 930 |

Source: DLTLD annual report 2008

The program has 12 control zones (provinces) formed from the 8 administrative provinces each headed by a provincial TB and Leprosy coordinator (PTLC). Each province has a several District TB and Leprosy coordinators (DTLCs) supervising TB control activities in the districts, with a total of 148 DTLCs.

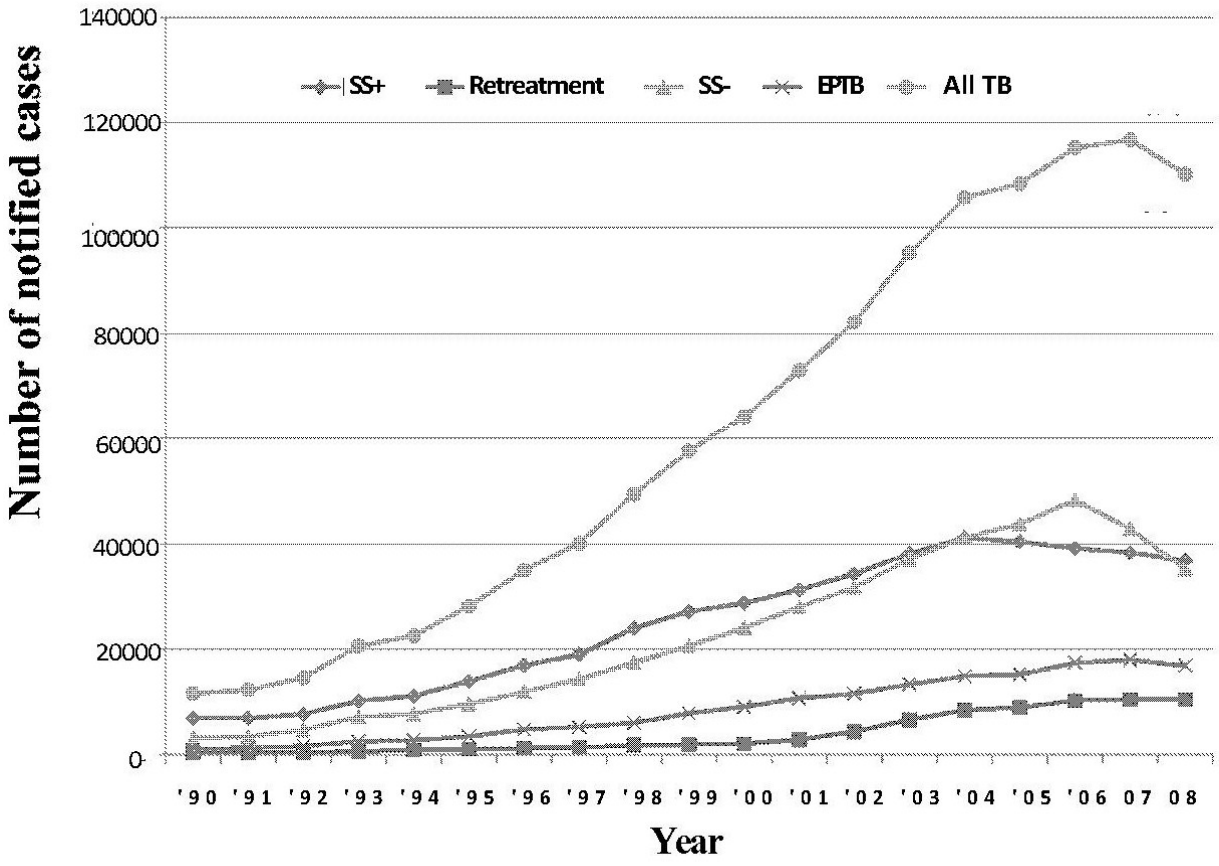
### Burden of Tuberculosis

The WHO in its latest report estimates that there are 13.7 million people infected with TB disease in 2007 worldwide. Out of these, 9.27 million were new cases and this which was an increase from 9.24 million new cases in 2006 (WHO 2009a). Kenya is ranked 13$^{th}$ worldwide in 2007 among the countries with the highest burden of TB, with HIV identified as a key factor in fuelling the spread of TB. Since 1990 when Kenya notified 11,625 cases, TB has been gradually on the increase but the case notification rate (CNR)[1] seems to be now levelling off. In 2008, 110,251 cases of all forms of TB were notified with a CNR of 329:100,000 for all forms and 98:100,000 for new sputum smear positive TB cases (SS+). This was a 5.5% decline from 116,723 cases

[1] The total number of new TB cases per 100,000 population

notified in 2007. However, this may not represent the true burden of considering that in the first quarter of 2008 Kenya experienced post election violence. This disrupted TB control activities in many parts of the country and may have had an effect on the cases detected (DLTLD 2009).

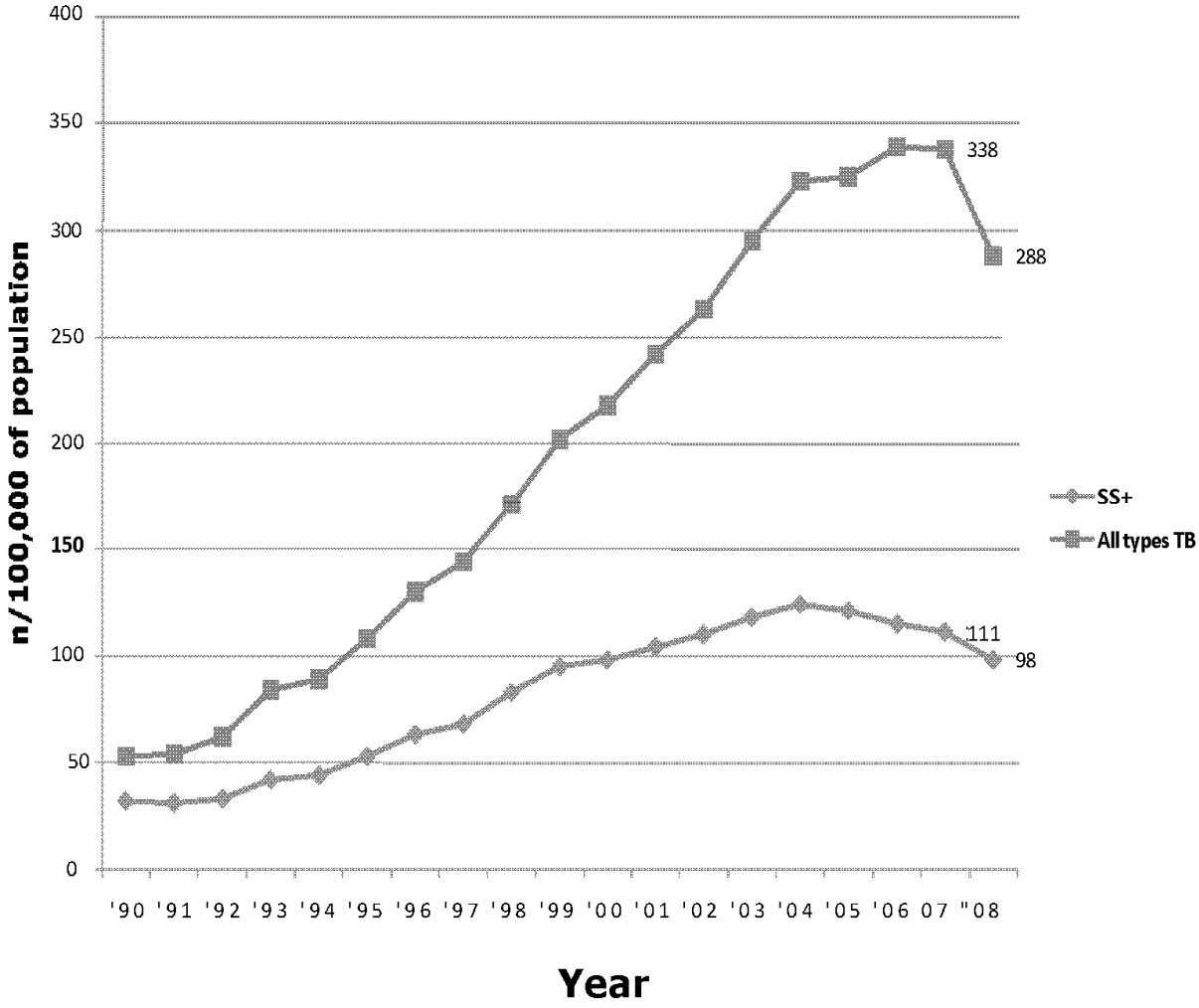
**Figure 1: Burden of TB over years in Kenya.**




Source: DLTLD annual report 2008

The case notification rate for SS+ had also been on the increase up to 2004 but has since then been declining as shown in figure 2.

**Figure 2: Case notification rate for TB in Kenya**




Source: DLTLD annual report 2008

## Chapter 2 PROBLEM STATEMENT

The exact burden of MDRTB in Kenya is currently not known as no recent drug resistance survey (DRS) has been done. This poses a challenge because it is hard to make informed decisions or to rate progress made in MDRTB control without an accurate reference. However, through mathematical modelling, WHO estimates that the current prevalence of MDRTB in Kenya at 1.9% and 7.9% among the new cases and retreatment cases respectively. This gives a total of 6,272 incident cases of MDRTB between 2005 and 2007 (WHO 2009a). Assuming that this is an accurate estimate, this is a huge challenge because Kenya diagnosed and notified only 215 cases over the same time, a paltry 3.4% of the total incident cases. A further 102 cases were detected in year 2008 but the estimates of the incident cases are not yet available (DLTLD 2009). The challenge to DLTLD is to diagnose these new infections and equally importantly enrol the patients under appropriate care and treatment.

**Table 5: Estimated new cases of sputum positive MDRTB in Kenya.**

| YEAR | ESTIMATED NEW CASES | NUMBERS DIAGNOSED AND NOTIFIED | PROPORTION OF CASES DETECTED |
|---|---|---|---|
| **2005** | 2196 | 44 | 2% |
| **2006** | 2060 | 89 | 4.3% |
| **2007** | 2016 | 82 | 4.1% |
| **Total for the 3 years** | 6272 | 215 | 3.4% |

Adapted from: WHO (2009)

Efforts in case detecting for MDRTB have been focused on retreatment cases only. This effectively leaves out other high risk groups for MDRTB, especially new SS+ patients who may have primary MDRTB. In 2008, Kenya notified a total of 36,811 new SS+ and 35,232 new sputum smear negative (SS-) TB cases (DLTLD 2009). Using the WHO estimates that 1.9% of all new cases have MDRTB, this is a considerable missed opportunity in case detection for MDRTB. Many more patients may have mono or poly resistance as new cases and these are patients who can easily develop additional drug resistance, including MDRTB during the course of treatment. Studies show that it is critical to detect drug resistance early enough, preferably before starting TB treatment. This is because patients with drug resistance at the start of treatment do poorly

with the standard TB short course chemotherapy (SCC) and may develop MDRTB (Espinal et al. 2000; Lew et al. 2008; Migliori et al. 2008; Seung et al. 2004).This is further supported by Cox et al (2007) who showed further amplification of drug resistance to TB drugs, including development of MDRTB, drugs once patients with drug resistant strains were started on SCC.

Diagnosis of MDRTB in Kenya is largely reliant on sputum culture and drug susceptibility testing (DST). Rapid diagnosis kits for MDRTB are not available as they are expensive and require specific technical expertise and infrastructure. Overreliance on culture means that patients have to wait for long, usually 8-12 weeks before they can get to know the results. The implication is delayed detection and diagnosis of drug resistance and subsequent care (Migliori et al. 2008).The culture and DST service for diagnosis of MDRTB is centralised in Nairobi, at the central reference laboratory (CRL). Sputum specimens are transported by courier to the CRL from all over the country. This poses a challenge in diagnosing patients especially from remote areas of the country where the courier service is not yet available. The transport of sputum specimens from the health facilities to the Courier Company and onward transmission to the CRL may at times take a long time in the author's experience.

Treatment of MDRTB is quite expensive, with the drugs 100 times more expensive than drugs for SCC (Parry 2009) even with the green light committee (GLC) cost subsidy. This excludes personal costs which are incurred by the patient when accessing treatment and program costs including laboratory follow up tests which can be substantial. This is clearly beyond the reach most patients needing treatment and even national TB programs (Nathanson et al. 2006). Kenya has been approved by the GLC and can therefore procure MDRTB drugs at a cheaper price. The funds from the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM) make the treatment free to the patient at the point of delivery. The GLC agreement entails that the patient receives a small stipend to cover costs incurred when accessing treatment, especially for transport. However, the stipend may not be enough to cover all the direct and indirect costs incurred by patients. Additionally, the nature of the treatment is also quite enduring for the patients as they require at least 6 months of one injectable drug daily on top of the oral drugs. The total treatment duration of 2 years also poses a challenge in ensuring adherence.

There are many patients who have been diagnosed with MDRTB but have not been started on treatment. These are in a waiting list awaiting the next phase of funding for MDRTB drugs due to financing constraints.

However, failure to treat these patients promptly bears a high opportunity cost to both the patients and the country. These untreated patients are a potential pool of ongoing MDRTB transmission hence may influence the future epidemiology of MDRTB in Kenya. They also may suffer possible avoidable morbidity, mortality and reduced quality of life (Ormerod 2005; Guo et al. 2009).

