FACTORS ASSOCIATED WITH UNFAVOURABLE TUBERCULOSIS TREATMENT OUTCOMES IN LUSAKA, ZAMBIA, 2015; A SECONDARY ANALYSIS OF ROUTINE SURVEILLANCE DATA

BY

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DECLARATION

I, **NANZALUKA FRANCIS H**, declare that the work presented in this dissertation is my own work and that it has been produced in accordance with the guidelines for the Master of Science in Epidemiology dissertation for the University of Zambia. It has never been presented or submitted elsewhere in part or whole for the award of a degree or any qualification from any institution Various sources to which I am indebted are clearly indicated in the text and in the references.

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I **Dr GERSHOM CHONGWE** having supervised and read this dissertation is satisfied that this is the original work of the author whose name is being presented.

I confirm that the work has been completed satisfactorily and is ready for presentation to the examiners.

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CERTIFICATION OF APPROVAL

This dissertation for **Francis H Nanzaluka** has been approved as partial fulfilment of the requirements for the award of the Master of Science degree in Epidemiology at the University of Zambia.

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ABSTRACT

Tuberculosis (TB) is a major public health challenge in low and middle income countries. Factors associated with unfavourable treatment outcomes have been known to affect treatment and control of the disease. However, analysis of routine data in Zambia does not show the factors associated. We determined the proportion of tuberculosis treatment outcomes and factors associated. Unfavourable outcome was defined as death, lost-to-follow-up, treatment-failure, or not-evaluated, and favourable outcome as a patient cured or completed-treatment. Data were abstracted from treatment registers at a referral hospital, an urban-clinic and peri-urban (purposively selected) for all TB cases on treatment from 1st January to 31st December, 2015. Proportions were calculated for treatment outcomes, and associations between unfavourable outcome and factors including age, HIV status, health facility, and patient type, were analysed using univariate logistics regression. Multivariable stepwise logistic regression was used to control for confounding, report adjusted odds ratios (AOR), and 95% confidence intervals (CI). A total of 1724 registered TB patients from the urban-clinic (40%), 1st Level Hospital (38%) and peri-urban-clinic (22%) were included in the study. Of the total patients overall unfavourable outcome was 43%. Total unfavourable outcome was treatment-failure (0.3%), lost-to-follow-up (5%), death (9%) and not-evaluated (29%). The odds of unfavourable outcome were higher among patients >59 years (AOR=2.9, 95%CI:1.44–5.79), among relapses (AOR=1.65, 95%CI:1.15–2.38), patients who sought treatment at the Urban clinic (AOR=1.76, 95%CI:1.27–2.42) and among TB/HIV co-infected patients (AOR=1.56, 95%CI:1.11–2.19). The overall unfavourable treatment outcome found in the study was high in the selected facilities. Being >59years old, being a relapse case, being HIV positive and seeking treatment at the urban clinic were factors found to be associated with unfavourable treatment outcomes. Special attention to patients of >59years old, relapse cases and HIV positive in the TB treatment is recommended and also close monitoring of health facilities in increasing efforts aimed at evaluating all the outcomes. Studies are required to identify and test interventions aimed at improving treatment outcomes.

Key words: Surveillance, Tuberculosis, Treatment, Outcomes Lusaka; Zambia

DEDICATION

This dissertation is dedicated to my mother Catherine Sikaale and all my brothers for their unwavering support during the period of the program. To all my friends and relatives for the spiritual support and believing in me. Above all am grateful to God for giving the strength and keeping me alive. To all TB patients and health care workers, past present and future who will find this work very useful.

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ABBREVIATIONS AND ACRONYMS

AFB	Acid Fast Bacilli
ART	Antiretroviral therapy
CDC	Center for Disease Control
CSO	Central Statistical Office
CXR	Chest X-Ray
DOTS	Directly observed treatment short course
DST	Drug-susceptibility testing
EPTB	Extra-pulmonary tuberculosis
ERES	Excellence in Research Ethics and Science
HIV	Human Immunodeficiency Virus
MDR-TB	Multi-Drug Resistant
MOH	Ministry of Health
PTB	Pulmonary Tuberculosis
SSA	Sub-Saharan Africa
TB	Tuberculosis
UNOPS	United Nations Office for Project Services
WHO	World Health Organisation
XDR TB	Extensively drug-resistant TB

OPERATIONAL DEFINITIONS

Smear-positive pulmonary TB (PTB+). A patient with at least two sputum specimens which were positive for acid fast bacilli (AFB) by microscopy, or a patient with only one sputum specimen which was positive for AFB by microscopy, and chest radiographic abnormalities consistent with active PTB.

Smear-negative pulmonary TB (PTB-). A patient with symptoms suggestive of TB, with at least two sputum specimens which were negative for AFB by microscopy, and with chest radiographic abnormalities consistent with active PTB, or a patient with two sets of at least two sputum specimens taken at least two weeks apart, and which were negative for AFB by microscopy, and radiographic abnormalities consistent with PTB and lack of clinical response to one week of broad spectrum antibiotic therapy.

Extra pulmonary TB (EPTB). Included TB of organs other than the lungs, such as lymph nodes, abdomen, genitourinary tract, skin, joints and bones, the meninges and others.

According to (WHO, 2013b), treatment outcomes were categorized into :

1. **Favourable outcome:** If TB patients were **cured** (a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion) or **completed treatment** (a TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable) (WHO, 2016).

2**. Unfavourable outcome**: If treatment resulted in treatment failure (remaining smear-positive after 6 months of treatment), **lost to follow up** (did not start treatment or treatment interrupted for 2 consecutive months or more), not evaluated or died (WHO, 2016).

Death was defined as a TB patient who died for any reason before starting or during the course of treatment

Not evaluated: no treatment outcome is assigned. Includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit (includes previous *Transfer out* category)

Treatment failure sputum smear or culture is positive at month 5 or later during treatment (did not include systematically any case with confirmed MDR-TB)

Previously Treated was a case of TB diagnosed in a patient who has received 1 month or more of anti-TB drugs in the past.

Treatment after failure: previously treated for TB and whose *treatment failed* at the end of their most recent course of treatment

New case was defined as never having been treated for TB or have taken anti-TB drugs for less than 1 month

Relapse: previously treated for TB, were declared *cured* or *treatment completed* at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection)

MDR-TB was defined as TB resistant to both isoniazid and rifampicin,

XDR-TB was defined as MDR-TB that is resistant to at least one injectable second-line TB drug (kanamycin, amikacin, capreomycin) and any of the fluoroquinolones.

Treatment success" is defined as the sum of cure and treatment completion (Motta et al., 2016).

Urban Clinic: TB treatment and diagnostic centre that exists in a properly planned area in the city

Peri-Urban Clinic: TB treatment and diagnostic centre which exists in an unplanned settlement due to rural urban migration

CHAPTER ONE-INTRODUCTION

1.1 Background of the Study

TB has continued to be one of the major public health problems and still remains a global (figure 1) emergency for the 21st century (WHO, 2015). The disease has been linked to socio-economic issues in communities (Samuel et al., 2016). Treatment outcomes and analysis of the affecting factors is an important indicator of the performance of a country's TB control programs (Gebrezgabiher et al., 2016). Monitoring and evaluation of treatment outcomes of TB patients as an integral part in the treatment and prevention of TB has been given priority in the End TB Strategy (UNOPS, 2015). World Health Organisation (WHO) recommends a 90% TB treatment success rate and this can be achieved through case finding, early diagnosis, availability of medicines, and direct observed therapy in a TB control programme (WHO, 2015). It is a requirement that treatment outcomes are reported on quarterly and annual basis in order to assess the performance of a TB control programme. The report should show the favourable outcome or treatment success rate (cured and treatment completion) and also unfavourable outcome (loss to follow up, death, treatment failure and not evaluated) for all TB cases (WHO, 2013a).

