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**PREVALENCE AND FACTORS ASSOCIATED WITH NON-CONVERSION OF POSITIVE
SPUTUM SMEARS AT 8 WEEKS OF TREATMENT AMONG NEW PULMONARY
TUBERCULOSIS PATIENTS IN KAMPALA**

BY

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DECLARATION

I do hereby declare that this work has not been submitted or presented to any institution or university for any award. All work is original unless otherwise acknowledged.

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DEDICATION

To all the Nurses who work tirelessly to provide quality health care and counseling to tuberculosis patients, to ensure that they adhere to the treatment regimens.

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LIST OF ACRONYMS

AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
AOR	Adjusted Odds Ratio
BCG	Bacillus Calmette-Guerin
CWRU- MU	Case Western Reserve University-Makerere University
HIV	Human Immunodeficiency Virus
JCRC	Joint Clinical Research Center
MDR –TB	Multi Drug Resistant Tuberculosis
MoH	Ministry of Health
MTB	Mycobacterium Tuberculosis
NTLP	National Tuberculosis and Leprosy Programme
OR	Odds Ratio
PTB	Pulmonary Tuberculosis
WHO	World Health Organization

OPERATIONAL DEFINITIONS

A **new case of TB** is a patient with initial episode TB and has never had treatment for TB or who has taken anti-TB drugs for less than one month (4weeks).

Sputum smear non-conversion: persistent positive sputum smear at 8 weeks of anti-tuberculosis treatment of a new sputum smear positive, pulmonary tuberculosis patients.

ABSTRACT

Background: Tuberculosis, despite being a curable disease, has remained a public health challenge the world over. Control of tuberculosis involves the prompt identification and cure of the infectious patients to prevent them from transmitting the disease. However, despite the intensive and adequate treatment given to the patients, some persist with a sputum smear positive with Acid Fast Bacilli. This poses a major setback in the control of tuberculosis.

Objective: To determine the prevalence and factors associated with non conversion of positive sputum smears among new smear positive, pulmonary tuberculosis patients attending the CWRU-MU Research collaboration clinic.

Methods: This study employed two designs; a cross-sectional to determine the prevalence and a case-control to determine the associated factors. The participants were new smear positive pulmonary tuberculosis patients who had completed 8 weeks of tuberculosis treatment, and had a 2-months sputum smear result. Cases, selected consecutively and Controls, selected randomly had a positive and negative smear result respectively, in a ratio of 1 to 3. Pretested structured data extraction forms were used to obtain information from the patients' medical records by trained research assistants. The baseline characteristics were descriptively summarized in percentages and patient characteristics compared using the chi-square(χ^2) or Fischer's exact test. Significant variables in the bivariate analysis with $p < 0.2$ were considered for multivariable analysis.

Results: 85 out of the 393 participants that were studied remained smear positive at 2 months of anti-tuberculosis treatment, 21.6% (95%CI 20.8-25.7). On multivariable analysis factors found to be significantly associated with sputum smear non conversion included male sex ($p=0.032$) and a positive smoking history ($p=0.047$), while age was a confounder.

Conclusion: The prevalence of sputum smear non conversion is high among tuberculosis patients in Kampala. Male sex and a positive smoking history are factors predictive of sputum smear non conversion; hence patients with those factors should be given special attention to accelerate their sputum clearance.

CHAPTER ONE

1.0 Introduction

Nearly one third of the global population is infected with *Mycobacterium tuberculosis* and at risk of developing the disease (WHO, 2003). Among the world's 22 countries with the largest tuberculosis burden, Uganda ranks 16th (WHO,2010) and tuberculosis has continued to be among the major public health problems in the country with an annual incidence of 330 cases of all forms per 100,000 population and 136 new sputum smear positive pulmonary tuberculosis cases per 100,000 people per year (MOH, 2010). This high burden might be due to the high prevalence of HIV/AIDS, which is one of the major risk factors in the development of active tuberculosis among individuals infected with mycobacterium tuberculosis complex (Verma etal, 2007). Tuberculosis is also a leading cause of morbidity and mortality for people living with HIV/AIDS and accounts for 30% of all death among them (MOH, 2010).

Programmes for tuberculosis control aim to reduce the spread of infection and the most effective method for preventing transmission is identification and cure of infectious pulmonary tuberculosis patients (WHO, 2003). Pulmonary tuberculosis cases account for about 80% of all forms of tuberculosis (Verma etal, 2007), and these patients particularly the sputum smear positive patients can transmit the bacilli to others.