Kenya has relied heavily on donor support to avail the drugs, with very limited Government funding for drugs for MDRTB drugs. The GFATM offered funds to procure drugs for 40 patients in 2008. But what is the fate of the other patients? This is a challenge the county needs to address if it will be successful in MDRTB control.

Treatment of MDRTB using GLC approved drugs is centralised at the two referral hospitals in Kenya, Kenyatta national hospital (KNH) and at the academic model for prevention and treatment of HIV (AMPATH) centre at the Moi teaching and referral hospital (MTRH). Médecins Sans Frontiéres (MSF), an international nongovernmental organization (NGO), is also providing treatment to a limited number of patients but outside the GLC system. Both MSF and AMPATH only offer care and treatment to patients who come from facilities where their programs cover. At KNH, there is an inclusion criterion to be eligible for treatment. One is that the patient needs to reside in Nairobi during treatment for daily observed treatment. Patients who come from far flung areas in the country may therefore not easily access treatment. The districts and communities play a very limited role in MDRTB control. This is despite the enormous potential of community MDRTB control. The proposed special MDRTB ward in KNH is not yet operational, although the Government has made a commitment to finish its construction in the near future. The patients are treated in a small tent outside the hospital (Alsop 2008)

Lastly, HIV has remained a serious public health problem in Kenya. The current prevalence is 7.4% among people aged 15-64 years old (NASCOP 2008). The association between TB and HIV is strong, with HIV positive people at a higher risk of getting both TB and MDRTB. Much of the TB burden in Kenya and other sub-Saharan African countries has been blamed on the HIV pandemic. The risk of death and poor outcome in people with both HIV and MDRTB infection is higher than in HIV negative MDRTB patients on treatment (Kawai et al. 2006). Therefore additional specialised services are needed to ensure that patients with both HIV and MDRTB have better TB treatment outcomes.

## 2.1 Objectives of the study

### Overall objective
To assess the progress and challenges of MDRTB control in Kenya and propose informed recommendations to improve the quality of MDRTB control for the country.

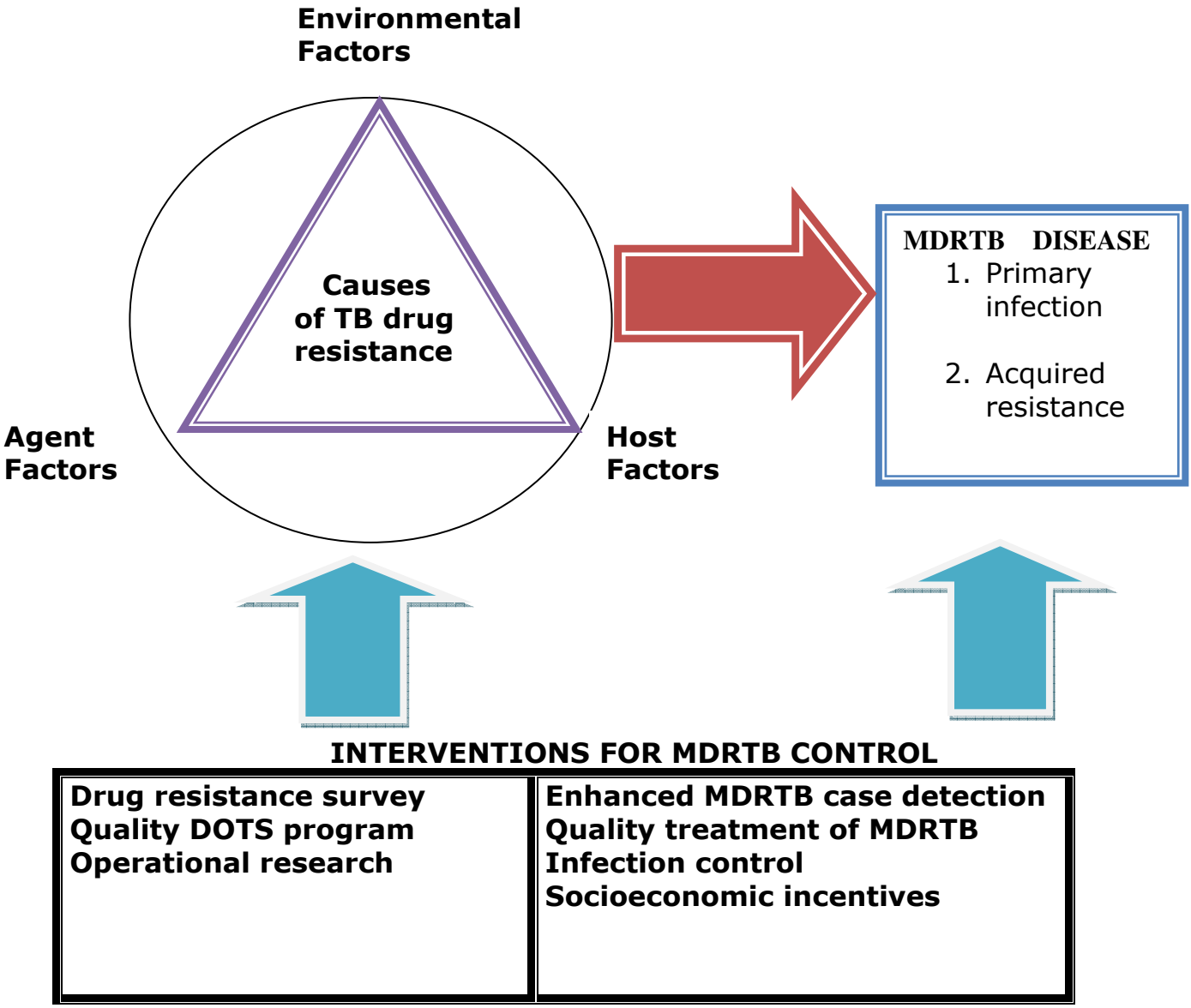
### Specific objectives
1. To explore the etiologic and epidemiologic characteristics of MDRTB as described in literature.
2. To discuss the challenges of MDRTB control in Kenya.
3. To identify and discuss the best practices in MDRTB control especially in the areas identified as challenges in Kenya.
4. To analyze the current health service response to MDRTB in Kenya.
5. To propose recommendations for Kenya to adopt in control of MDRTB.

## 2.2 Methodology
This study will be descriptive in nature. To better understand MDRTB, this study will review literature of aetiology of MDRTB and best practices on MDRTB control. A descriptive analysis of the MDRTB cases diagnosed in Kenya will be done using the available data. An analysis of the progress of MDRTB treatment will also be done. The findings in Kenya will be compared with the findings in literature during the discussion with the aim of assessing the progress made and identifying successes and bottlenecks in MDRTB control. This will then guide the final recommendations. Very limited research on MDRTB has been done in Kenya, so this study will borrow heavily from literature and studies from outside Kenya.

## 2.3 Conceptual framework
In the description and understanding of MDRTB, the drug resistance model will be adopted. The possible causes of TB drug resistance will be discussed from the point of the host (the patient) the agent (TB bacilli) and the environment through various factors as described in the literature. This will help identify the factors which eventually lead to development of TB drug resistance and subsequent MDRTB. This analysis will help understand principle cause of MDRTB. The development of MDRTB may occur as a result of primary infection or by acquired drug resistance. These concepts will also be reviewed to then better understand how MDRTB develops. Having looked at these factors, the approach to MDRTB control will be explored from different

perspectives based on best practices as described in the literature as shown in the framework below.

**Figure 3: The conceptual framework**



Sources of information used:

- Internet search – PUBMED, Google scholar, World health organisation, International union against TB and lung diseases (IUATLD).
- Country reports from the Ministry of Health, DLTLD and National HIV control program
- Books
- My personal experience in Kenya

**Search words**: Multidrug-Resistant tuberculosis, MDRTB, program model, tuberculosis, drug-resistant tuberculosis, Africa, Kenya, TB, review, epidemiology, community, DOTS, DOTS plus, pathogenesis, implications, infection control, HIV.

## 2.4 Study limitations

Monitoring and evaluation of MDRTB in Kenya is just at a nascent stage. The data recording and reporting for MDRTB has been quite weak. Therefore, only limited data is available from the DLTLD and CRL which will be used to assess the program findings. Only data reported to the DLTLD is used, if there are some patients may be accessing care and treatment privately and not reported. Out of the 82 patients diagnosed in 2007, data is available for 72 patients and this is what will be analyzed together with the cases diagnosed in 2008.

# CHAPTER 3: UNDERSTANDING MDRTB

## 3.1 General overview

TB is chronic infectious disease caused by *Mycobacterium tuberculosis*. During the course of treatment, resistance to one or more of the drugs may develop, leading to drug resistant TB strains. MDRTB is, by definition, a strict diagnosis referring to TB bacilli which are resistant to both Rifampicin (R) and Isoniazid (H). These two drugs are the most potent first line anti TB drugs (Dye 2009; Johnson et al. 2006; Ormerod 2005). The principal contributing factor to development of MDRTB is inadequate treatment of drug sensitive TB. It is due to this reason that several authors have referred to MDRTB as essentially a "man-made phenomenon" (Coker 2004; Farmer & Kim 1998; Fraser et al. 2006; Pablos-Mendez et al. 2002).

**Table 6: Definitions of TB drug resistance.**

| TYPE | Definition |
|---|---|
| **Mono resistance** | Resistance to only one drug. |
| **Poly resistance** | Resistance to more than one drug except to both H and R |
| **Multi –Drug resistance** | Resistance to at least both H and R with or without resistance to any other TB drugs |
| **Extensive – Drug resistance** | **MDRTB,** and on top, resistance to a fluoroquinolone and at least one injectable second line MDRTB drug. |

Source: WHO (2008b)

Resistance to TB drugs was recorded almost immediately after they were introduced into clinical use. Drug resistant surveys carried out later by WHO since 1994 showed increasing drug resistance, and more importantly, increasing prevalence of MDRTB in the 1990s (WHO 1997). The highest prevalence rates were in some eastern European countries like Estonia and Latvia, but the prevalence in sub-Saharan African countries was estimated to be low (Drobniewski & Balabanova 2002; Pablos-Mendez et al. 2002; Wright et al. 2009). However, this finding is disputed by Ben et al (2008) arguing that African countries may have higher MDRTB prevalence levels than previously thought, considering most of these countries had not done any drug resistance surveys. Generally, males are more affected by MDRTB than females, just as is the case for drug sensitive TB, and young people aged between 25-44 years are equally also the most affected (WHO 2008).

## 3.2 CAUSES OF DRUG RESISTANCE

Several factors will collectively lead to development of resistance to TB drugs as explained below.

### 3.2.1 Host factors

***Prior exposure***: Prior exposure to TB medication is an important risk factor for the development of drug resistance. This usually occurs due to previous treatment of either TB or MDRTB (WHO 2008b; Ormerod 2005). Mono therapy is especially strongly linked to development of drug resistance (Loddenkemper et al. 2002). The most known form of mono therapy is Isoniazid preventive therapy (IPT). Before using IPT, it is crucial to rule out active TB disease (WHO 1998). Use of SCC in a patient with prior drug resistance will further predispose the patient to possible resistance to the additional drugs given, including possible MDRTB. As a minimum, 4 drugs are recommended during the intensive phase of treatment of TB as per WHO guidelines (Cox et al. 2007; Sharma & Mohan 2004).

***Poor adherence to treatment***: Patients who do not take the drugs as prescribed and those who default treatment are at a high risk of development of resistance. It is important to look out for factors which may potentially affect treatment adherence and address them timely (Andrews et al. 2008; Jain & Dixit 2008; PIH 2003).

**Table 7: Factors which may affect drug adherence**

| | |
|---|---|
| **Psychiatric illness**<br>**Alcoholism**<br>**Drug addition**<br>**Homelessness**<br>**Travel away to a different place** | **Symptomatic relief after treatment**<br>**Adverse drug reactions**<br>**Long duration of treatment**<br>**Inability to afford treatment**<br>**Lack of money for transport**<br>**Lack of information** |

Adapted from**:** Jain & Dixit (2008); WHO (2008b)

***Malabsorption of TB drugs:*** Virtually all first line drugs for TB are given through the oral route. Poor absorption in the digestive system may lead to suboptimal drug levels in the blood hence favouring the development of resistance (WHO 2008b). Patients who are HIV positive may be at a greater risk as they may have additional gastro intestinal diseases (Gillespie 2002).

***Genetic susceptibility***: Although not widely researched, some patients may have a slightly higher genetic probability to develop MDRTB than others (Sharma & Mohan 2006). Patients with specific HLA types (HLA-DRB1*14) were found to be at a higher risk of developing MDRTB than the general population in an Indian study (Sharma et al. 2003).

***Nature of the infection:*** The higher the population of the mycobacteria in a patient, the higher the risk of development of resistance during

treatment. In addition, cases which have localised TB infection and lung cavities with necrotic tissues or pus will lead to less drug penetration. This will mean exposure to fewer and lower drug concentrations promoting the risk of resistance (Gillespie 2002).

### 3.2.2 Environmental factors

***Inefficiency in the TB program:*** TB program inefficiency can contribute to inadequate provision of timely and high quality drugs. When stock outs occur, or the drugs are of poor quality, the risk of development of drug resistance may be high as many patients may easily miss treatment (Jain & Dixit 2008). Poor storage conditions of the drugs may make them lose potency. Other factors may include lack of capacity to treat TB, lack of clear national guidelines on TB control, and a weak monitoring and evaluation system for the TB program (Sharma & Mohan 2006; WHO 2008b).