Sub-Saharan Africa bears the highest global TB/HIV burden and over 50% of TB cases in SSA are co-infected with HIV (WHO, 2017). Relapse cases, having a positive smear at the second month of follow-up, smear-negative pulmonary TB, being older than 55 years and being male have been found to be associated with unfavourable TB treatment outcomes (Ogbudebe et al., 2016b, Wen et al., 2018). A study found that being male, having a negative smear result at diagnosis, being HIV positive and being retreatment cases were associated with unfavourable treatment outcomes (García-Basteiro et al., 2016, Ukwaja et al., 2016).

In Zambia, previous studies conducted in Lusaka (Kapata et al., 2013a), (Chanda-Kapata et al., 2016) and Ndola (Ngula et al., 2016) found that socio-demographic factors including poverty, being female, having extra-pulmonary TB, old age and residence of the patients, marital status, HIV co-infection and the form of TB were associated with treatment outcomes. In 2015, 36,741 new and relapse TB cases were notified and about 36% of these cases came from Lusaka district (WHO, 2016). The

estimated TB incidence in 2015 was 391/ 100,000 population for all ages and treatment success rate of 85% was reported (WHO, 2016).

The Zambia National TB program has put in place aims in TB treatment and management which focus on curing patients and restore their quality of life and productivity, prevent further transmission of TB in the communities, prevent relapse, prevent death from active TB and prevent the development of drug resistance including MDR-TB and XDR-TB. This is in its quest to prevent unfavourable outcomes in the treatment and management of TB. The recommended essential first line anti-TB medicines are Rifampicin (R), Isoniazid (H), Ethambutol (E) Pyrazinamide (Z) and Streptomycin (S) (MOH, 2017a). Therefore, we determined the proportion of TB patients who had unfavourable and favourable outcomes and risk factors associated with unfavourable outcomes in the treatment of TB in Lusaka, Zambia for 2015**.**

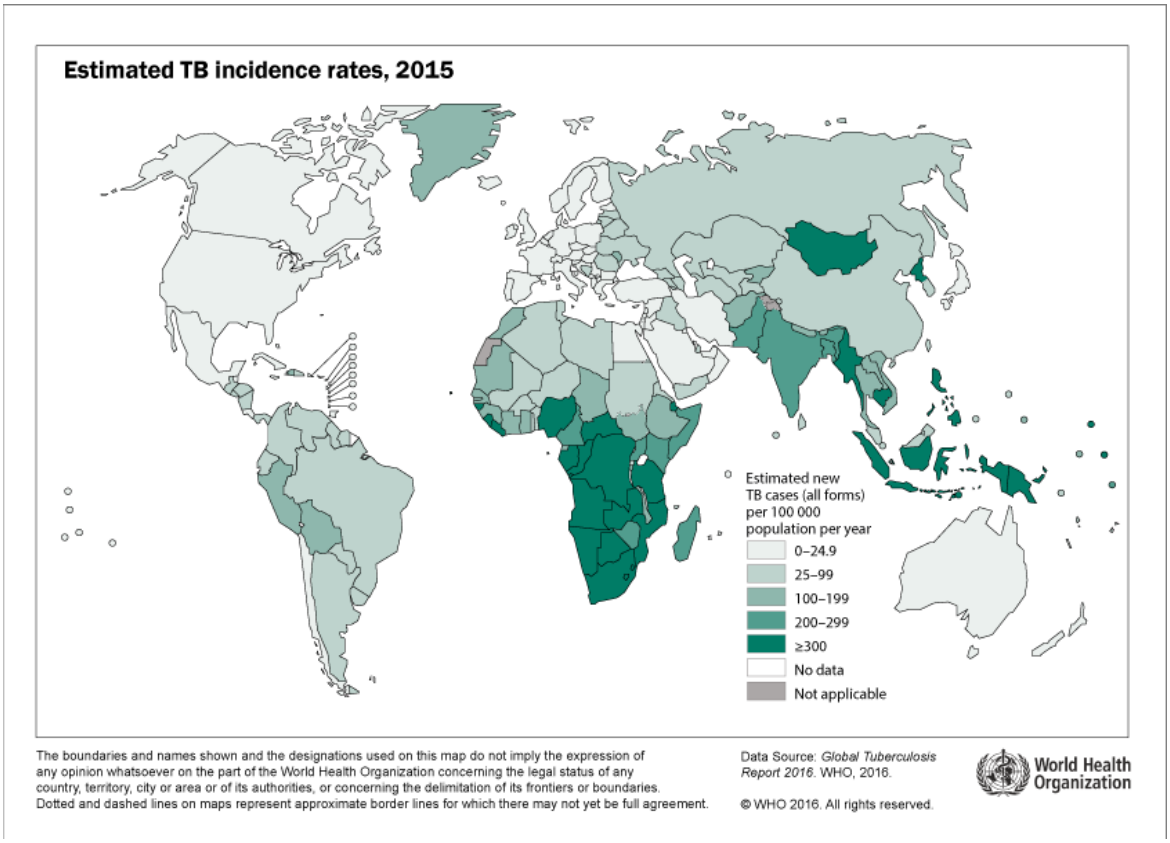

Figure 1: Global TB Incidence Rates 2015

Source: WHO 2016 Global TB Report

1.2 Statement of the Problem

Tuberculosis (TB) is a major global health problem. Although the expansion of TB treatment services and coverage through the end TB strategy have resulted in considerable progress in TB control in high TB burden countries (Ukwaja et al., 2016) there is limited information on factors associated with unfavourable outcomes of TB treatment which can be used to inform the program. TB causes ill-health among millions of people each year and ranks alongside the human immunodeficiency virus (HIV) as a leading cause of death worldwide (WHO, 2015). Death is one of the unfavourable TB treatment outcomes alongside others such as lost to follow up, treatment failure and not evaluated category worldwide (WHO, 2013a).

Africa, home to 11% of the world's population, carries 29% of the global burden of tuberculosis, 75% co-infected TB patients and 34% of related deaths. This is attributed to the high prevalence of HIV in the region (WHO, 2015). Failure of treatment completion or cure is believed to be another reason for difficulties in controlling the disease (Adane et al., 2013).

The burden of TB in Zambia is among the highest in the African region due to high rates of missing TB cases which stands at 42% and low utilization of TB preventive therapy current at 18% (MOH, 2017a). Data from the national tuberculosis control program shows the number of deaths, relapse cases, treatment failure (MOH, 2017b) however information on the factors that associated is not documented which makes it difficult to implement tailored interventions aimed at curbing the problem. The prevalence was estimated at 388/100,000 population according to the World Health Organization (WHO) and an estimated incidence rate of 427/ 100 000 population before the survey. According to the TB prevalence survey 2013/2014 the bacteriologically confirmed TB prevalence was 638 /100,000 population (Kapata et al., 2016).

1.3 Justification of the Study

Unfavourable treatment outcomes which include death, treatment failure, loss to follow up, and its predicting factors such as age, sex, residence, type of TB, HIV status have been shown to be associated with TB unfavourable treatment outcomes (García-Basteiro et al., 2016) (Amante and Ahemed, 2015). These studies indicate that different factors have been associated with TB treatment outcomes in different

countries as well as in different communities in the same country. Therefore, information and identification of factors which affect treatment outcomes in different settings is important to understand specific problems and accordingly design community/ population-based appropriate strategies to reduce the disease burden. Assessing the outcomes of TB treatment is essential for the evaluation of the effectiveness of the service delivery (Cardoso et al., 2017). Furthermore, identifying the specific determinants for unfavourable outcomes is important to design interventions that would improve treatment systems (Ukwaja et al., 2016).