Bacteriological monitoring of sputum smear positive cases is important during treatment in order to establish the patients' treatment outcome and to measure the effectiveness of treatment (Zhao, 1997). Smear Microscopy is the commonest method used for monitoring the patients in general health service especially in resource poor settings because it is rapid, inexpensive and easy to carry out. Sputum specimen are to be obtained for examination at the

time of diagnostic evaluation, completion of the initial phase of treatment (8weeks), 5 months to assess treatment failure and at the end of the continuation phase to confirm success of treatment (Senkoro et al, 2010). Sputum smear and culture conversion are important indicators for the infectivity of the patient and effectiveness of treatment (Tiyas et al, 2009).

Non conversion of a positive sputum smear at the end of the initial phase of treatment poses a great public health risk of spreading the epidemic and prolonged isolation of tuberculosis patients (Siddiqui et al, 2010). Previous studies have associated this non conversion with diabetes mellitus, increasing age, male gender, extensive disease and high pre treatment bacillary load. However no current study has been done in Uganda to assess the associated factors and there is also limited data on the influence of *Mycobacterium tuberculosis* strain type on sputum smear conversion at 8 weeks of tuberculosis treatment. Therefore the aim of the current study was to determine the prevalence and factors associated with non conversion of positive sputum smears among new pulmonary tuberculosis patients in Kampala district, the results of which may be used to enlighten on the burden of transmission among pulmonary tuberculosis patients at the end of the initial phase of treatment and also to devise means of accelerating sputum smear conversion in addition to helping in identifying patients that require the most medical resources and attention such as prolonged respiratory isolation so as to improve treatment outcome.

1.1 Problem statement

Patients with a positive sputum smear at completion of two months of therapy are at increased risk of relapse with the standard 6 month regimen, which puts them at risk of developing acquired drug resistance especially if therapy was not directly observed (CDC, 2003). Drug resistant tuberculosis is complex to treat in terms of cost and patients' response to the treatment.

Secondly, patients who remain smear positive at the end of the initial phase of treatment are likely to transmit the disease to contacts and also require extension of their initial phase for one more month (MOH, 2010). A longer duration of treatment is associated with noncompliance of patients with treatment (Jing Jin et al, 2008), which is also another risk factor for developing drug resistant tuberculosis. Persistent positive smears are associated with unfavorable treatment outcomes especially default during the course of treatment (Kuaban, 2009). Sputum smear non conversion after the initial phase of treatment is an important predictor of treatment success and failure to convert predicts treatment failure (Zhao Feng-Zeng, et al 1997) (Namukwaya E, et al 2011). It also requires prolonged isolation of the patient (Siddiqui et al, 2010). This calls for an added cost from the family of the patient, the health facility and sometimes stigma to the patient. The treatment compliance rates in Uganda are low (Nuwaha, 1997) and this may fuel up the problem of sputum smear non conversion in the country. There is also limited data on the influence of *Mycobacterium tuberculosis* strain type on sputum smear conversion at 8 weeks of tuberculosis treatment

1.2 Justification of the study

According to the Uganda's Ministry of Health Manual of the National Tuberculosis and Leprosy Programme, a patient who is sputum smear positive at the end of the initial phase of treatment gets his initial phase extended for a month and the sputum smear exam repeated at the end of the third month. Extension of the duration of treatment affects compliance of patients with treatment and the repeat sputum examination is inconveniencing to the patient and requires an added cost. This strains the health system further.

In addition, factors to be considered as possible explanation for the persistent positive smear as per the policy are poorly supervised treatment, high bacillary load and rarely multi-drug resistance. Results from this study could be used by health policy makers to plan in advance for tuberculosis patients who might need an additional sputum smear examination and also add on the factor list above. The results can also aid clinicians to identify patients who may not need or benefit from a sputum examination at 8 weeks of anti-tuberculosis treatment. This can help in saving time and resources that would otherwise have been used for the additional smear exam at the third month. In addition, knowledge of the factors that are associated with non conversion of positive smears may be useful to clinicians to better manage their patients and improve outcomes.