***Prescriptions errors****:* TB drug resistance may occur when fewer than the recommended drugs are used to treat TB (Ormerod 2005) Other factors may include inappropriate TB treatment regimes which don't follow national guidelines, poor dosing and adding a single drug to the treatment to which the patient has had poor response (Jain & Dixit 2008).

### 3.2.3 Agent factors

***Genetic changes***: Drug resistance to TB drugs usually occurs through genetic mutations. These mutations are usually acquired, due to exposure to the drugs or may occur spontaneously (Gillespie 2002; Dye 2009).

***Mycobacterium genotype***: The development of resistance can be influenced by the genotype or strain of the mycobacterium. The "W-Beijing" strain of mycobacterium has the highest probability of becoming drug resistant following exposure to TB drugs than the non-Beijing strains (Sharma & Mohan 2006; Glynn et al. 2002; Iwamoto et al. 2008). It also has a higher capacity to be spread compared to the non Beijing strains. The "W-Beijing" subtype has already been isolated in many countries with high rates of MDRTB especially in Eastern Europe (Cox et al 2007; Loddenkemper et al. 2002; Sharma & Mohan 2006).

## 3.3 DEVELOPMENT OF MDRTB

A patient can develop MDRTB in two ways

- Acquired drug resistance resulting into MDRTB
- Primary infection with MDRTB

### 3.3.1 Acquired drug resistance

Acquired drug resistance occurs when drug resistance occurs during the course of treatment due to exposure to TB drugs (Sharma & Mohan

2006). This is caused by mutations occurring in specific genes in the mycobacterium influenced by exposure to TB drugs. Acquired resistance mostly develops from poor treatment protocols and especially where DOTS is done well adhered to (Dye 2009; Chan & Iseman 2008; Sharma & Mohan 2004).

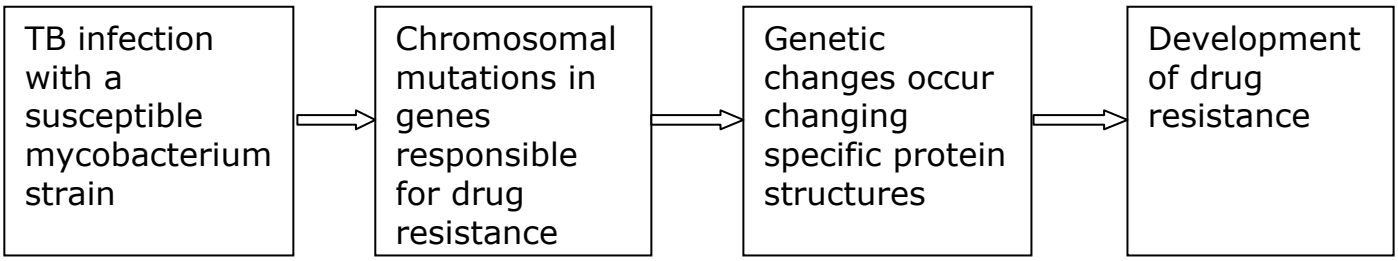
### 3.3.2 Primary infection with MDRTB

Primary MDRTB occurs when a patient develops MDRTB as a result of a new infection with MDRTB. This occurs when patients without known exposure to TB drugs develop new TB infection which is already MDRTB (PIH 2003; WHO 2009b). This mainly occurs in close contacts of MDRTB patients, especially close family members and also healthcare workers as a result of hospital acquired infection. Re infection and super infection with a new resistant strain of TB bacillus is also possible in a MDRTB patient during treatment, hence the patient responds poorly to treatment (Cox et al. 2007; Sharma & Mohan 2004). This is even more common among HIV positive people (Horsburgh Jr 2008).

### 3.3.3 Evolution of drug resistance

Genetic mutations in genes coding for TB drug resistance in the mycobacterium genome can occur leading to development drug resistant strains. These mutations can occur either spontaneously or due to exposure to TB drugs. The frequency of spontaneous mutations is too low (1 in every $10^6$ to $10^8$ replications) to result in significant levels of drug resistance (Sharma & Mohan 2006; Sharma & Mohan 2004). These genetic mutations occur at different sites for each drug, the rates differ between drugs (Ethambutol has the highest risk with Rifampicin being lowest) and are mutually exclusive. This means that resistance to Isoniazid may not necessarily lead to resistance to Rifampicin or to other TB drug. The probability of significant spontaneous resistance to more than one drug is actually very low. This means getting MDRTB from spontaneous mutations is highly unlikely (Sharma & Mohan 2006; Coker 2004; Gillespie 2002; Sharma & Mohan 2004).

**Figure 4: Development of TB drug resistance**




Adopted and modified from: Jain & Dixit 2008

The mycobacteria colonies which develop spontaneous drug resistance and the drug sensitive colonies do coexist in a patient. When treatment is initiated, there is need to give multiple drugs preferably in fixed drug

combinations (Dye 2009; Yew & Leung 2008) to avoid the patients selectively leaving out some drugs or clinicians mistakenly using fewer drugs which may selectively eliminate drug sensitive strains and leaving the resistant strains to predominate in the patient. This is a typical scenario which can occur with use of one or 2 drugs. Subsequent re treatments will increase the risk of development resistance to the additional drugs used leading to a spectrum of resistance, from mono to poly resistance and even MDRTB (Johnson et al. 2006).

### 3.4 VIRULENCE OF MDRTB

Many studies have gone into checking the virulence (also called fitness) of MDRTB as compared to drug sensitive TB. The results are highly variable but all seem to point that MDRTB is probably either equally or less virulent, and less capable of survival than drug sensitive TB. MDRTB strains have also been shown to be a bit less infectious that drug sensitive TB (Cohen et al. 2003; Hannah et al. 2000; Sharma & Mohan 2006). However, future trends are hard to predict because the constant mutations may in future produce other strains of MDRTB which are either more or less fit (Gillespie 2002; Cohen et al. 2008; Yew & Leung 2008). The "W-Beijing" subtype as described above is, however, an exception (Sharma & Mohan 2006; Glynn et al.).

### 3.5 DEVELOPMENT OF XDRTB

Further development of resistance to drugs used for MDRTB can occur if treatment is not strictly adhered to, resulting in XDRTB. Already, many countries worldwide (over 49) have reported cases of XDRTB (LoBue 2009) including Africa where there was a big outbreak in South African (Andrews et al 2007). Other southern African countries too have reported cases including Lesotho, Botswana and Mozambique (Satti et al. 2008; Madariaga et al. 2008). The prevalence of XDRTB is estimated to be around 6.6% of all MDRTB patients worldwide. In a survey in Msinga sub district in South Africa, 54 (24%) of the 224 MDRTB cases detected were found to be XDRTB (Gandhi et al. 2006; Jain & Dixit 2008; Shah et al. 2007; WHO 2008b). There are not many options for treatment of XDRTB and the treatment outcome is usually worse than for MDRTB, with quite high case fatality rates. In Kwazulu Natal, South Africa, where there was a large outbreak of MDRTB and XDRTB, the death rate was at 98% for the patients with XDRTB although most were co infected with HIV (Andrews et al. 2007). In fact, Matteelli et al (2007) described XDRTB as "potentially untreatable" showing how serious this is. This opinion may, however, begin to change with Dye (2009) stating that with the use of different drug combinations to which the patient is still sensitive to, it may be possible to cure some cases of XDRTB.

# CHAPTER 4: REVIEW ON BEST PRACTICES FOR MDRTB CONTROL

## 4.1 UNDERSTANDING THE LEVEL OF DRUG RESISTANCE.

For a long time there have been perceptions that the levels of MDRTB in African countries are low. However, this is challengeable as many African countries had not done DRS in the recent past. Ben et al (2008) argues that the threat of MDRTB in Africa is markedly underreported, and concludes that the DRS are "critically needed" in African countries. He further argues that the later introduction of Rifampicin into the SCC in many African countries may not necessarily translate to lower levels of MDRTB. This is because the high levels of HIV in the region may hasten Rifampicin resistance and hence speed up the MDRTB pandemic. A model by (Cohen et al. 2008) further reveals that the current methods being used for DRS may be underestimating the real burden of drug resistance and may need review to capture the real extend of drug resistance. The international union against TB and lung diseases (IUATLD) together with WHO started the global drug resistance survey in 1994 (WHO 1997) and this is subsequently done every 3 years.

Knowledge on the main pattern of drug resistance will help countries determine areas to put emphasis in addressing MDRTB in their local context (Andrews et al. 2008). A review by Mak et al (2008) showed that the presence of drug resistance before initiation of DOTS leads to a significant reduction in treatment success. Before initiating MDRTB treatment programs, Lambregts-van Weezenbeek & Reichman (2000) recommended that a representative DRS should be an initial requirement for all TB control programs if MDRTB control is to be successful.

## 4.2 HIGH QUALITY DOTS PROGRAM

MDRTB has been blamed on poor TB control where DOTS is not well practiced. The most important and cost effective step in controlling development of drug resistance and MDRTB is to adequately detect and treat drug sensitive TB using DOTS and achieve high cure and treatment success rates (Coker 2004; Farmer & Kim 1998; Fraser et al. 2006; Pablos-Mendez et al. 2002).

### 4.2.1 High case detection and treatment success rate

The WHO recommends six components in the STOP TB strategy to be adopted by all countries as the best way to control TB. This initiative is aimed at reducing the global burden of TB by the year 2015 as delineated in the millennium development goals (MDGs).

**Box 1: Stop TB strategies**

1. Pursue high quality DOTS expansion and enhancement
2. Address TB-HIV, MDRTB and the needs of poor and vulnerable populations
3. Contribute to health system strengthening based on primary health care
4. Engage all healthcare providers
5. Empower people with TB, and the communities through partnerships
6. Enable and promote research

Source: WHO Stop TB strategy (WHO 2006a)

Patients diagnosed with TB should be put on high quality SCC under a strong DOTS program. It is essential to assure high treatment success to avoid the calamity of drug resistance and achieve good treatment success (Dye & Williams 2000, Dye 2009). To illustrate this, TB programs which reported high cure rates (over 80%) over many years like Chile, Uruguay, Cuba and Algeria have also correspondingly reported very low MDRTB rates (below 1%) in DRS done since the seventies (Dye et al. 2002). A strong DOTS program will also lead to lower overall transmission of all forms of TB, including MDRTB in the population (DeRiemer et al. 2005). A mathematical model by Dye & Williams (2000) indicates that a cure rate above 80% using SCC and active case finding to detect over 70% of infectious TB cases, both resistant and non resistant, can reduce the overall resistance to TB drugs. This in turn will help can help slow down the MDRTB epidemic. However active case finding is also needed for the existing MDRTB cases and appropriate treatment given. For the achievement of the MDGs to be realised, the WHO has set critical targets for TB control as shown in box 2.

**Box 2: Targets for TB control**

1. Detect at least 70% of all smear positive TB cases using the DOTS strategy

2. Achieve a cure rate of at least 85%

Source: WHO Stop TB strategy (WHO 2006a)

### 4.2.2 SCC Treatment regimes for TB

The type of treatment of TB may have an influence on the development of drug resistance and treatment outcome (Heldal et al. 2001). The 6 months SCC is far superior to the 2 months SCC in improving treatment outcome and reducing probability of drug resistance (Mak et al. 2008). A systematic review by Lew et al (2008) showed a higher treatment failure (35-40%) in patients using the 8 month SCC than the ones using the 6 month SCC (20%) in patients who has drug resistance at the start of treatment.

### 4.2.3 TB Retreatment regime

The retreatment regimen as recommended by WHO has been blamed by many studies as exacerbating the problem of drug resistance and may need to be re looked again (Ormerod 2005). The challenge is, however, the limited options as there are no new TB drugs in the market yet. The retreatment regimen as used in most countries only adds one extra drug, Streptomycin, to patients who may have failed in the first treatment. Furthermore, Streptomycin was the first ever TB drug developed and resistance to Streptomycin started to develop almost immediately afterwards (Shenoi & Friedland 2009). Streptomycin resistance is common in many African countries, with resistance ranging from a high of 28.2% in the Democratic Republic of Congo and 24.5% in Ethiopia to a low of 0.8% in Zimbabwe (WHO 2008a). If the patient had mono or poly resistance, reintroduction of the same drugs (as done in TB retreatment only adding Streptomycin) increases the probability of extra drug resistance, one of them being MDRTB. The retreatment regime may actually succeed in exposing more resistance to the added drug (Drobniewski & Balabanova 2002; Ormerod 2005).

## 4.3 Enhanced Case Detection for MDRTB

The best way to ensure that all incident cases of MDRTB are detected is prompt DST on all the sputum positive cases. This may be costly but can help identify cases of primary MDRTB infection sooner (PIH 2003). In resource poor settings, the alternative way is to identify the people who may have a higher probability of having MDRTB as shown in box 3 and target them for DST.