In Zambia, analysis of routinely collected surveillance data does not show factors affecting treatment outcome. In an effort to reach the global target of 90% treatment success rate, it is compelling to identify, describe, and deal with factors determining TB treatment outcome.

Determination of the pattern of unfavourable treatment outcome and the predicting factors helps to design the possible future of TB treatment and control strategies in the community. Furthermore, assessment of the performance of the tuberculosis control programme will help inform health policy solutions crucial for improving programme performance, hence contributing to the national goal of eliminating TB.

1.4 Research Questions

1. What were the proportions of unfavourable and favourable outcomes in the treatment of TB patients in Lusaka district for 2015?

2. What are the risk factors associated with unfavourable outcomes (treatment failure, loss to follow up, not evaluated and death) in the treatment of TB patients in Lusaka district for 2015?

1.5 Objectives

1.5.1 General Objective

To determine the proportion of and factors associated with TB treatment outcomes in selected facilities within Lusaka district for the period 1st January to 31st December, 2015.

i.5.2 Specific Objectives

i. To determine the proportion of TB patients who had unfavourable and favourable outcomes in Lusaka district for 2015.

ii. To identify risk factors associated with unfavourable outcomes (treatment failure, loss to follow up, not evaluated and death) in the treatment of TB patients in Lusaka district for 2015.

CHAPTER TWO - LITERATURE REVIEW

Tuberculosis is a chronic infectious disease which affects all age groups, however it affects mainly children, old aged people and HIV co-infected patients (Wen et al., 2018, Yen et al., 2017, Wondale et al., 2017).

2.1 Childhood TB

A study to describe the incidence, presentation, treatment and treatment outcomes of tuberculosis (TB) in human immunodeficiency virus (HIV) infected children was done in in Europe, Thailand and Brazil and showed that previous diagnosis of acquired immune-deficiency syndrome, not being virologically suppressed on ART at TB diagnosis and region (Brazil) were significantly associated with unfavourable TB outcomes (Turkova et al., 2016).

A study looking at treatment outcomes in children with tuberculosis in southern Ethiopia was conducted. They calculated risk factors for unfavourable outcome (failure, default or death) and found that of the 851 (165 with smear-positive, 475 smear-negative and 206 extra pulmonary TB) children, 655 (77%) were cured or completed and 124 (14.6%) had unfavourable outcome. Treatment success rate increased with age from 66% in children <5 years old to 81% in 5-9-year-olds and 85% in >/=10-year-olds. They found that 75% of patients with smear-negative TB had favourable outcome compared to 80.6% for smear-positive cases. Age <5 years, lack of smear conversion in the second month and living in rural areas were independent risk factors for unfavourable treatment outcome. The study concluded that, the outcome of TB treatment in children varies with age, residency and smear results (Munoz-Sellart et al., 2009). A similar study was conducted in Nigeria and its concluded that male children, age 0-4years old and being HIV-positive were factors associated with unfavourable outcomes (Ogbudebe et al., 2018). Another study from Ethiopia reports similar findings were risk factors were being <5years old and also being HIV positive (Tilahun and Gebre-Selassie, 2016). Permanent residence, being HIV positive but not on antiretroviral therapy, <5years old and adherence to treatment were found as factors associated with unfavourable treatment outcomes separate studies done in Ethiopia and Kenya (Kebede et al., 2017, Onyango et al., 2018).

A study on trends of childhood TB in Zambia 2004-2011 found that 74% of childhood TB cases were notified from the more urbanized areas situated along the 'line of rail', and only 26% were notified from the rural provinces. The study reported that accurate diagnosis of TB in children remains difficult and poses several diagnostic challenges. Clinical diagnostic algorithms have been complicated by co-infection with human immunodeficiency virus (HIV), malnutrition and the non-specific nature of most symptoms and signs. Children often develop extra-pulmonary TB, such as lymph node disease or meningitis, which are easily overlooked and contribute to unfavourable outcomes (Kapata et al., 2013b).

2.2 HIV Co-Infection TB

TB/HIV co-infection is one of the main drivers of unsuccessful treatment outcome in TB treatment (Teklu et al., 2017). The findings of different studies on the impact of HIV and ART status on TB treatment outcomes show that the odds ratio for death in relation to treatment success was found to be higher in HIV-positive patients not on ART than in those HIV-positive on ART. Similarly, the odds ratio for default in relation to treatment success was found to be higher in HIV positive patients not on ART than in those HIV positive on ART. In addition, increase age was associated with higher death rates in relation to treatment success (Nglazi et al., 2015, Wondale et al., 2017).

According to a study done in North-western Ethiopia showed that TB/HIV co-infected were significantly associated with the unsuccessful TB treatment outcome (Sinshaw et al., 2017). A study on the magnitude and treatment outcomes of pulmonary tuberculosis patients was conducted in a poor urban slum of Abia State, Nigeria. They found that treatment success rate was 88.5% among smear-positive patients and 79.3% among smear-negative patients. More patients with smear-negative TB were lost to follow up compared with smear-positive TB patients. HIV co-infection was associated with unfavourable treatment outcomes. Among them, those who received ART had better outcomes (Ogbudebe et al., 2016a).

The Zambia national TB survey 2013-2014 demonstrated the importance of the TB/HIV co–morbidity, with the HIV positive having a 5 times higher risk of developing unfavourable TB treatment outcomes than their HIV negative counter parts (MOH, 2017a). However, the survey found more participants with TB among

the HIV negative individuals compared to the HIV positive, therefore it is important to note the fact that there is a high TB burden of HIV negative individuals in the communities (MoH, 2013). A study was conducted to analyse the impact of scaling up ART services on tuberculosis (TB) treatment outcomes in Mumbwa District, Zambia and the findings were that treatment success rates increased in ART sites compared to non-ART sites (Miyano et al., 2013). This study demonstrates that non provision of ART to TB patients is associated with unfavourable treatment outcomes.

2.3 Risk Factors for TB

A study on Tuberculosis in Malaysia and another done in India reported one fifth (21.5%) had unfavourable outcomes; of these, 46% died, 49% transferred out or defaulted and 1% failed treatment. In this study Predictors of unfavourable outcomes were older age, male sex, foreign citizenship, lower education, no Bacille Calmette-Guérin (BCG) vaccination scar, treatment in tertiary settings, smoking, previous anti-tuberculosis treatment, human immunodeficiency virus infection, not receiving directly observed treatment, advanced chest radiography findings, multidrug-resistant TB (MDR-TB) and extra-pulmonary TB (Liew et al., 2015, Mundra et al., 2018).

According to a study looking at treatment outcome of Tuberculosis patients under DOT and factors affecting outcome in Southern Ethiopia, socio-demographic factors such as gender, age and residence of the patients and the form of TB have been reported to affect the treatment outcome. The study found that the risk of unfavourable TB treatment outcome was significantly higher among TB patients from rural areas compared to their urban counterparts. It further showed that, unfavourable treatment outcome was observed in PTB- patients compared to the PTB+ patients (Gebrezgabiher et al., 2016). These findings are also in line with what other studies done in Nigeria (Ukwaja et al., 2016, Ogbudebe et al., 2016b) found. On the contrary a study done at a hospital in Ethiopia found TB treatment outcome was not associated with age, sex, type and history of TB, or co-infection with HIV (Worku et al., 2018)

Two studies done in Mogadishu, Somalia and Ethiopia looking at factors associated with favourable treatment outcomes unlike this study which focused on unfavourable outcomes and their findings were that being married, educated, HIV-negative, being >/=45 years of age, being female, being a rural resident, being a new treatment case,

having a negative smear result at the second month of treatment and knowledgeable on TB had increased odds of favorable outcomes (Ali et al., 2017, Melese et al., 2016).