1.3 Research questions

1. What is the prevalence of sputum smear non conversion at 8 weeks of anti-tuberculosis treatment among new sputum smear positive pulmonary tuberculosis patients in Kampala?
2. What are the factors associated with sputum smear non conversion at 8 weeks of anti-tuberculosis treatment among new sputum smear positive pulmonary tuberculosis patients in Kampala?

1.4 Study Objectives

1. To determine the prevalence of sputum smear non conversion at the end of 8 weeks of anti-tuberculosis treatment among new sputum smear positive pulmonary tuberculosis patients in Kampala.
2. To determine the factors associated with sputum smear non conversion at 8 weeks of anti-tuberculosis treatment among new sputum smear positive pulmonary tuberculosis patients in Kampala.

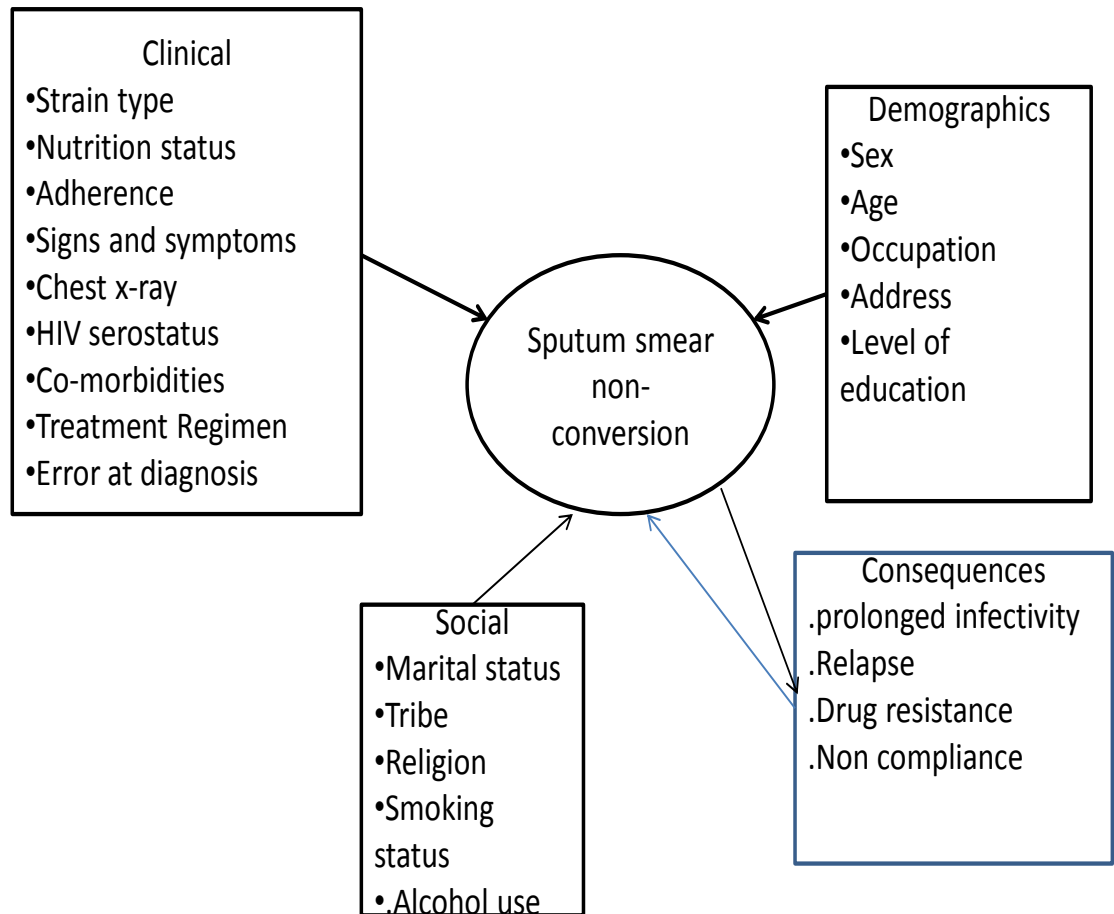
1.5 Research Hypothesis

H_0 : There is no association between *Mycobacterium tuberculosis* strain type and sputum smear non conversion among new PTB patients in Kampala.

H_a : There is an association between *Mycobacterium tuberculosis* strain type and sputum smear non conversion among new PTB patients in Kampala.