**Box 3: Patients to prioritise for DST**

- Treatment failures during SCC
- Failure in TB treatment from private sector
- Retreatment failures
- Patients who are sputum positive after 2-3 months of SCC
- Known contacts of MDRTB cases
- TB relapse
- Patients who resume treatment after defaulting
- Prisoners in settings with high MDRTB
- HIV positive patients
- Hospital staff, especially the ones in close contact with TB patients
- Contacts of TB patients who died during treatment under DOTS
- Residents in areas with high MDRTB prevalence rates
- History of use of TB drugs of unknown or poor quality
- Treatment in programs of unknown quality

Adapted from: PIH (2003) and WHO (2008b)

Studies point to retreatment failure as a good indicator of MDRTB. In Brazil Kritski et al (1997) demonstrated the risk of MDRTB in retreatment failures to be 10 times than defaulters of first line SCC or people who had recurrence of TB. This is supported by Heldal et al (2001) who found that 89% of retreatment failures done DST in Nicaragua to have MDRTB.

Diagnosis can take several forms, either by use of culture and DST, or use of the more rapid genetic and phenotypic testing methods, which are faster and have high sensitivity but are more expensive (Ormerod 2005; Palomino 2006). Conventional culture can be done using liquid or solid media, or can use newer methods like the MGIT960 which has been adopted by some centres and gives results relatively faster (Somoskovi et al. 2003). Culture and DST is cheaper and hence this is the method used more in resource limited settings. However, because of its long duration to getting results it may contribute to reduced efficiency by having a long lag time before diagnosis is made. This method takes long as mycobacteria generally take a long to multiply (over 24 hours) and production of visible growth in culture will take over a month. This leads to delayed diagnosis and hence treatment may never be started in time in programs relying only on culture and DST (Grant et al. 2008; Johnson et al. 2006; Matteelli et al. 2007). The rapid tests may be more expensive, but give faster and more reliable results. A trade-off between actual cost and efficiency must be made by

countries as they make decisions on which diagnostic measures to adopt.

To ensure reliability of results, the WHO recommends that central reference laboratories should have strict quality control and quality assurance programs. Links should also be made with one of the supra national reference laboratories network worldwide for external quality assurance (WHO 2008b)
*(See annex 5 for various methods of diagnosis of MDRTB)*

**Decentralization of DST**
A major constrain to access of diagnosis is the centralised nature of diagnostic services. Many developing countries have to rely on one national CRL, as these services are expensive to run, and require highly trained staff. Decentralization of DST needs some consideration in these countries. Peru is one of the examples of successful decentralization of DST to the districts. The program there also started to use rapid diagnostic tests which were considerably simple, cheaper and faster enhancing faster diagnosis (Asencios et al. 2008). This started as a pilot then was rolled out systematically over time and has been a major success in MDRTB control.

## 4.4 QUALITY MDRTB TREATMENT

To address the challenge of cost and access to MDRTB drugs, the WHO formed the working group on MDRTB in 1999. This group was also asked to give technical assistance to countries on MDRTB treatment. This later led to the formation of the GLC in June 2000. Negotiations were done by the GLC with drug manufacturing companies to avail high quality MDRTB drugs at highly reduced prices (over 90% cost reduction) to GLC approved MDRTB programs (Pablos-Mendez et al. 2002; WHO 2000).
Cost effectiveness studies for MDRTB treatment have shown that despite the high costs, MDRTB treatment using the WHO recommended guidelines is a very cost effective strategy even for poor countries (Resch et al. 2006; WHO 2007; Suarez et al. 2002). All Countries need to adopt DOTS plus[2] treatment for MDRTB and avail treatment for MDRTB as a key component of TB control. Treatment of MDRTB also helps to reduce its potential of transmissibility and hence cause an overall decline in the prevalence of MDRTB in the population as shown in a model by Rodrigues et al. (2007). However, Lambregts-van Weezenbeek & Reichman (2000) calls for caution in introducing treatment for MDRTB. All components of the MDRTB treatment strategy need to be put in place with a very strict drug management system in

[2] This is the WHO recommended strategy for MDRTB treatment, to avoid confusion with DOTS for TB, some authors use the term "WHO recommended treatment strategy for MDRTB"

addition to supervised daily treatment. Failure to implement DOTS plus fully may lead to disastrous results as expressed in the quotation below.

> "*Failure to institute this entire DOTS plus package is likely to destroy the last tools available to combat tuberculosis, and may ultimately result in the victory of the tubercle bacillus over mankind*" Lambregts-van Weezenbeek & Riechman (2000)

### 4.4.1 Basic components of the DOTS plus

DOTS plus for MDRTB is based on the basic principles of DOTS but with more emphasis on each of the strategies due to the demanding nature of MDRTB treatment. There is need for clear coordination of treatment at the national, regional, health facilities and community level to ensure successful implementation of DOTS plus (WHO 2000).

**Table 8: Comparison between DOTS and DOTS plus strategies**

| DOTS expansion for TB | DOTS plus for MDRTB |
|---|---|
| ✚ Political and administrative commitment<br>✚ Quality diagnosis by sputum microscopy<br>✚ Uninterrupted supply of good quality first line drugs for standardised treatment through outpatient therapy<br>✚ Directly observed treatment<br>✚ Systematic monitoring and accountability | ✚ Sustained political and administrative commitment<br>✚ Accurate, timely diagnosis through quality assured culture and DST<br>✚ Uninterrupted supply of quality assured first and second line drugs; appropriate treatment strategies utilizing second line drugs under strict supervision<br>✚ Directly observed treatment<br>✚ Standardised monitoring and reporting systems that enable performance monitoring and evaluation of treatment outcome |

Source: Sharma & Mohan (2006) and WHO (2008b)

MDRTB treatment poses serious challenges as compared to drug sensitive TB. The drugs used are less potent as compared to drugs used in first line SCC. This is why the treatment has to take a longer duration (recommended 18-24 months of treatment).

**Table 9: Challenges in the treatment of MDRTB**

| | |
|---|---|
| Treatment | MDRTB is difficult to treat<br>Well trained and experienced staff needed<br>Complicated and challenging treatment<br>Treatment is more expensive |
| Drugs used in MDRTB treatment | Less effective<br>More toxic and side effects are more common<br>Expensive |

Adapted from: Jain & Dixit (2008)

### 4.4.2 Side effects of MDRTB drugs

Many drugs used in MDTRB treatment have many side effects and drug toxicities which may have influence on adherence to treatment. Among the HIV positive patients on treatment for MDRTB, drug interactions can reduce efficacy of the treatment hence lead to poor treatment outcome (Wells et al. 2007). Even without HIV, patients on MDRTB treatment may experience many side effects. However, studies show that these may not be of substantial effect to the treatment as can be managed locally to avoiding the risks of stopping treatment (Nathanson et al. 2004; WHO 2008b; Franke et al. 2008; Yew & Leung 2008).

**Table 10: Frequency of side effects as recorded from 5 programs**

| **>10%** | **5-10%** | **<5%** |
|---|---|---|
| **Nausea & vomiting**<br>**Diarrhoea**<br>**Joint pains**<br>**Dizziness**<br>**Hearing disturbances**<br>**Electrolyte imbalance**<br>**Abdominal pains** | Anorexia<br>Gastritis<br>Peripheral neuropathy<br>Depression tinnitus<br>Allergic reactions | Rash<br>Visual disturbances<br>Seizures<br>Hypothyroidism<br>Psychosis<br>Hepatitis<br>Kidney failure |

Adapted from: WHO (2008b)

### 4.4.3 Decentralization of treatment

Management of MDRTB is expensive, and efforts need to be put to lower unnecessary costs involved. A possible strategy is to decentralize treatment to the districts and the community using trained community health workers working closely with the healthcare facilities (WHO

2008b). This may lessen the bottleneck of transport logistics for daily DOTS which may precipitate non adherence. Decentralization can also help build community capacity in control of MDRTB and gain local acceptance of treatment. This is mainly because many countries have an established community TB framework (WHO 2008b). Community DOTS plus for MDRTB showed marked success and achieved good treatment outcomes in a resource limited setting in Peru. The costs were markedly minimised as compared to a centralised hospital setting. It was also found out that because the local staffs were trained, case finding was improved. Contact screening was also good and there was markedly good treatment adherence and lowered defaulter rate (Farmer & Kim 1998; Mitnick et al. 2003; Shin et al. 2004).

The concept of decentralisation of care and treatment was also proposed by Padayatchi and Friedland (2008) who identified a similar problem of centralised care and treatment of MDRTB in South Africa.

### 4.4.4 Follow up during treatment

After initiation of treatment, follow up with serial sputum smear and culture is recommended to check for time to sputum conversion as shown in table 11. This acts as a predictor to the progress of treatment and helps determine the treatment outcome.

**Table 11: Follow up assessment**

| | |
|---|---|
| Sputum microscopy and culture | At beginning of treatment<br>Then monthly from the 2$^{nd}$ month till the 6$^{th}$ month<br>Then every 3 months till end of treatment |
| DST | At start of treatment, then every 3 months till the sputum cultures are negative. |

Adapted from: WHO (2000)

### 4.4.5 Treatment outcome and cohort analysis

Cohort analysis is usually done after 36 months, due to the long duration of therapy. However, it is possible to do a 12 and 24 months analysis as a midterm review using the sputum conversion as a guide to treatment response. Standardised treatment outcomes are as defined below.

**Table 12: Definitions of treatment outcome**

| Definition | Description |
|---|---|
| ***Cure*** | During the last 12 months of treatment, a patient consistently has a minimum of 5 or more consecutive negative smear results obtained by sputum culture. |
| ***Treatment completed*** | Patient who has successfully finished treatment but has not had all the last 5 cultures in the last 12 months of treatment done to achieve the definition of cure |
| ***Treatment failure*** | During the last 12 months of treatment, at least 2 of the last 5 sputum culture results are positive or if at least one of the last 3 culture results is positive or if a clinical decision is made to stop treatment due to side effects or poor response. |
| ***Death*** | Defines a patient who dies due to any reason during the course of treatment |
| ***Treatment default*** | When treatment is interrupted due to any reason for at least 2 consecutive months |
| ***Transfer out*** | When a patient transfers to another centre for treatment and his/her outcome to treatment is not known. |

Adapted from: Laserson et al (2005) and WHO (2008b)

Despite the lower efficacy of MDRTB drugs compared to the first line drugs, many treatment programs have achieved variable but good cure rates for MDRTB. In a review by Chan & Iseman (2008), treatment success rates for MDRTB in several countries reviewed ranged from a low of 33% in Canada to high of 82.5% in South Korea, with the majority being over 50%. Another systematic review of many countries showed an average cure rate of 69% (CI 64%-73%) when patients were treated for over 18 months with daily observation for MDRTB (Orenstein et al. 2009). An analysis of 75 MDRTB patients stated on treatment in Latvia in 2002 showed a treatment success rate of 73% (Riekstina et al. 2007) and in Bangladesh a cure rate of 69% was achieved (Van et al. 2004).

## 4.5 INFECTION CONTROL

Among the areas with the highest risk of TB transmission is the healthcare settings. Numerous studies in Malawi, South Africa, Thailand and Brazil have shown presence of hospital acquired TB by healthcare workers in a review by Menzies et al. (2007), hence underpinning the relevance of infection control. Other studies also found that the prevalence of both TB disease and infection among healthcare workers is also higher than community controls and than in the general

population (Joshi et al. 2006; Menzies et al. 2007) due to hospital acquired TB. The risks are even higher in settings of high HIV/AIDS prevalence which is common in most countries in sub-Saharan Africa. Staff who have more direct contact with TB patients are at a higher risk of infection, especially Nurses, Laboratory workers and Radiographers (Andrews et al. 2007; Joshi et al. 2006; Menzies et al. 2007; Naidoo & Jinabhai 2006; WHO 1999a). Infection control measures have been shown in a model by Basu et al. (2007) in South Africa reduce the risk of transmission of drug resistant TB by half if well implemented. Most infection control measures are simple and fairly effective. It is therefore necessary for TB programs and hospitals to ensure infection control guidelines well implemented and known to all health workers (Mehtar 2008; Scano et al. 2008).

*(See annex 3 for a detailed list of infection control measures)*

## 4.6 SOCIO-ECONOMIC INCENTIVES

Non adherence to MDRTB can be catastrophic and easily lead to the feared onset of XDRTB. To address some of the issues which may limit adherence, there is need to provide specific socioeconomic incentives to make the patients more comfortable and adhere to treatment (WHO 2008b; Nathanson et al 2006). These can be tailored to the specific contexts.

**Box 4: Possible socioeconomic incentives for MDRTB patients**

1. Free health care
2. Transport fees
3. Food parcel for the patients and their immediate family
4. School fees for children
5. Temporary shelter/housing
6. Advice and assistance in all matters on treatment
7. Provision of life skills to heal them when in the community after treatment
8. Assistance in defending their rights and knowing their responsibilities

Adapted from: WHO (2008b)

## 4.7 MANAGEMENT OF HIV IN MDRTB PATIENTS

HIV poses a serious challenge in patients with MDRTB. HIV increases the risk of death, even with treatment for MDRTB. HIV can also lead to activation of latent MDRTB if the patient was exposed to the bacillus before, resulting in a primary MDRTB (PIH 2003). A study in Peru showed HIV to be a strong indicator of poor treatment outcome in patients with MDRTB as compared to MDRTB patients who were HIV negative (Kawai et al. 2006). Many studies seem to agree that HIV does

not lead directly to MDRTB, but the immune suppression caused by HIV increases the risk of development of TB, including MDRTB. Dye et al. (2002) also gives five concrete reasons why HIV may predispose development of drug resistance.