The Zambia national TB survey 2013-2014 indicated that there are wide variations in the burden of TB by location, sex, social economic status and age category. The prevalence of MTB was two to three times higher in the urban than in the rural areas; this was true for all the forms of TB, smear, culture and bacteriologically confirmed. The risk of TB was higher in males than females in the ratio of 2:1 for all forms; this is in line with what is normally observed with notifications in data from the routine surveillance system in this group, (Kapata et al., 2016)

2.4 Conceptual Framework

The framework below (Figure 2) is based on the Input-Process-Output model adopted from Worku and modified for this study (Worku et al., 2018), it shows a number of processes that are put in place leading to TB treatment outcomes. The context is that of Lusaka district having 23 TB diagnostic centres and as of 2015 was leading in terms of TB notification in the country. The levels of these are activities are at both community and facility level. The inputs include those at community level and health facility level and these targeting at making sure the TB treatment and control is well coordinated. There are also processes that are involved at community level and facility level in terms of diagnosis, treatment and control of TB example given is research, analysis of data reported to see who when and where is TB coming from. What follows are outputs from the indicator process put in place and here we have identified for example who is affected the most in terms age and sex, where is TB coming from and when do we see an increased number of cases. The outcome of such an output will be then enable us to quantify favourable outcomes (cured and treatment success) and unfavourable outcomes (death, relapse, lost to follow up, not evaluated) and put in intervention measures and evidence which is helpful in improving treatment of TB. This will lead us to the impact which is the ultimate goal of eliminating TB.

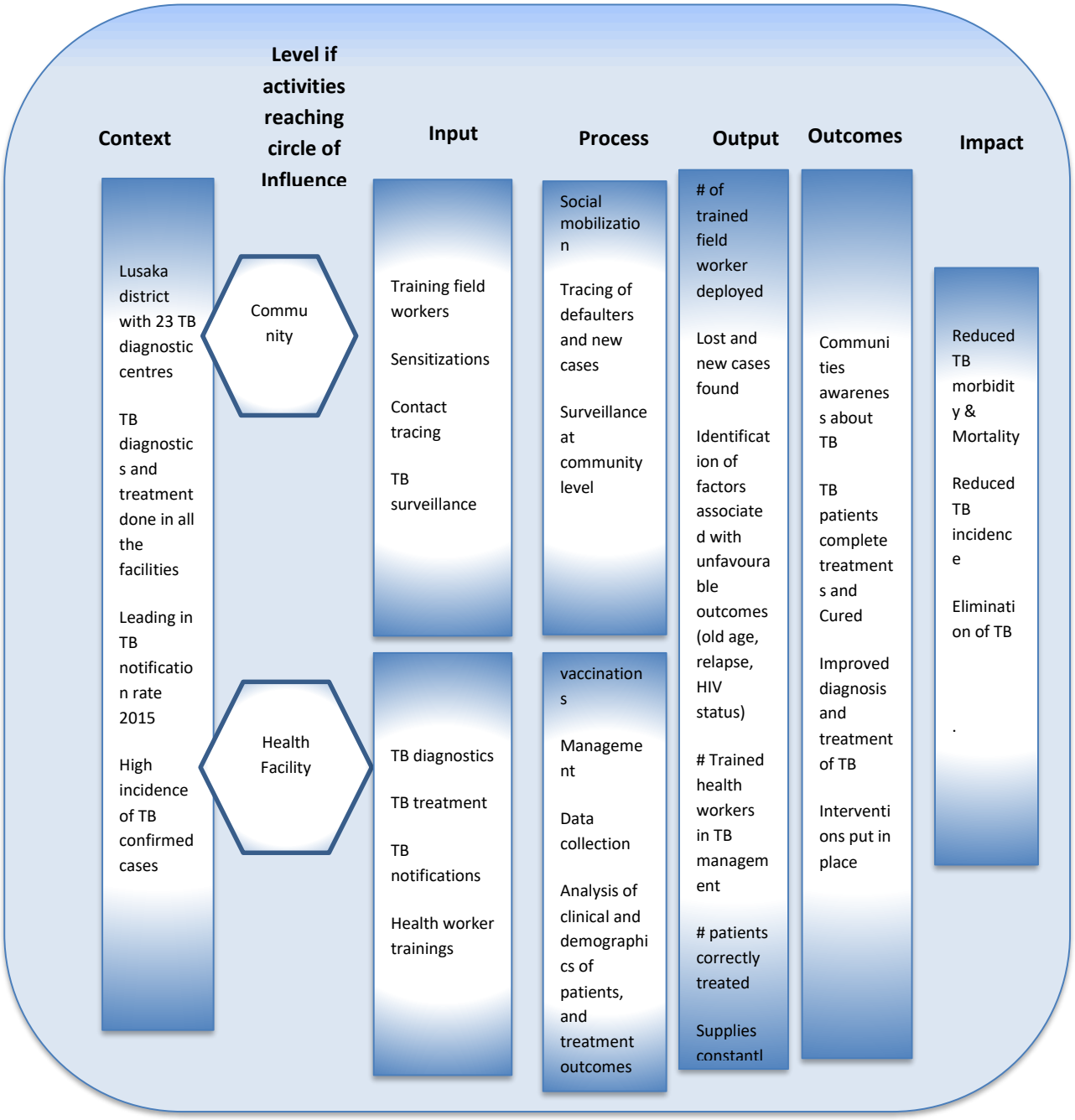

Figure 2: Conceptual frame for inputs, processes and outcomes in TB treatment

Based on: *Input-Process-Output framework adopted from Worku et al*

CHAPTER THREE - METHODOLOGY

3.1 Study Design

A cross sectional study design which involved a review of TB bacteriologically confirmed and clinically diagnosed case records at three purposively selected Health Facilities in Lusaka district for 2015.

3.2 Study Site

This research was conducted in Lusaka district which had a population of 2,330,200 as of 2015. The district has a total of 28 health facilities and of these, 23 are TB diagnostics centres. Lusaka reported 8,074 TB notifications which was highest recorded number in the province for 2015. All the 23 TB diagnostic facilities had reported above 300 TB confirmed cases hence a decision of purposively selecting three facilities was arrived at. Among the selected health facilities, one peri-urban clinic, one urban-clinic and one first level referral hospital.

3.3 Study Population

All TB confirmed cases for all ages in 3 of the 23 TB diagnostic centres in Lusaka district for 2015.

3.4 Inclusion Criteria

All PTB and EPTB TB confirmed cases enrolled on treatment, in 2015 were included in the study.

3.5 Exclusion Criteria

Patients who transferred in from other TB diagnostic centres where excluded because the transfer in patients have their outcomes recorded at the referring facility. Drug resistant TB was also excluded from the treatment outcome evaluation as this is reported separately according WHO guidelines.

3.6 Sample Size and Sampling Methods

The sample size was estimated by using the following formula for survey sample estimation at 95% level of confidence.

$$\mathbf{n = z^2 p\ (1\text{-}p)/d^2}$$

Where n = required sample size

p = estimated proportion set at 0.5

d = precision 5%

Z = value of the standard normal distribution corresponding to a significance level of a 1.96 for a 2-sided test at the 0.05 level.