1.6 Conceptual framework

Figure 1: Conceptual framework of the factors associated with sputum smear conversion among newly diagnosed pulmonary tuberculosis patients



Scope of the conceptual frame work

The conceptual frame work above shows the factors which may be associated with sputum smear non conversion and the consequences of sputum smear non conversion. However the current study only assessed for association of the factors with sputum smear non conversion.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

This chapter contains the available literature on the prevalence and factors associated with non conversion of positive smears at 8 weeks of tuberculosis treatment among new pulmonary tuberculosis patients.

2.1 Prevalence of sputum smear non conversion at 8 weeks of tuberculosis treatment

A study assessing the Rwandan tuberculosis control program, which involved review of TB treatment registers in 89 health facilities around the country, showed that 187 out of the 1039 new smear positive pulmonary tuberculosis patients, with a 2 months sputum smear result (18%) had remained smear positive (Kayigamba et al, 2012). A retrospective analysis, in which sputum smear conversion rates of new smear positive pulmonary tuberculosis patients at the tuberculosis research center in India were compared, showed that 111 out of 278 patients (39.7%) remained smear positive (Banu Rekha VV et al, 2007). Contrary, a prospective study done by Bawri and colleagues (2008) at the DOTS center still in India, in which 100 new smear positive pulmonary tuberculosis patients were studied, gave a much lower prevalence of 16%.

In their prospective cohort study, done in 1999 in South Eastern Uganda at St. Francis Hospital, Buluba, in which they followed up 457 new smear positive pulmonary tuberculosis on tuberculosis treatment for two months, Bwire and colleagues found that the proportion of patients that had not converted to a negative sputum smear among HIV positive and HIV negative was 22% and 24% respectively. They then concluded that other factors, other than HIV are responsible for delaying sputum smear conversion.

In Tanzania, Senkoro and colleagues (2010) prospectively followed up 502 smear positive pulmonary TB patients and found the prevalence of sputum smear on conversion at 8 weeks of treatment to be 1.4% and 3.0% in HIV positive and HIV negative patients respectively.

2.2 Factors associated with sputum smear non conversion at 8 weeks of tuberculosis treatment.

HIV/AIDS has been found not to be associated with a persistent positive sputum smear. A retrospective cohort study done in Tanzania by Mbazi Senkoro and colleagues (2010), in which they followed up 502 new smear positive pulmonary tuberculosis patients, showed no significant difference in the sputum conversion rates after the initial phase of anti-tuberculosis treatment between HIV sero-negative and HIV sero-positive patients($p=0.52$). Bwire R and colleagues(1999) in their prospective cohort study of 457 new smear positive pulmonary tuberculosis patients carried at St.Francis Leprosy Centre, Buluba, Uganda also found out that HIV sero-status is not a principal factor in delaying sputum smear conversion among patients receiving the intensive phase of anti-tuberculosis treatment(OR 0.9 95%CI 0.6-1.5).

However, Kuaban and colleagues (2009) demonstrated a borderline significant association between HIV sero status and non conversion of sputum smears ($p=0.06$) at 5% level of significance, in their prospective study of 413 new smear positive pulmonary tuberculosis patients in Cameroon.

Increasing age is another factor that has been associated with non conversion of positive sputum smears among new tuberculosis patients. A hospital based clinical intervention type of case series study of 112 sputum positive tuberculosis patients done by Singla and colleagues in 2003 showed that age groups 41-60 years and more than 60 years were significantly associated

with persistent sputum smear positivity at 2 months of treatment ($p < 0.0001$). Kuaban (2009) also found similar results, age ≥ 40 years (OR: 2.716, 95%CI: 1.412-5.223).

Siddiqui et al (2010) in London, in their retrospective study of 53 microbiologically confirmed cases of pulmonary tuberculosis in Ireland, found that smoking was associated with delayed sputum smear conversion in pulmonary tuberculosis patients on treatment (Age-Sex AOR: 4.42, 95%CI: 1.23-15.9). Visser and colleagues (2012) found a similar result in their prospective cohort study of 113 new smear and culture positive pulmonary tuberculosis patients attending two primary health care clinics in Cape town, South Africa.