**Box 5: How HIV predisposes to MDRTB**

1. The less virulent strains of MDRTB are able to easily manifest in HIV positive that HIV negative patient due to immune suppression
2. HIV and MDRTB may have common risk factors e.g. hospitalization (risk in hospital acquired MDRTB) and injection drug use.
3. Primary infection is easier for TB in HIV positive
4. Patients with both TB and HIV may have very high load of mycobacteria leading to higher possibility of treatment failure
5. HIV patients may continue to have bacterial replication in the continuation phase. When drugs are switched from 4 to 2 drugs in the continuation phase and the patient is resistant to one they are effectively getting mono therapy. This further predisposed to MDRTB

Adapted from: Dye et al (2002)

In a systematic review by Suchindran et al (2009), out of all the countries reviewed in Africa, there was no association between MDRTB prevalence and HIV. In the review, Studies in Cote d`Ivoire, Tanzania, Botswana and South Africa found no statistically significant difference in the prevalence of MDRTB between HIV positive and HIV negative patients. Mak et al (2008) explains that this may be due to the very high general prevalence of HIV and relatively lower MDRTB levels compared to other areas like Asia and Europe. This was however different in most of the countries from Asia, Latin America and Europe in the review, where there was more significant association between HIV infection and MDRTB (Suchindran et al 2009).

The duration of conversion from sputum positive to sputum negative during treatment is longer in HIV positive than HIV negative patients. With the knowledge that the conversion time from sputum positive to negative is longer in MDRTB than in drug sensitive TB, it then follows that the duration the patient with both MDRTB and HIV remains sputum positive longer and has a longer infectious duration even with treatment (Kawai et al. 2006).These dually infected patients also have a higher case fatality rate than HIV negative patients with MDRTB.

Large scale outbreaks of both MDRTB and XDRTB have been associated with HIV. The best examples are the New York City outbreak of MDRTB (Moss et al. 1997) and South Africa where over 90% of the patients with were infected with HIV (Gandhi et al. 2006; Shenoi et al. 2009).

HIV positive patients are usually also on treatment with other drugs, and may probably be less well compliant to treatment due to the pill load and the great possibility of drug interaction and drug side effects. HIV positive people with MDRTB also have relatively poor absorption of TB drugs in the gastro intestinal tract compared with HIV negative people. Management of a patient with both MDRTB and HIV is hence complex and technically demanding. TB/HIV collaboration and especially timely provision of anti retroviral therapy (ART) is hence essential as a way to tackle dual infection and avert growing numbers of potential MDRTB cases (Getahun et al. 2009; Gandhi et al. 2009; Scano et al. 2008).
*(See annex 4 for the WHO recommended TB/HIV collaborative activities)*

## 4.8 OPERATIONAL RESEARCH

Operational research is critical for successful TB Control, and this includes MDRTB (Scano et al. 2008; WHO 2006b). Research will help TB programs identify key gaps and address them within the local context. Indeed the WHO (2006b) recommends that national TB programs should allocate funds for research in order to achieve better TB control. MDRTB being a new phenomenon in many countries warrants research to better control it. Cobelens et al. (2008) identified the following priority areas for research in MDRTB:-

a) Laboratory support strategies

b) Research on the local epidemiology of drug resistant TB

c) strategies for treatment of drug resistant TB

d) Research the various programmatic areas in MDRTB

e) Strategies to manage contacts of MDRTB patients

Lastly, apart from program based research, more efforts need to be put in research to the development of new diagnostic tools, drugs and vaccines for future control of TB (Brewer & Heymann 2004). The Global TB community, led by WHO and IUATLD has already put a lot of efforts on this front (WHO 2006b).

## CHAPTER 5: FINDINGS IN KENYA: RESPONSE TO MDRTB

### 5.1 DRUG RESISTANCE LEVEL IN KENYA

Resistance to TB drugs was recorded since the early 60s in drug resistance surveys done in Kenya. However, the regime then excluded Rifampicin up to until 1993 when Rifampicin was introduced in the first line short course chemotherapy for TB. This marked the starting point for potential MDRTB cases.

The last DRS was done in 1995, and covered 22 out of the then 42 districts in Kenya. However, this survey found no cases of MDRTB (Githui et al. 1998). Since then no other survey has been done to quantify the extent and pattern of TB drug resistance in Kenya. However, MDRTB is now prevalent in Kenya, including the "W-Beijing" subtype as described by Githui et al (2004) in a study in Nairobi. A different study done on new SS+ and retreatment cases in a refugee population (mainly from Somalia and South Sudan) in North Eastern Kenya also found significant prevalence of TB drug resistance. Mono-resistance was at 18.3% and MDRTB was found in 2.9% of the cases assessed. Levels of TB drug resistance were comparatively higher in the refugee population than in local Kenyan residents in the area (Odds ratio 3.7; 95% CI=1.42-9.68 and P= 0.007) (Githui et al. 2000). The study found no cases of MDRTB in the local resident population and also identified previous exposure to TB drugs as the most important risk factor for the developing drug resistance. Unlike most areas in the country, Githui et al (2000) found in this study that females were at a higher risk of TB drug resistance than males in both refugees and local citizens (Githui et al 2000).

However the real level, burden and pattern of TB drug resistance in Kenya is not known, and needs further assessment. Due to the recognition of the potential impact of MDRTB, an officer has recently been appointed to coordinate MDRTB control activities at the DLTLD.

### 5.2 DOTS EXPANSION AND ENHANCEMENT

Kenya adopted DOTS expansion for TB control as delineated in the STOP TB strategy of 1993. The DOTS coverage for all SS+ cases has been consistently at 100% for the whole country since 1996, with treatment of TB integrated into the primary health care delivery system. Treatment is delivered free of charge to the patients at the point of delivery in all public and most mission health care facilities. Private public mix (PPM) for TB control has been adopted in major cities. In 2008, a total of 2,051 patients were notified from the private sector (DLTLD 2009).

**Table 13: Implementation of DOTS expansion in Kenya**

| Strategy | Progress in Kenya |
|---|---|
| **Political commitment** | A national TB and Leprosy strategic plan was drafted in 2006<br>30% of TB control costs funded nationally. However, the funding is not enough to cover all the TB control activities and there is hence significant donor funding for TB control, mainly from the GFATM. |
| **Early case detection through quality assured bacteriology** | Sputum microscopy is the main tool for TB diagnosis in Kenya.<br>There are 930 diagnostic centres doing sputum microscopy (2.5 per 100,000 population), 5 laboratories doing sputum culture (0.7 per 5 million population) and 1 DST facility at the CRL |
| **Standardised treatment with supervision and patient support** | All new TB patients are treated using a standardised SCC ( 6 to 8 months duration)<br>100% DOTS coverage countrywide |
| **Drug supply and management system** | No stock outs for TB drugs and diagnostics either centrally or peripherally |
| **Monitoring and evaluation and impact measurement** | Annual reports produced since 1994<br>Common data collection tools were developed and used Countrywide<br>Data for individual patients not accessible centrally, however, all data from the regions is collected and submitted centrally. |

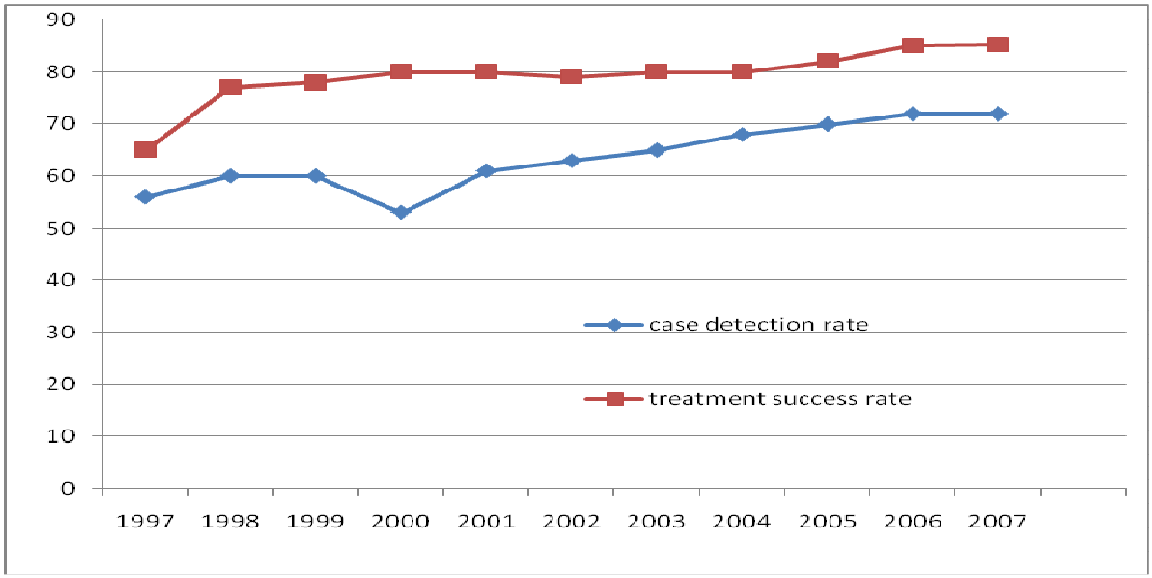
Adapted from: WHO (2009) and DLTLD (2008)

### 5.2.1 Case detection and Treatment success

Kenya has made considerable efforts to improve TB control and achieve MDG targets for TB control. The country reached the 70% target for detecting and notifying at least 70% of all incident SS+ cases in 2005 (WHO 2009a). This is steadily improving because in 2007, Kenya achieved a case detection rate (CDR)[3] for SS+ of 72% and a treatment success rate of 85% for the 2006 treatment cohort (DLTLD 2009). This milestone made Kenya recognised as the only sub-Saharan African country to achieve WHO set standards in TB control (WHO 2009a).

[3] All total SS+ diagnosed and notified in a year divided by total incident SS+ cases

Figure 5: Case detection rate and treatment success rate




Adapted from: WHO (2009) and DLTLD annual report 2008

### 5.2.2 Short course chemotherapy

Kenya has been using the 8 months SCC for all new TB cases. The 6 months SCC was introduced as a pilot in Nairobi province in April 2007. Currently, 5 provinces are using the 6 months SCC while 7 provinces are using the 8 months SCC. Coast and Central provinces are earmarked to start the 6 months SCC next and gradually the DLTLD hopes to have countrywide use of the 6 month SCC by end of 2009 (DLTLD 2009). It is also worth noting that Nyanza North and South provinces, which have the highest burden of TB (DLTLD 2009) and HIV (NASCOP 2008) in Kenya, are still using the 8 month SCC.

## 5.3 CASE DETECTION FOR MDRTB

The diagnosis of MDRTB in Kenya is done at the CRL in Nairobi. Sputum specimens for all suspects are collected at the health facilities, labelled, packed well and transported by courier to the CRL. On average the results should take 6-9 weeks to reach the facilities after delivery to the CRL (DLTLD 2008), but no studies have been done to validate the exact time taken. This system faces challenges as courier services are only available in major urban areas. Sputum specimens from health facilities away from urban areas may take long to reach the courier service offices and thereafter to reach the CRL and this may have an effect on the viability of the mycobacteria.

Surveillance of MDRTB is done mostly on categories of patients undergoing retreatment for TB as shown in table 14.

**Table: 14: Criteria for sputum culture and DST in Kenya**

| Inclusion criteria for culture and DST in Kenya | Not currently protocol for culture and DST in Kenya |
|---|---|
| 1. Treatment failures during SCC<br>2. Patients who are still sputum positive after 2-3 months of SCC<br>3. Patients who resume treatment after defaulting<br>4. Retreatment failures<br>**5.** TB relapse | 1. All new smear positives<br>2. Known contacts of MDRTB patients<br>3. Prisoners<br>4. HIV positive patients with TB<br>5. Hospital staff, especially the ones in contact with TB patients<br>6. Contacts of TB patients who died during treatment under DOTS |

Source: DLTLD (unpublished)

At the CRL, 2 methods are used for culture:-

a. The conventional culture using Lowenstein-Jensen medium and
b. Mycobacterium growth indicator tube(MGIT) 960

**Table 15: Progress in culture and DST**

| YEAR | TOTAL SPECIMENS EXAMINED | Proportion of all retreatment |
|---|---|---|
| **2005** | 1190 | **10%** |
| **2006** | 2511 | **23%** |
| **2007** | 4403 | **40%** |
| **2008** | 5138 | **60%** |

Source: DLTLD (2009)

For quality assurance, the CRL utilizes the Queensland mycobacterium reference laboratory in Brisbane, Australia as the supranational reference laboratory (WHO 2008).

Over the years Kenya has made considerable progress in surveillance of MDRTB, but is yet to achieve the 80% target that all TB retreatment cases to be done culture and DST.

## 5.4 EPIDEMIOLOGICAL PROFILES OF MDRTB PATIENTS

Of the patients diagnosed with MDRTB, data is available for the 102 patients diagnosed in 2008 and 72 out of the 82 patients in 2007 giving a total of 174 patients for the 2 years. Of these, 114 (65.5%) are male and 60 (34.5%) are female. In this study, the total cases for the 2 years will be reviewed together.