The minimum sample size to be used was n=384, despite having a minimum sample size of 384 we did a complete review and abstraction of all records for confirmed TB cases on treatment during the year 2015 from the standard paper TB treatment registers, and verified the recorded information with individual patient TB treatment cards and our total sample size came to 1724.

Out of the 23 TB diagnostic centres in Lusaka district these were put into three categories namely hospitals, urban clinics and peri-urban clinics. Based on the anecdotal data from the ministry of health each of these facilities had reported above 300 cases of TB. We therefore selected one 1st level Hospital, one urban-clinic and one peri-urban clinic using purposive sampling. From the anecdotal data there were 2608 records but after review and data cleaning only 1724 case records were used for this study. This difference may be attributed to poor record keeping over time as some registers had missing pages.

3.7 Data Collection Methods

For objective number one, the number of patients who had unfavourable and favourable outcomes by type was obtained from individual health facilities, using data from TB registers for 2015. Visit to the health facilities in Lusaka district and abstraction of TB confirmed cases (diagnosis date 1st January to 31st December 2015) from TB registers into a Microsoft Excel database was done**.**

For objective number two, data was abstracted using a data abstraction form in an Excel database and exported to Stata version 13 (Stata Corp, College Station, Texas 77845 USA). The collection was done by the principal investigator with the help of the TB focal point persons at the health facilities. The data abstraction form was piloted at a place outside the study area to ensure that it has details that match with the registers. Every form was checked for data quality and completeness during data abstraction. The data abstraction form collected information on social demographic characteristics of the patients, type of TB, HIV status, location of health facility, outcomes such as cure, treatment completion/failure, death, loss to follow up for TB confirmed cases from 1st January to 31st December 2015.

3.9 Data Analysis Methods

Data collected was analysed using Stata Version 13 (Stata Corp, College Station, Texas 77845 USA). A histogram was used to graphically check for normality (graphs not shown). The continuous variable age which was normally distributed was categorised to see the various effects in different age categories. Categorical data such as sex was reported using numbers and percentages, Chi-square test was used to ascertain associations with unfavourable outcomes. Odds ratios were reported as a measure of association for categorical variables using logistic regression.

- For objective 1 the proportions were calculated using the number of cases recorded per type of outcome (that is favourable and unfavourable diagnosis dates 1st January to December 2015) data abstracted as the numerator and using the total TB confirmed cases as denominator.
- For objective 2 univariate and multivariable logistic regression was performed, the outcome variable was whether or not the individual had unfavourable outcome (treatment failure, died, not evaluated or lost to follow up) or not in 2015. Risk factors assessed include age, sex, location of health facility, HIV status, type of TB, patient type (new, relapse, transfer in or treatment resume case).

For the logistic regressions performed as part of objective 2, using alpha= 0.05, odds ratios and corresponding 95% confidence intervals were calculated for the various risk factors. To keep some priori variables in the model for the multivariable logistic regression, investigator led backward stepwise logistic regression was performed. Subtracting of variables in the model was influenced by literature review. Selection of the best model was guided by the likelihood ratio test, Akaike Information Criteria and Bayesian Information Criteria after estimation of the nested models by eliminating variables one at a time. To further understand the outcomes, an analysis was performed in multivariable analysis by excluding the not evaluated category from the unfavourable outcomes as it was missing the actual outcome of the patient.

3.10 Ethical Considerations

Ethical clearance was sought and obtained from Excellence in Research Ethics and Science (ERES) Ethics Committee (Ref: 2017-June-013). Further permission to conduct the study was sought from Ministry of Health. No harm was caused to the

participants because the study utilized secondary data. No personally identifying information was collected and the data collected was used for the study and not any other purpose. The data was kept in a secure place to prevent any access for use other than the study to maintain confidentiality. The names health facilities were withheld to prevent patients from shunning seeking care from the selected facilities. The study will provide evidence that will influence in planning of effective interventions in the management of TB in Zambia.

3.11 Limitations and Strengths

The study was a review of data records in the sampled three health facilities. Socio demographic information such as drinking habits, education levels, marital status and employment (Kapata et al., 2013a, Tesfahuneygn et al., 2015) were not available. Any bias introduced by lack of availability of this data, may have underestimated the association between potential risk factors and treatment outcomes; availability of missing information would have strengthened the association between risk factors and treatment outcomes.

Our study purposively sampled three health facilities in Lusaka district. Because of this, it is possible that bias might have been introduced which may have led to over or underestimation of the true magnitude of the relationship between the exposures and the outcome. This may affect the generalizability of results obtained to the Lusaka district.

However, this study was able to identify the risk factors associated with unfavourable outcome in the treatment of TB at three different types of TB diagnostic health facilities in Lusaka. These findings may help the national TB programme to adopt effective strategies in the prevention and treatment of TB in Zambia.

CHAPTER FOUR - RESULTS

4.1 Socio-demographic characteristics and outcome of patients

A total of 1724 registered TB patients was included from urban-clinic (40%), 1st Level Hospital (38%) and peri-urban-clinic (22%) (Table 4.1). The majority were males 1128 (65.4%), the age range was from 0 to 91years with majority (51%) in the range 30 to 44 years and 985 (57%) had favourable outcomes. Among those with favourable outcomes, 307 (18%) were cured and 678 (39%) had completed treatment, giving a treatment success rate of 57%. We found that 506 (29%) patients were not evaluated, 138 (8%) died, 90 (5%) were lost to follow up, and 5 (0.3%) had treatment failure giving an unfavourable outcome of 43%.

Table 4.1: Socio-Demographic Characteristics and Treatment Outcomes of the Registered TB Cases (N = 1724) at three Health Facilities in Lusaka District, Zambia, 2015.

Characteristic	Urban-Clinic n(%)	1st Level Hospital n(%)	Peri-Urban-Clinic n(%)	Total n(%)	P-Value
TOTAL (n)	694	654	376	1724	<0.001 [a]
SEX					0.57[a]
Male	445 (64)	430 (66)	253 (67)	1128 (65)	
Females	249 (36)	224 (34)	123 (33)	596 (35)	
AGE GROUP					0.17[a]
0-14	33 (4)	37 (5)	7 (2)	77 (4)	
15-29	174 (25)	162 (25)	110 (29)	446 (26)	
30-44	358 (52)	324 (50)	192 (51)	874 (51)	
45-59	94 (14)	91 (14)	48 (13)	233 (14)	
> 59	35 (5)	40 (6)	18 (5)	93 (5)	
OUTCOME					<0.001[a]
Favourable					
Cured	186 (27)	87 (13)	34 (9)	307 (18)	
Treatment Complete	210 (30)	368 (56)	100 (27)	678 (39)	
Favourable outcome [Treatment success rate (%)]	396 (57)	455 (70)	134 (36)	985 (57)	<0.001[a]
Unfavourable					<0.001[a]
Not evaluated	173 (25)	117(18)	216 (57)	506 (29)	
Died	51 (7)	67 (10)	20 (5)	138 (8)	
Lost To Follow Up	74 (11)	10 (2)	6 (2)	90 (5)	
Failure	0 (0)	5 (0.3)	0 (0)	5 (0.3)	
Unfavourable outcome (%)	298 (43)	199 (30)	242 (64)	739 (43)	<0.001[a]

[a]Chi-square test.