### 5.4.1 Resistance pattern

On top of resistance to Isoniazid and Rifampicin which defines MDRTB, DST to Streptomycin and Ethambutol was also done for these patients. The results, as illustrated in table 16 below shows that almost half of the patients (49.4%, n= 86) were resistant to all the 4 first line drugs assessed.

**Table 16: Resistance to other TB drugs on top of MDRTB**

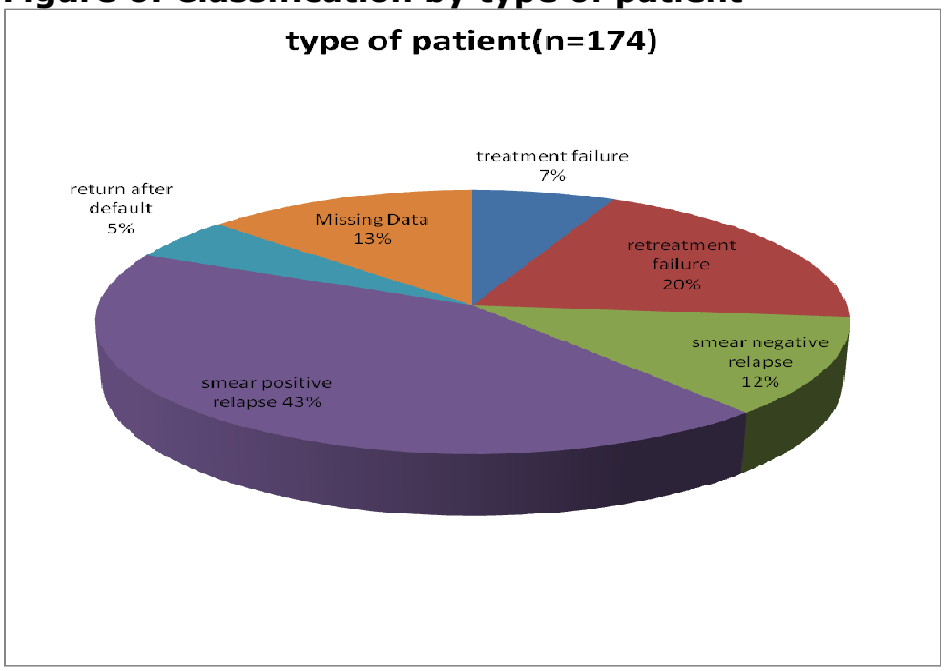
| Drug | Total resistant (n=174) |
|---|---|
| ***Ethambutol*** | 103 (59%) |
| ***streptomycin*** | 127 (73%) |
| ***Streptomycin & Ethambutol*** | 86 (49.4%) |

Source DLTLD surveillance data

### 5.4.2 Type of patient

The majority of the cases (43%, n=75) were smear positive TB relapse followed closely by retreatment failures (20%, n=34) as shown in figure 6.

**Figure 6: Classification by type of patient**



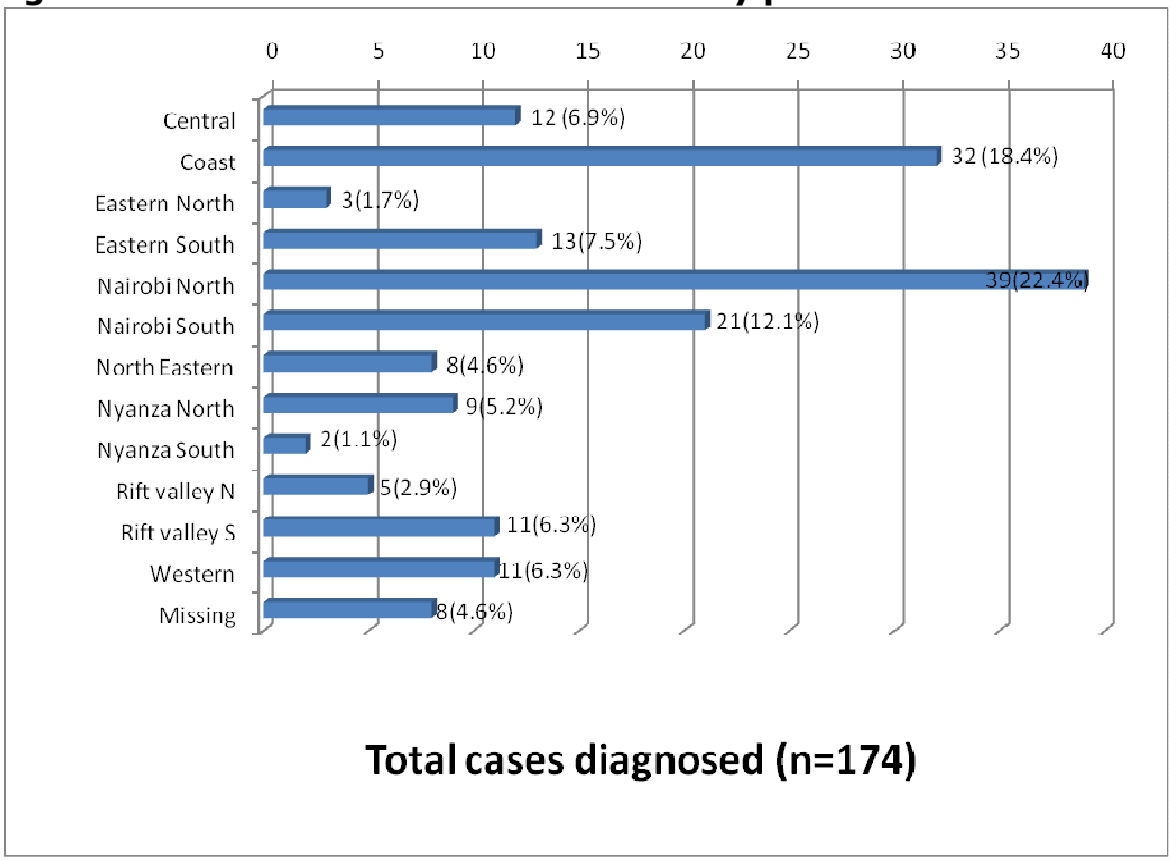

Source: DLTLD surveillance data

### 5.4.3 Geographical distribution

Most of the patients came from Nairobi North province (22.4%, n=39) closely followed by coast province (18.4%, n= 32) as shown in figure 7. The lowest cases came from Nyanza South with only 2 cases (1.1%). This is a new TB control province formed in 2008, so cases for 2007 and possibly some for 2008 may have been notified in Nyanza North. A total of 11 cases (6.3%) were not classified in any province as the data was missing. However most had addresses in Sudan and Somalia so were probably refugees.

In general, relatively very few patients came from Nyanza which bears 20% of the burden of TB in Kenya (DLTLD 2009).

**Figure 7: Classification of MDRTB cases by province**

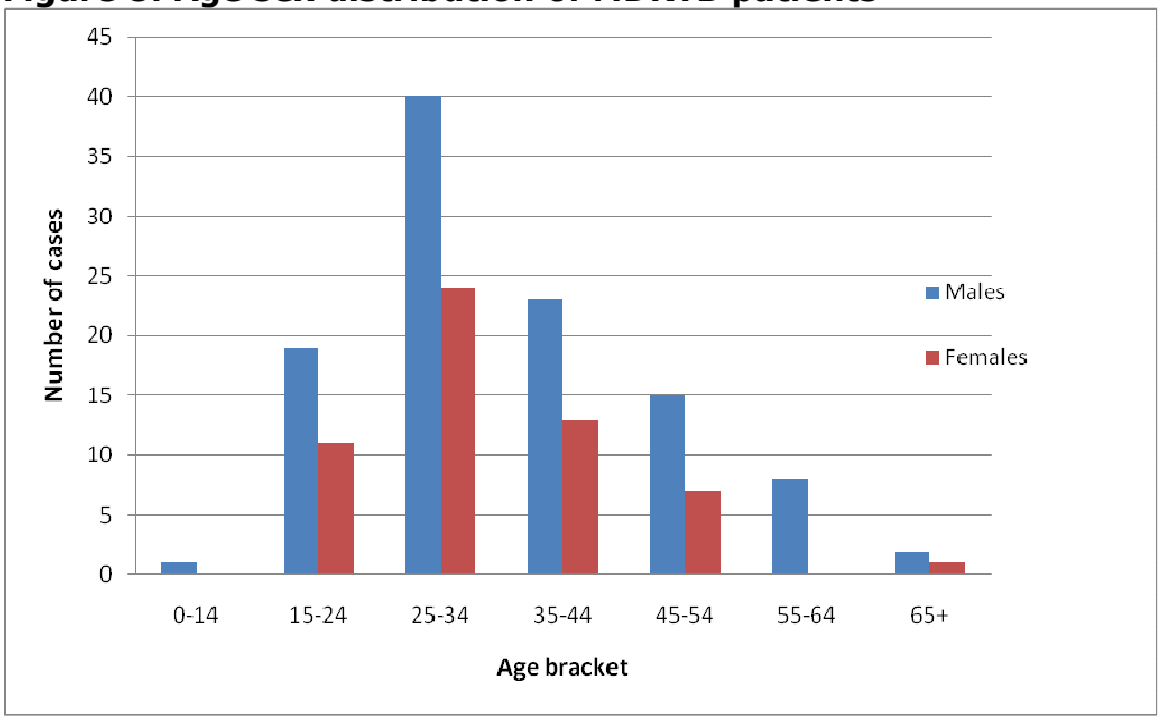



Source: DLTLD surveillance data

### 5.4.4 Age and sex distribution

Of the 174 MDRTB patients 164 (94.2%) had information on age and sex available. However for 10 patients (4 female and 6 male), this information was missing. Most of the cases were in the 25-34 age category as shown in figure 8. Like in all cases of TB in Kenya, there was a predominance of males at 114 (65.5%) over females 60 (34.5%) across all age categories.

**Figure 8: Age sex distribution of MDRTB patients**




Source: DLTLD surveillance data

## 5.5 TREATMENT OF MDRTB

Access to MDRTB treatment is a big challenge to MDRTB control in Kenya. Out of all the diagnosed patients, only 40 have been started on treatment using drugs procured through the GLC. MSF also is treating a total of 30 patients in 2 treatment centres (Homabay and Blue house) giving a total of 70 patients on treatment countrywide.

Many of the other diagnosed patients are still on a waiting list for treatment. The key constraint is financing the treatment and the logistical challenges of transport and accommodation due to the centralised nature of treatment under the GLC program. The government has not committed any internal funds for purchase of MDRTB drugs. This means patients have to wait for funds from the GFATM. A proposal has been done to the GFATM and treatment will be availed for 50 new patients yearly starting in year 2010 (Dr Kamene, Personal communication). The international facility for the purchase of drugs to treat HIV/AIDS, Malaria and Tuberculosis (UNITAID) is considering a proposal to fund treatment to a limited number of patients. Due to these constraints an inclusion criterion for treatment has been drawn. (*See annex 6 for the inclusion criteria*)

The treatment centres have a MDRTB management committee to ensure all aspects of quality treatment are followed including measures to ensure adherence. The standardised treatment adopted in Kenya is shown in table 17.

**Table 17: Recommended MDRTB treatment in Kenya**

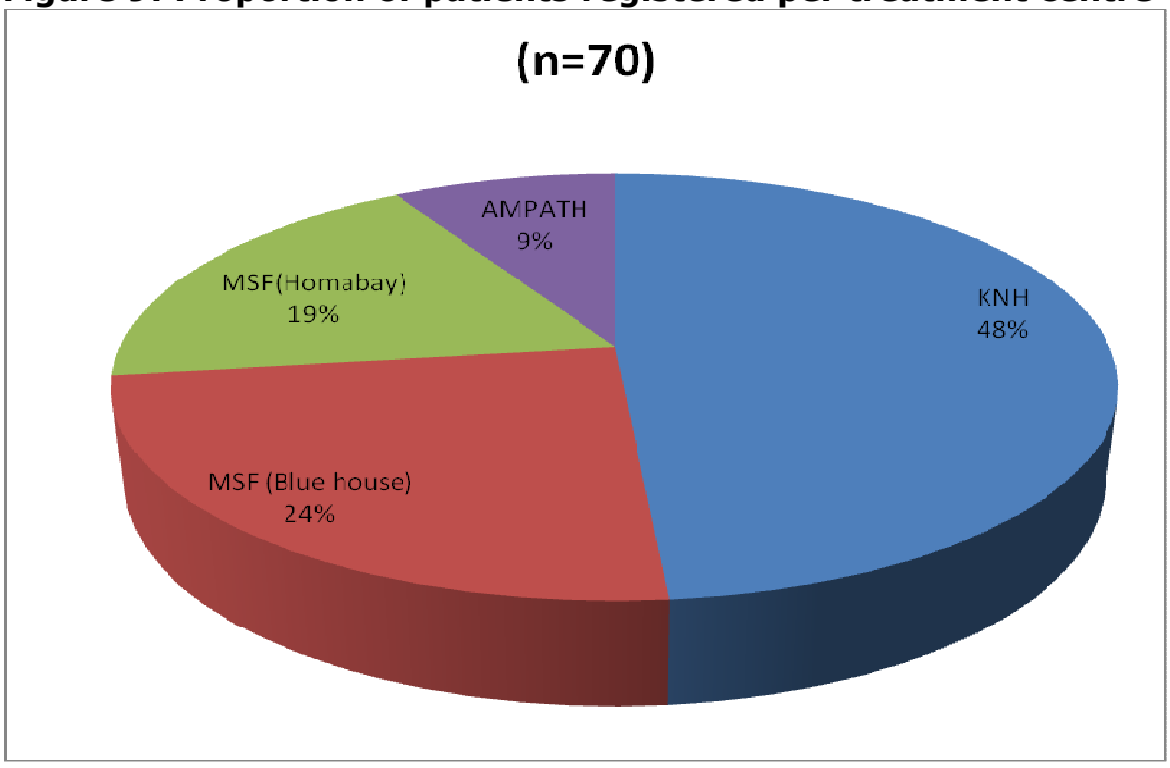
| | |
|---|---|
| Intensive phase (6 months) | Capreomycin (injectable) , Prothionamide, Cycloserine, Ofloxacin and Pyrazinamide |
| Continuation phase (18 months) | Ofloxacin, Prothionamide, and Cycloserine |

Source: DLTLD (2008)

### 5.5.1 Patients registered for treatment

The majority patients are registered for treatment in KNH (48%, n=34) with the others being treated at AMPATH (8.6%, n=6). These are using drugs from the GLC. MSF has registered 13 patients (18.5%) in Homabay and 17 (24.3%) in Blue house.