4.2 Association between Demographic/Clinical Characteristics and Treatment Outcome among TB Patients in Lusaka, Zambia, 2015

Univariate logistic regression analysis (Table 4.2) revealed that TB patients aged above 59 years old had higher odds (unadjusted odds ratio (OR) =1.65, 95% CI: 1.02, 2.68, p=0.04) of developing TB compared to those age 45-59 years, relapse patients were more likely to develop unfavourable outcome (OR = 1.55, 95% CI: 1.22–1.97, p<0.001) compared to new patients. Patients who sought treatment at the urban-clinic (OR = 1.7, 95% CI: 1.36–2.14, p<0.001) and peri-urban-clinic (OR = 4.1, 95% CI: 3.13–5.36, p<0.001) were more likely to develop unfavourable outcomes compared to 1st Level referral hospital. Male TB patients were more likely (OR = 1.24, 95% CI: 1.02–1.52, p=0.03) to develop unfavourable outcomes compared to females TB patients. HIV positive TB patients had an increased chance of developing unfavourable outcomes compared to negative TB patients, the association was statistically significant.

Table 4.2: Association between Demographic /Clinical Characteristics and Treatment Outcome among TB Patients in Lusaka, Zambia, 2015

Characteristic	Number (%) Favourable Outcomes	Number (%) of Unfavourable Outcomes	UOR (95% CI)	P-Value
Sex n=1724				
Female	361 (61)	235 (39)	1.00	
Male	623 (55)	505 (45)	1.24 (1.02, 1.52)	0.03
AGE GROUP n=1723				
45-59	144 (62)	89 (38)	1.00	
0-14	52 (68)	25 (32)	0.78 (0.45, 1.34)	0.40
15-29	258 (58)	188 (42)	1.17 (0.85, 1.63)	0.32
30-44	484 (55)	390 (45)	1.3 (0.96, 1.75)	0.08
>59	**46 (49)**	**47 (51)**	**1.65 (1.02, 2.68)**	**0.04**
Patient Type n=1718				
New	799 (60)	542 (40)	1.00	
Relapse	**166 (49)**	**175 (51)**	**1.55 (1.22, 1.97)**	**<0.001**
Treatment Resume	16 (44)	20 (56)	1.84 (0.95, 3.59)	0.07
TB Type n= 1720				
Extra Pulmonary	161 (57)	120 (43)	1.00	
Pulmonary	821 (57)	618 (43)	1.00 (0.78, 1.31)	0.94
HIV Status n=1675				
Negative	351(61)	224 (39)	1.00	
Positive	617 (57)	483 (43)	1.22 (1.0, 1.51)	0.05
Health Facility n=1724				
1st Level Hospital	356(54)	298 (43)	1.00	
Urban-Clinic	**494 (71)**	**200 (31)**	**1.7 (1.36, 2.14)**	**<0.001**
Peri-Urban-Clinic	**134 (36)**	**242 (64)**	**4.1 (3.13, 5.36)**	**<0.001**

CI; Confidence interval Odds Ratio; uOR, Unadjusted Odds ratio;

4.3 Analysis of factors associated with Treatment Outcome among TB Patients in Lusaka, Zambia, 2015

The multivariable logistic regression (Table 4.3) showed that the odds of unfavourable outcome was significantly higher among relapse patients (aOR = 1.8, 95% CI: 1.42–2.26, p<0.001) compared to new patients after adjusting for patient type, location of health facility, age-group, and HIV status. Patients who sought treatment at the urban-clinic (aOR = 1.8, 95% CI: 1.42–2.26, p<0.001) and peri-urban-clinic (aOR = 4.3, 95% CI: 3.22–5.66, p<0.001) were more likely to develop unfavourable outcomes compared to the 1st Level referral hospital after adjusting for all other factors. The odds (aOR = 1.05, 95% CI: 0.84–1.30, p=0.67) of unfavourable outcomes were higher among HIV positive compared to HIV negative TB patients after adjusting for all other factors, the association was however not statistically significant. TB patients aged above 59 years old had higher odds (aOR =1.8, 95% CI: 1.09, 3.10, p=0.02) of developing TB compared to those age 45-59 years after adjusting for all other factors.

When the not evaluated category was excluded (Table 4.3) in the multivariable logistic regression the main difference was that the odds (aOR = 1.56, 95% CI: 1.11–2.19, p=0.01) of unfavourable outcomes was significantly higher among the HIV positive TB patients compared to those HIV negative TB patients after adjusting for all other factors.

Table 4.3: Analysis of Factors Associated with Treatment Outcome among TB Patients in Lusaka, Zambia, 2015

Characteristic	AOR (95% CI)	P-Value	AOR (95% CI) Excluding not Evaluated Category	P-Value
AGE GROUP				
45-59	1.00		1.00	
0-14	1.11 (0.62, 1.96)	0.73	1.17 (0.50, 2.70)	0.72
15-29	1.2 (0.85, 1.72)	0.28	1.30 (0.77, 2.19)	0.32
30-44	1.4 (0.99, 1.86)	0.06	1.37 (0.80, 2.04)	0.3
>59	**1.8 (1.09, 3.10)**	**0.02**	**2.90 (1.44, 5.79)**	**0.003**
Patient Type				
New	1.00			
Relapse	**1.8 (1.42, 2.26)**	**<0.001**	**1.65 (1.15, 2.38)**	**0.007**
Treatment Resume	1.5 (0.71, 3.01)	0.31	2.20 (0.88, 5.54)	0.093
Health Facility				
1st level hospital	1.00		1.00	
Urban-Clinic	**1.8 (1.42, 2.26)**	**<0.001**	**1.76 (1.27, 2.42)**	**0.001**
Peri-Urban-Clinic	**4.3 (3.22, 5.66)**	**<0.001**	1.05 (0.64, 1.74)	0.834
HIV Status				
Negative	1.00		1.00	
Positive	1.06 (0.85, 1.32)	0.62	**1.56 (1.11, 2.19)**	**0.01**

CI; Confidence interval Odds Ratio; aOR, Adjusted Odds ratio;

CHAPTER FIVE - DISCUSSION

The WHO has set standards for reporting of outcome of anti-tuberculosis treatment (WHO, 2013a) and is one of the major indicators in the assessment of the performance of a national TB programme (WHO, 2015). In this study most of the TB patients were males which is similar to findings from a other studies (Kapata et al., 2016, Murphy et al., 2018). One suggested reason for a higher proportion of males having TB is that they are probably more exposed to the infections because of the type of jobs or social behavioural factors such as smoking as compared to women (Sinshaw et al., 2017, Khan et al., 2015). Another possible explanation is that males and females have different societal roles (such working in a mine) that can influence not only their risk of exposure to TB but also their access to care (Ngahane et al., 2016, Murphy et al., 2018). Sex differences in TB notification could also be explained by a higher rate of progression to disease in males than in females (Thorson and Diwan, 2001). Women have been known to have good patient and self-care in their families and this has made them more compliant to TB treatment compared to males hence the seen differences (Carlsson et al., 2014).

This study found an overall treatment success rate of 57% for the three facilities sampled, and this was lower than the 86% reported for the entire Lusaka district. This finding may mean that overall figures reported in Lusaka district are likely to mask lower treatment success levels in health facilities not performing well. It also suggests that achieving the treatment success target for some health facilities is a major challenge that needs to be tackled. The overall unfavourable TB treatment outcome rate was higher than the unfavourable treatment outcome reported from Ethiopia (Gebrezgabiher et al., 2016, Melese and Zeleke, 2018, Melese et al., 2016). This result is also higher than another study conducted in Malaysia which reported a rate of 21.5% (Liew et al., 2015). High rates of missing TB cases which stand at 42% and low utilization of TB preventive therapy current at 18% could be contributing to the unfavourable outcome seen in the study (MOH, 2017b). The findings of this study show a high number of cases not evaluated which shows that there is poor record keeping in the three health facilities. The high unfavourable treatment outcome found in this study affects the country's overall goal of achieving the 90% treatment success

rate as recommended by the WHO hence there is need to put in measures aimed at addressing the challenges.