**Figure 9: Proportion of patients registered per treatment centre**




Source: DLTLD surveillance data

The majority of the patients were started on treatment in 2008, when the GLC drugs were availed. Eight patients (11.4%) were enrolled in 2006 and a further 13 (18.6%) in 2007. 2008 had 43 (61.4%) patients

enrolled and as of March 2009, 6 (8.5%) patients had been started on treatment.

### 5.5.2 Treatment outcomes

After treatment was initiated, a small midterm review has been done. The full treatment outcome report will take long to come considering the bulk of the patients were started on treatment in 2008. Of all the 70 patients started in treatment, 5 (7.1%) have been cured, 11 (15.7%) have died while 4 patients (5.7%) have defaulted on treatment. The patients who are still on active treatment are 50 (71.4%). The outcome for each treatment centre is shown in table 18.

**Table 18: Treatment outcomes for MDRTB**

| Treatment centre | Cured | Died | Defaulted | Still on treatment |
|---|---|---|---|---|
| **KNH (n=34)** | 1 (2.9%) | 4 (8.8%) | 2 (5.8%) | 27 (79.4%) |
| **AMPATH (n=6)** | 0 (0%) | 0 (0%) | 0 (0%) | 6 (100%) |
| **Blue house(MSF) (n=17)** | 3 (17.6%) | 2 (11.7%) | 1 (5.9%) | 11 (64.7%) |
| **Homabay (MSF) (n=13)** | 1 (7.7%) | 5 (38.5%) | 1 (7.7%) | 6 (46.1%) |
| **Total for Kenya (n=70)** | **5 (7.1%)** | **11 (15.7%)** | **4 (5.7%)** | **50 (71.4%)** |

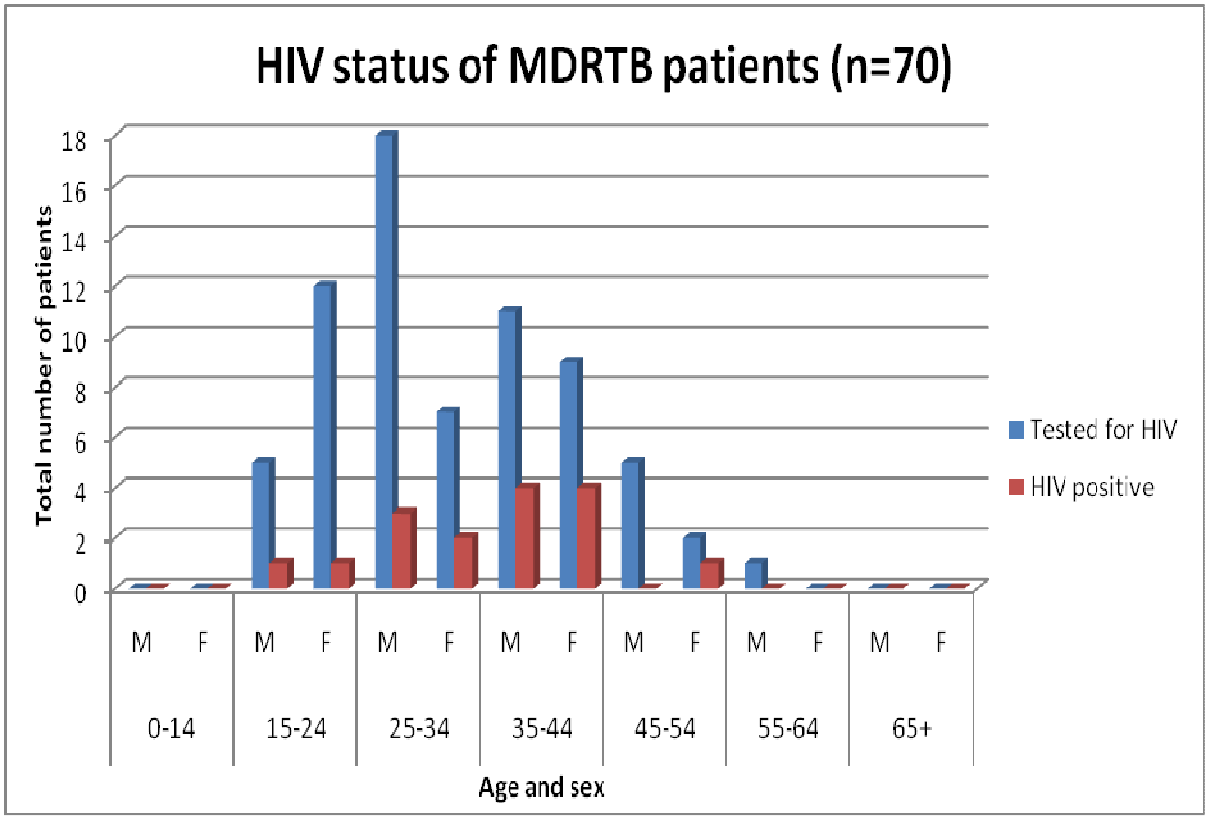
Source: DLTLD surveillance data

### 5.6 HIV and MDRTB

Data on the HIV status of all cases detected for MDRTB in not available. However, all the seventy patients enrolled on treatment were counselled and tested for HIV, and 16 (23%) were HIV positive. This is almost half of the HIV prevalence rate in TB patients which was 45%[4] in 2008 (DLTLD 2009). The age category with the highest number of HIV positive patients was 35-44 years, with 34% of the males and 44% of the females HIV positive. This is the same age group with the highest HIV prevalence in Kenya and among the general TB patients (DLTLD 2009; NASCOP 2008).

[4] Only 83% of all TB patients were tested for HIV

**Figure 10: HIV status of patients under treatment**




Source: DLTLD surveillance data

Access to ART among HIV positive MDRTB patients is not documented. However provision of ART countrywide is not vastly decentralised. Even among TB patients who are HIV positive, only 31% (n=12,426) of were started on ART while 94% (n=37,757) received CPT in 2008 (DLTLD 2009)

## 5.7 INFECTION CONTROL

TB services are provided in the general health care system in Kenya which is grossly underfunded and understaffed. In the author's experience, most TB clinics are very small, congested. Kenya has adopted some infection control measures but the implementation and impact is not well documented.

A case control study done in KNH, Kenya's largest hospital, found a very high incidence of TB among the hospital staff. The risk was high across all cadres regardless of job description, but progression from infection to

disease was more with HIV infection. The study also revealed that infection control measures were poorly practiced (Galgalo et al. 2008).

**Table 19: Rates of TB among hospital staff at KNH**

| Year | Number of staff cases | Rate /100,000 |
|---|---|---|
| **2001** | 34 | 645 |
| **2002** | 54 | 1026 |
| **2003** | 58 | 1115 |
| **2004** | 41 | 796 |
| **2005** | 40 | 828 |

Source: Galgalo et al. (2008)

Training for infection control was recently conducted but the impact needs re assessment. The division has also produced infection control guidelines to be distributed to most healthcare facilities. Information, education and communication (IEC) materials have been also produced and distributed, and the health facilities are supposed to form infection control committees.

For MDRTB, there are no special wards with negative pressure ventilation, but one is under construction at KNH. The MDRTB outpatient treatment clinic is conducted in an outdoor environment with maximum natural ventilation.

Lastly, operational research is needed to confirm implementation and challenges in infection control. In the author's experience, infection control measures are not highly prioritised in many parts of the country.

## 5.8 SOCIO ECONOMIC INCENTIVES

As part of the GLC agreement the DLTLD provides some amount of money for transport to patients who are accessing care for daily attendance to the clinics. However this is grossly inadequate considering the high cost of accessing treatment. An equivalent of 300 Kenya Shillings (€3) is given for daily transport expenses (Dr Kamene, personal communication). Provision of a food basket and an additional stipend for personal expenses is being discussed for possible implementation. Patients are required to have a treatment supporter at home to help with adherence on top of support groups being formed in the treatment centres.

## 5.9 RESEARCH

The DLTLD has committed itself to improvement of TB control by doing operational research. Recently PTLCs and other staff had a training done on operational research and some progress has been done in TB research. However research on MDRTB is very limited as found in this study.

# CHAPTER 6: DISCUSSION

MDRTB is now clearly a problem in Kenya and there is need to ascertain the exact burden and pattern of TB drug resistance. Among the MDRTB cases diagnosed between 2007 and 2008 in Kenya, the majority were found to have poly-resistance to other TB drugs on top of Rifampicin and Isoniazid. Almost half of the patients were resistant to all the first line drugs assessed and almost three quarters had Streptomycin resistance. Primary drug resistance is currently difficult to detect in Kenya as all new TB cases are treated using a standard SCC without DST being done. This will definitely result in unfavourable treatment outcome and this may be a factor in promoting the development of MDRTB. Among the cases diagnosed with MDRTB, it is hard to know the proportion of cases caused by either primary infection or acquired resistance. To adequately plan for MDRTB control, a nationally representative DRS to ascertain the true magnitude and pattern of TB drug resistance in Kenya is needed.

Kenya is doing well in the implementation of the STOP TB strategy. The DOTS expansion and enhancement has done well as evident from the high case detection and treatment success rates. This is clearly the best and most cost-effective strategy for preventing the development of TB drug resistance as evident from studies. A sustained strong DOTS program will over years will, all factors held constant, translate to low drug resistance levels. Cases of drug sensitive TB if well treated under DOTS will achieve high cure rates and are least likely to lead in drug resistance assuming optimal treatment compliance with very minimal defaulter rates.

The country is still using the 8 months SCC for new TB cases in seven provinces, with only 5 provinces using the 6 months SCC. Research has shown the 6 months SCC to be far more superior in improving treatment response and results in less drug resistance levels and better treatment outcome. The 6 months SCC is also better tolerated as the treatment duration is shorter. The DLTLD needs to fast track the switch to 6 months SCC for all new TB cases countrywide as per its commitment. This will result in even better treatment outcomes and reduce the overall risk of drug resistance and recurrence of TB due to the longer duration of Rifampicin in the 6 months SCC.

There is also evidence that the WHO recommended retreatment regime may in fact be fuelling the development of MDRTB. Fundamental questions arise on MDRTB patients diagnosed from retreatment failure actually develop MDRTB. There is a possibility these patients are initially mono-resistant or poly-resistant, and then in the course of the retreatment develop MDRTB. Another possibility is that they actually

have MDRTB during initiation of retreatment and this implies that the retreatment is bound to fail. This is an area which needs further research and also underscores the need for and rapid DST to detect cases of MDRTB before initiating the retreatment.

Case detection of MDRTB is poor as found in this study. Only 3.4% of the incident cases of MDRTB were diagnosed between 2005 and 2007, this shows that many incident cases of MDRTB are never detected and this will have a negative impact on MDRTB control. The reliance on only culture and DST will lead to delayed diagnosis of MDRTB, and there is need consider provision of rapid DST. The weak linkage between the CRL and health facilities may also hamper adequate case detection and this will have an impact on case detection.

The majority of the cases diagnosed with MDRTB arise from TB relapse followed by retreatment failure as found in this study. TB relapse (both sputum smear positive and negative) therefore seems to play a key role in the epidemiology of MDRTB in Kenya more than retreatment failure. The reverse is what is could have been expected and research is needed to explain these findings. Possible reasons could be due to the less duration of Rifampicin used during SCC, unreported poor treatment adherence during DOTS or that many patients could have died of MDRTB before diagnosis of retreatment failure is ever made.

Patients with untreated MDRTB pose a danger of transmitting the infection to the public. Those with the highest at risk being close contacts, especially family members and health care workers. Active case finding for MDRTB for close family contacts is important to ensure any primary cases of MDRTB due to infection from the index patient are detected early. However, this study found this to be lacking in Kenya and needs to be strengthened.

The current guideline for culture and DST in Kenya effectively locks out many potential suspects. These include known contacts of MDRTB patients, all HIV positive patients with TB, new SS+ cases, contacts of patients who died under DOTS and hospital staff in TB clinics. Without reviewing these guidelines it will be difficult to ensure improved case detection. As a minimum, it is necessary to include close contacts of MDRTB patients and new SS+ patients who are HIV positive for routine culture and DST. The other can be factored in gradually as more investment is made in expanding capacity for DST.
Access to DST is essential for a successful active case finding campaigns as it will go a great length in making diagnosis faster so that treatment is not delayed unnecessarily. Kenya should seriously look at decentralizing DST services to one or two other Labs which have the

capacity to do sputum culture. This will ensure that case detection for MDRTB is more effective. This is a huge task with financial and logistical implications and needs to be done gradually.

Treatment for all patients diagnosed with MDRTB but still in the waiting list for treatment is a challenge Kenya needs to address. Cost effectiveness studies have shown that management of MDRTB is cost effective and hence a worthwhile investment for any country. Kenya is currently GLC approved hence the prices for the drugs are now relatively cheaper. The greatest challenge is the financing of care and treatment for which the DLTLD needs to provide leadership in exploring financing avenues. The GFATM has provided some funds for procuring MDTRB drugs, but the government needs, as part of sustained political commitment, to provide additional funding from its own sources or look for alternative funding for these patients. Other new global health initiatives like the UNITAID, Clinton foundation, Bill and Melinda Gates foundation which are operational in Kenya can provide additional funding.

Defaulting from MDRTB treatment is a known recipe for potential XDRTB. So far 5.7% of the cases on treatment in Kenya have defaulted. Active contact tracing for these patients needs to be done to establish the reasons for defaulting. Some possible reasons for this may be the high indirect costs of accessing treatment due to its centralised nature, social constraints, ignorance or even death. There is possibility of development of XDRTB in the treatment defaulters. Although currently Kenya currently does not have the capacity to diagnose XDRTB, the supranational laboratory in Brisbane can be utilised in surveillance of XDRTB among these suspects. XDRTB is a great challenge to TB control and the best way to address it is to prevent it from occurring.

The care and treatment of MDRTB was started as a pilot in KNH. There are many challenges in accessing care and treatment by patients in Nairobi away from their homes. Patients from all over the country who cannot afford or manage to arrange for accommodation in Nairobi may not be able to be treated. The stipend given for transport is also too small to cover for the indirect costs involved in accessing treatment. The fate of these patients is serious as they spread the infection or easily die, because of the high case fatality rate associated with MDRTB if not well treated. To address this there is need to rethink on the approach of MDRTB treatment. Considering that Kenya has an existing community based DOTS system, this is a possible avenue to bring the services nearer the patients. The WHO is actually recommending community based treatment of MDRTB as an ideal model where practically feasible provided the quality of care is maintained. To do this, Kenya needs to

build technical capacity and decentralize care and treatment to the provinces systematically. Peru has already noted success in this front and won accolades from the WHO Kenya can learn from their model.
Although many of the MDRTB patients were started on treatment in 2008, the interim review shows quite a high death rate (15.7%). While it is clear from studies of the high mortality associated with MDRTB, all efforts should be geared to achieve a considerable cure rate at the end of treatment. An assessment on the cause of this high death rate needs to be done and any lessons learned used to further improve treatment. A good data bank for monitoring and evaluation of cases diagnosed and awaiting treatment needs to be done and proper follow up done to ensure these patients can be easily traced.

Infection control has been adopted as a policy by DLTLD but the effectiveness of its implementation countrywide is not well known. The study in KNH by Galgalo et al (2008) showed that these measures were not being taken seriously at the hospital. The DLTLD needs to seriously address this by ensuring at least the administrative measures of infection control are implemented in all health facilities.

HIV is the single most important contributor of increasing TB burden in Kenya and other sub Saharan countries. HIV makes MDRTB challenging both technically and epidemiologically. The impact of HIV on MDRTB cannot be ignored considering the high prevalence rates of HIV in Kenya. The low prevalence of HIV in the patients under treatment needs to be researched. This may imply that many of the HIV positive patients with MDRTB may have died before diagnosis. Additionally, some of the HIV positive patients with TB and MDRTB may also be smear and culture negative, and so are not diagnosed. NASCOP has strived to reduce new number of new HIV infections in Kenya with considerable success. However, access to ART in HIV positive patients and particularly among TB patients who are HIV positive TB patients is still low. TB/HIV collaboration is necessary to achieve this, and both the DLTLD and NASCOP need to work closely to ensure access to ART to HIV positive MDRTB and TB patients.

Lastly, operational research needs to be carried out in Kenya to identify gaps in TB and MDRTB control and learn on the best way to adopt in control activities. This study found very limited literature on MDRTB control in Kenya the author is challenging the DLTLD to invest more in operational research. Research will provide answers to the many gaps identified in MDRTB control in Kenya and other countries as they strive to achieve universal access to MDRTB care and treatment.

# CHAPTER 7: CONCLUSION AND RECOMMENDATIONS

This study concludes MDRTB control in Kenya is a big challenge and which needs serious investment and attention. Kenya has done well in TB control by use of DOTS as per the WHO stop TB strategy. However, access to diagnosis, care and treatment for MDRTB is grossly inadequate. Many of the patients infected with MDRTB are never diagnosed and the few diagnosed find it difficult to access treatment. the main constraint is financing for MDRTB control activities. There are many cases of MDRTB which are neither detected nor treated in Kenya and this may affect the future pattern of MDRTB in the country. DOTS expansion and enhancement needs to be maintained as the best way to control MDRTB, but there is need to aggressively tackle to present burden of drug resistance. All the issues discussed need to be taken seriously by the DLTLD if MDRTB control is to be a reality in Kenya.

From the findings of this study, the following recommendations need to be adopted by the DLTLD for MDRTB control

1. A nationally representative DRS needs to be carried out. This will help Kenya get a better estimate of the true burden and pattern of TB drug resistance, and particularly MDRTB.
2. Maintain and sustain high quality DOTS program with high case detection and treatment success as the best strategy to prevent TB drug resistance.
3. Change of treatment regimes- The country needs to urgently roll out the 6 months SCC countrywide. Preference needs to be given to Nyanza North and South provinces as they have the highest burden of both TB and HIV.
4. Strong TB/HIV collaboration needs to be enhanced including improved access to ART for HIV TB patients who are HIV positive.
5. Kenya needs to review the MDRTB surveillance guidelines to include other categories of high risk suspects. As a beginning, all new SS+ cases who are HIV positive needs to be included in the guidelines. The country also needs to look at the cost effectiveness of rapid DST and consider introducing this service as it expands the scope of MDRTB surveillance.
6. Decentralization of DST to the provinces in Kenya needs consideration. This may, however, be a technically demanding and expensive venture. However, considering there are some facilities doing sputum culture, DST services should be easily introduced to 2 more sites in the short term.
7. The DLTLD needs to scale up the number of MDRTB patients on treatment and aim to enrol all cases under care and treatment for MDRTB.

8. Decentralisation of MDRTB treatment needs to be gradually done. Community based MDRTB treatment is a cost effective strategy and helps eliminate the barriers posed by decentralised care and treatment.
Infection control reduce primary infections should be strengthened to reduce the level of hospital acquired MDRTB. The current implementation of infection control also needs to be researched to find out the effectiveness of its implementation and any impact thereof.
9. Financing for all the MDRTB control needs to be increased. The government needs to commit funds for this as part of political commitment to TB control. Proper and timely investment in this will ensure that MDRTB is well contained and does not become generalised as happened to TB before.
10. Technical capacity to control of TB and MDRTB at all levels needs to be built. This can be done by training and mentoring staff countrywide to be able to participate in MDRTB control activities.
11. Operational research is urgently needed for MDRTB control. This will held the DLTLD to get answers to the many challenges in MDRTB control.

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# ANNEXES

## Annex 1: Categories of anti TB drugs

| | |
|---|---|
| **First line oral drugs** | Isoniazid, Rifampicin, Pyrazinamide, Ethambutol. |
| **Second line oral drugs** | Ethionamide, Prothionamide, Cycloserine, Terizidone, Para-aminosalicylic acid, Thioacetazone |
| **Injectable drugs** | Streptomycin, Kanamycin, Amikacin , Capreomycin |
| **Fluoroquinolones** | Moxifloxacin , Ofloxacin, Gatifloxacin, Ciprofloxacin, Levofloxacin |
| **Drugs without clear efficacy** | Clofazimine, Clarithromycin, Amoxicillin-Clavulanate, Linezolid |

Adapted from WHO (2008b)

## Annex 2: TB treatment regimens used in Kenya for short term chemotherapy (SCC)

| | |
|---|---|
| 8 months SCC (2RHZE/6EH) and 6 months SCC (2RHZE/4RH) | New cases with SS+, SS- and extra-pulmonary TB |
| 2RHZ/4RH | For all new cases in children (less than 15 years of age) |
| 2SRHZE/1RHZE/5RHE | For retreatment of TB |

Source: DLTLD annual report 2007

## Annex 3: Infection control measures

| | |
|---|---|
| **Personal measures** | 1) Use of special Respirator masks<br>2) Educating patients on proper cough and respiratory hygiene (covering mouth and nose when coughing).tissues and clothes used should be disposed off well |
| **Institutional/administrative measures** | 1) Early diagnosis of cases so as to institute treatment in time<br>2) reduce length of admission to hospitals<br>3) attending fast to reduce hospital waiting time through a good triage system<br>4) train health care workers on infection control measures<br>5) develop and distribute guidelines for infection control<br>6) sputum collections in open areas away from many people<br>7) monitoring and evaluation of progress in IC<br>8) Provision of Isolation facilities for suspected cases of drug resistant TB<br>9) Separation of MDRTB patients with HIV positive patients<br>10) Comprehensive infection prevention and control pachage for health workers including HIV prevention, Isoniazid preventive therapy (IPT) and ART for those who are HIV positive. |
| **Environmental control measures** | 1) Design facilities to have good natural ventilation<br>2) Complex methods include<br>• negative pressure ventilation<br>• Waiting rooms well ventilated possibly in open air space<br>• Use of Air filters and ultraviolet germicidal irradiation |

Adapted from: Andrews et al (2007); WHO (2009b) Hannan et al (2000) and WHO (1999a) WHO (1999b)

**Annex 4: WHO Recommended TB/HIV collaborative activities**

| | |
|---|---|
| **Establish mechanisms for TBHIV collaboration** | **a. Set up TBHIV coordinating bodies at the national, provincial and district levels**<br>**b. Conduct surveillance of HIV prevalence among TB patients**<br>**c. Carry out Joint TBHIV planning**<br>**d. Conduct monitoring and evaluation** |
| **Decrease the burden of TB in People living with HIV/AIDS** | a) Establish intensified TB case finding<br>b) Establish mechanism for IPT<br>c) Ensure Infection control in healthcare and congregate settings |
| **Decrease the burden of HIV in TB patients** | a) Provide HIV testing and counseling for all TB patients<br>b) Introduce HIV prevention methods<br>c) Ensure HIV care and support<br>d) Introduce Anti retroviral therapy (ART)<br>e) Introduce Cotrimoxazole preventive therapy (CPT) |

Source: WHO (2004)

## Annex 5: Methods available for detecting MDRTB

**Phenotypic methods**

| ASSAY TYPE | DIRECT USE OF CLINICAL SPECIMEN | TIME FROM RECEIPT OF SPECIMEN TO RESULTS | ADVANTAGE/ DISADVANTAGE |
|---|---|---|---|
| Conventional susceptibility testing using solid media (culture and DST) | No- this method required pure culture | More than 6 weeks | This method is slow, technically laborious and requires various laboratory safety facilities |
| Automated susceptibility testing using liquid media | Possible, but most laboratories use pure culture | 2-4 weeks (1-2 weeks if used on clinical specimens | Fast, reliable and safe but requires expensive equipment |
| Microscopic observational drug susceptibility (MODS) assay | yes | 1 week | Fast not very expensive and safe. Requires an inverted microscope |
| Calorimetric methods | Possible, but most laboratories use pure culture | 4-6 weeks | Bacterial growth in the presence of drug is detected by colour change |

| **Genotypic methods** | | | |
|---|---|---|---|
| Commercial assays for detecting Rifampicin resistance | Yes | 2 days | Fast, safe and reliable, but expensive and the results require confirmation with conventional methods |
| DNA sequencing | Yes, requires amplification product or DNA from pure cultures | 2 days | The optimal methods for detecting mutations but expensive and technically demanding. Only available in reference laboratories and research institutions. |
| Real time polymerase chain reaction (PCR) | Yes | 1 day | May enhance speed and sensitivity when used on clinical specimens but yet to be evaluated in routine clinical practice |
| microarrays | Possible , requires amplification product or DNA from pure cultures | 2 days | Expensive research technique capable of detecting a large number of mutations Throughout the bacterial genome. Has been used experimentally to detect bacteria resistant to Rifampicin and Isoniazid in clinical specimen |

Adapted from (Grant et al. 2008)

## Annex 6: Local inclusion criteria to be eligible for registration for treatment

a) The patient lives near the treatment facility for easier follow up
b) Patient has been explained very well and several times the consequences of starting/not starting MDR-TB treatment, he understands and agrees
c) Treatment support is available
d) Patient has been examined by a qualified clinician and treatment recommended
e) Baseline laboratory tests have been done
**f)** There is a treatment supporter

Source: DLTLD (unpublished)

## Annex 8: Map of Kenya