Many studies have shown similar to this study that old age is associated with unfavourable outcome in TB treatment (Liew et al., 2015) and (Gebrezgabiher et al., 2016). This finding could be attributed to an increased risk of lower immunity, making them more susceptible to infections, as a person grows older which may lead to poor outcomes (Gebrezgabiher et al., 2016, Mok et al., 2018). This study did not examine this association between age and co-morbidities because secondary data were used. Findings of a study in Ethiopia (Worku et al., 2018) are different from what this study found this could be due differences in geographical location also possible confounders due to use of secondary data. This study also showed that relapse patients had higher odds of developing unfavourable outcomes compared to new cases. Similar to this, a study in India found that relapse cases had a higher risk of developing unfavourable outcomes compared to new cases (Santha et al., 2002). This result could be due to many factors, including lack of adherence, higher rates of lost to follow up and higher drug resistance rates among relapse patients (García-Basteiro et al., 2016). This association could not be shown in this study, because we used secondary data which did not capture these variables. A study conducted in Nigeria did not find any associations between new and relapse patients (Ukwaja et al., 2016).

In this study health facility where a patient was receiving care from was found to be associated with unfavourable outcome. This is similar to findings from a study done in northern Ethiopia where they compared treatment outcomes from different health facilities (Tesfahuneygn et al., 2015). This finding could be as a result of different levels of care received at the facilities. This may include availability of TB diagnostic facilities such as Gene-Xpert machines that makes diagnosis easy and fast compared to use of microscopes for culture. It may also be a behavioural factor that could be common in one side of the district, leading to unfavourable treatment outcomes (Samuel et al., 2016, Alobu et al., 2014). This is an area that calls for future research to see what risk factors exist in different locations that may put people at higher risk of unfavourable outcomes in the TB treatment. Different from this study, in Nigeria a study compared rural against urban facility and their finding was that patients in rural areas were more associated with unfavourable outcomes (Ukwaja et al., 2016). This

information tells us there is need to monitor health facilities to learn practices from those that are doing well and trickle them down to those that are not performing well.

The further analysis conducted revealed reviewed that after removing the not evaluated category whose outcomes where unknown, HIV positive TB patients were more likely to develop unfavourable outcomes. Similar to other studies (Chanda-Kapata et al., 2016, Nglazi et al., 2015) our study found HIV positive TB patients to be associated with unfavourable outcome. HIV is known to affect the immune system of individuals making them more susceptible to opportunistic infections such as TB (MoH, 2014). It has been suggested that HIV positive TB patients are more likely to become malnourished due to constant sickness, have diarrhoea that prevents absorption of nutrients, loss of appetite and sores of mouth that make eating difficult, and also experience more opportunistic infections (Sinshaw et al., 2017, Ukwaja et al., 2016). Another reason for unfavourable outcomes among HIV positive TB patients could be poor uptake of anti-retro viral therapy (ART) (Nglazi et al., 2015, Onyango et al., 2018). This study however did not analyse the association between ART and unfavourable treatment outcomes among HIV positive TB patients due to missing information from the registers. This therefore calls for improved action in ensuring that health facilities record and report all TB treatment outcomes. Failure to do so may lead to missing of very important information required for effective service delivery in the diagnosis and treatment of TB.

CHAPTER SIX – CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

In conclusion, overall treatment success rate and unfavourable outcome were 57% and 43% respectively. TB/HIV co-infection, being relapse patient, being > 59years old and receiving treatment at the urban clinic predictors for unfavourable outcomes. These findings could inform the National TB Control Programme for policy guidance on tuberculosis treatment.

6.2 Recommendations

i. Special attention to patients of >59years old, relapse cases and HIV positive in the TB treatment is recommended.
ii. Close monitoring of health facilities in increasing efforts aimed at evaluating all the outcomes.
iii. Further studies to identify and test interventions aimed at improving treatment outcomes.
iv. Health facilities to improve their record keeping

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APPENDICES

Appendix 1: Study Approval Letter from Ethics Committee

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LUSAKA.

Dear Mr. Nanzaluka,

RE: AN ASSESSMENT OF FACTORS ASSOCIATED WITH UNFAVOURABLE OUTCOMES IN THE TREATMENT OF TUBERCULOSIS IN LUSAKA PROVINCE FOR 2015

Reference is made to your corrections dated 31st July, 2017. The IRB resolved to approve this study and your participation as Principal Investigator for a period of one year.

Review Type	**Ordinary**	Approval No. **2017-Jun-013**
Approval and Expiry Date	Approval Date: 4th August, 2017	Expiry Date: 3rd August, 2018
Protocol Version and Date	Version-Nil	3rd August, 2018
Information Sheet, Consent Forms and Dates	• English.	3rd August, 2018
Consent form ID and Date	Version -Nil	3rd August, 2018
Recruitment Materials	Nil	3rd August, 2018
Other Study Documents	Questionnaires.	3rd August, 2018
Number of participants approved for study	-	3rd August, 2018

Specific conditions will apply to this approval. As Principal Investigator it is your responsibility to ensure that the contents of this letter are adhered to. If these are not adhered to, the approval may be suspended. Should the study be suspended, study sponsors and other regulatory authorities will be informed.

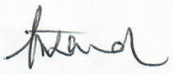
Conditions of Approval

- No participant may be involved in any study procedure prior to the study approval or after the expiration date.
- All unanticipated or Serious Adverse Events (SAEs) must be reported to the IRB within 5 days.
- All protocol modifications must be IRB approved prior to implementation unless they are intended to reduce risk (but must still be reported for approval). Modifications will include any change of investigator/s or site address.
- All protocol deviations must be reported to the IRB within 5 working days.
- All recruitment materials must be approved by the IRB prior to being used.
- Principal investigators are responsible for initiating Continuing Review proceedings. Documents must be received by the IRB at least 30 days before the expiry date. This is for the purpose of facilitating the review process. Any documents received less than 30 days before expiry will be labelled "late submissions" and will incur a penalty.
- Every 6 (six) months a progress report form supplied by ERES IRB must be filled in and submitted to us.
- ERES Converge IRB does not "stamp" approval letters, consent forms or study documents unless requested for in writing. This is because the approval letter clearly indicates the documents approved by the IRB as well as other elements and conditions of approval.

Should you have any questions regarding anything indicated in this letter, please do not hesitate to get in touch with us at the above indicated address.

On behalf of ERES Converge IRB, we would like to wish you all the success as you carry out your study.

Yours faithfully,
ERES CONVERGE IRB



Prof. E. Munalula-Nkandu
BSc (Hons), MSc, MA Bioethics, PgD R/Ethics, PhD
CHAIRPERSON

Appendix 2: Letter Authority to Conduct Study from National Health Research Authority

THE NATIONAL HEALTH RESEARCH AUTHORITY
C/O Ministry of Health
Haile Selaisse Avenue,
Ndeke House
P.O. Box 30205
LUSAKA

MH/101/23/10/1

25 August 2017

Nanzaluka Francis H
The University of Zambia
School of Public Health
P.O Box 32379
LUSAKA

Re: Request for Authority to Conduct Research

The National Health Research Authority is in receipt of your request for authority to conduct research titled **"Factors Associated with Unfavourable Outcomes in the Treatment of TB in Lusaka District-2015"**.

I wish to inform you that following submission of your request to the Authority, our review of the same and in view of the ethical clearance, this study has been approved on condition that:

1. The relevant Provincial and District Medical Officers where the study is being conducted are fully appraised;
2. Progress updates are provided to NHRA quarterly from the date of commencement of the study;
3. The final study report is cleared by the NHRA before any publication or dissemination within or outside the country;
4. After clearance for publication or dissemination by the NHRA, the final study report is shared with all relevant Provincial and District Directors of Health where the study was being conducted, and all key respondents.

Yours sincerely,

Sandra Chilengi-Sakala
For/Director
National Health Research Authority

Appendix 3: Letter Authority to Conduct Study from National TB Program

All Correspondence should be addressed to the Permanent Secretary
Telephone: +260 211 253040/5
Fax: +260 211 253344

In reply please quote:

No.....

REPUBLIC OF ZAMBIA
MINISTRY OF HEALTH

NDEKE HOUSE
P. O. BOX 30205
LUSAKA

23 August, 2017

Nanzaluka Francis H
The University of Zambia
School of Public Health
P.O Box 32379
LUSAKA

Dear Sir,

RE: REQUEST FOR AUTHORITY TO CONDUCT RESEARCH

Reference is made to the above captioned subject.

The National TB Control Programme is in receipt of the letter dated 22 August, 2017 with request for authority to conduct research titled **"Factors associated with unfavourable outcomes in the treatment of TB in Lusaka District 2015".**

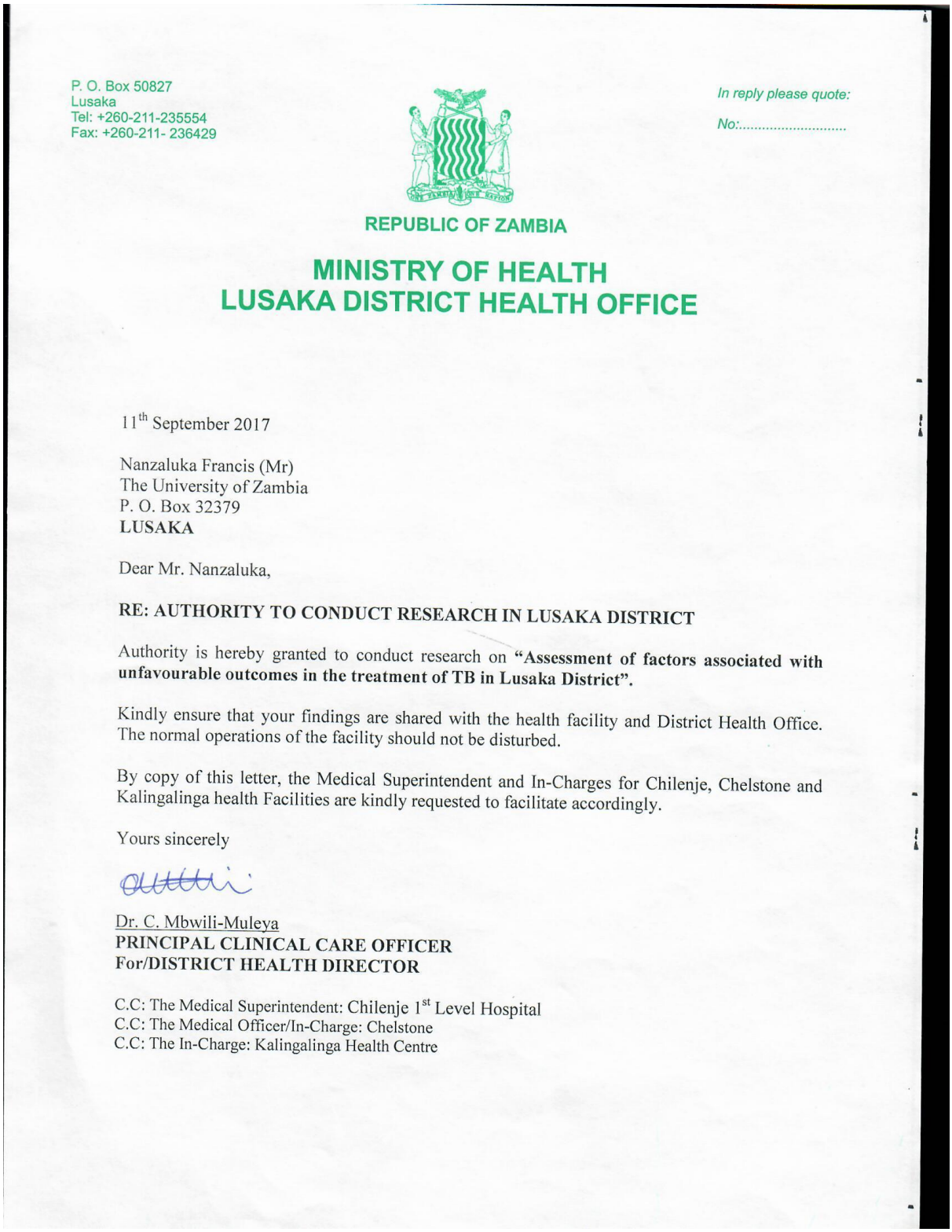
I wish to inform you that following submission of your request to the National TB Programme, permission has been granted for the study to be conducted under the following conditions:

- Progress updates are provided quarterly to the National TB Programme from the date of commencement of the study
- The final study report is shared with the National TB Programme and District Health Director where the study will be conducted.

Yours faithfully

Dr. Chila Simwanza
National TB Program Manager
MINISTRY OF HEALTH

Appendix 4: Letter of Permission to Collect Data in Health Facilities from Lusaka District Health Office



P. O. Box 50827
Lusaka
Tel: +260-211-235554
Fax: +260-211- 236429

In reply please quote:

No:.....

REPUBLIC OF ZAMBIA

MINISTRY OF HEALTH
LUSAKA DISTRICT HEALTH OFFICE

11th September 2017

Nanzaluka Francis (Mr)
The University of Zambia
P. O. Box 32379
LUSAKA

Dear Mr. Nanzaluka,

RE: AUTHORITY TO CONDUCT RESEARCH IN LUSAKA DISTRICT

Authority is hereby granted to conduct research on **"Assessment of factors associated with unfavourable outcomes in the treatment of TB in Lusaka District".**

Kindly ensure that your findings are shared with the health facility and District Health Office. The normal operations of the facility should not be disturbed.

By copy of this letter, the Medical Superintendent and In-Charges for Chilenje, Chelstone and Kalingalinga health Facilities are kindly requested to facilitate accordingly.

Yours sincerely

Dr. C. Mbwili-Muleya
PRINCIPAL CLINICAL CARE OFFICER
For/DISTRICT HEALTH DIRECTOR

C.C: The Medical Superintendent: Chilenje 1st Level Hospital
C.C: The Medical Officer/In-Charge: Chelstone
C.C: The In-Charge: Kalingalinga Health Centre

Appendix 5- Data Abstraction Form

TB DATA ABSTRACTION FORM 2017

NAME OF DATA COLLECTOR														NAME OF HEALTH FACILITY:								
SOCIAL DEMOGRAPHIC							PATIENT TYPE				RESULT OF SMEAR		TYPE OF TB		CO-INFECTION		OUTCOMES				
SN	ID	DIAGNOSIS DATE	AGE	SEX	WEIGHT AT START	DISTANCE TO HEALTH FACILITY	NEW CASE	RELAPSE	TRANSFER IN	TREATMENT RESUME	SMEAR POSITIVE	SMEAR NEGATIVE	PULMONARY	EXTRA PULMONARY	HIV STATUS	ART STATUS	TREATMENT COMPLETE	CURED	LOSS TO FOLLOW UP (DEAFUTER)	DEAD	FAILURE