Diabetes Mellitus has been linked to non conversion of positive smears among tuberculosis patients on treatment. Singla and colleagues (2003), in their retrospective review of 692 records of smear positive pulmonary tuberculosis patients with and without diabetes mellitus, found that the proportion of patients with numerous bacilli in the two groups was 65.2% and 54.1% respectively. A high pre-treatment bacillary load has been associated in many studies with non conversion of positive smears (Telzak, 1997; Singla, 2003; Kuaban, 2009)

Radiologically extensive disease, male sex, and thrombocytosis have been associated a persistent positive sputum smear by Guller and colleagues (2007) in their retrospective study of 737 new smear positive pulmonary tuberculosis patients attending a reference hospital in Turkey. Other factors found by Elvina Karyadi and colleagues (2002) in a double blind randomized community trial of 300 new smear positive pulmonary tuberculosis patients in Indonesia to be associated with failure to convert at 8 weeks of treatment are non-adherence to treatment, error at the time of diagnosis the strain of mycobacterium tuberculosis and nutritional supplementation.

2.3 Mycobacterium tuberculosis strain type: influence on sputum smear conversion at 8 weeks of tuberculosis treatment.

Mycobacterium tuberculosis (MTB) is divided into four main sub lineages;

- MTB Indo-oceanic
- MTB Euro-American
- MTB East-Asia (Beijing)
- MTB East-African-Indian (Cagri, 2011).

Significant genetic diversity in MTB is generated within species through deletion, duplication and recombination events. Gene exchange is rare in MTB resulting in evolution of distinct clonal lineages (Nicol & Wilkinson, 2008). Beijing genotype is the commonest and its wide geographical distribution suggests that strains belonging to this grouping might have a selective advantage over other MTB strains. It accounts for 50% of strains in East Asia and 13% of strains worldwide (Parwati, 2010). It is virulent, escapes BCG vaccination, causes more histopathological changes, higher out growth, increased mortality, linked to MDR-TB, treatment failure and relapse, associated with HIV infection (Visser, 2012; Lan et al, 2003; Burman, 2009; Cowley, 2008). These factors have been consequences associated with non conversion of positive smears among pulmonary tuberculosis patients. In Uganda, the commonest strain type accounting for 70% of all the strains is the T2 family belonging to the Euro-American lineage and also called the 'Ugandan strain' (Asimwe et al, 2008). There is limited evidence of on the influence of MTB genotype on the sputum smear conversion at 8 weeks of tuberculosis treatment among PTB patients especially in Uganda.

CHAPTER THREE

METHODS AND MATERIALS

3.1 Study Design

A cross sectional design was used to determine the prevalence of sputum smear non conversion and a case control design to determine the factors associated with sputum smear non conversion of positive smears among new smear positive pulmonary tuberculosis patients who have completed 8 weeks of anti-tuberculosis treatment attending Case Western Reserve University-Makerere University Research collaboration clinic (CWRU-MU).

3.2 Study Setting

The study was carried out at Case Western Reserve University-Makerere University Research Collaboration Clinic based in Mulago Hospital, founded on the basis of TB research.

CWRU is based in Cleveland, Ohio state in the United States of America, while Mulago is the Uganda's national referral hospital located 2 kilometers north of Kampala city center. The research collaboration dates back in 1980's. Currently, there are eight ongoing TB studies among which is the Kawempe community health study (KCHS). The collaboration thrives on funding from the National Institute of Health and Center for Disease Control and Prevention both based in the US. The collaboration works jointly with other organizations like National Tuberculosis and Leprosy control Programme (NTLP), Joint Clinical Research Center (JCRC), and National Tuberculosis Reference Laboratory (NTBRL). These laboratories are based at JCRC-Mengo and Wandegeya respectively, and help in the identification and confirmation of TB suspects that present at the research collaboration clinic located at upper Mulago Hospital. The

tests carried out in these laboratories include sputum smear microscopy, culture, isolation and genotyping as well as drug sensitivity testing of Mycobacterium bacilli.

Kawempe Community Health Study.

Kawempe is located in the north of Kampala city and it is one of the divisions with high environmental pollution due to many factories and encroachment on wet lands and has some of the worst health indicators in Kampala, including high cases of TB and HIV infection.

The KCHS is an epidemiological study being conducted in the Kawempe division of Kampala.

It employs a house hold contact design with embedded cross sectional and cohort hybrid designs to determine the critical host factors associated with primary Mycobacterium Tuberculosis, re-infection, re-activation and progression to clinical disease. Participants are recruited from NTLP and community clinics located in Kawempe and surrounding divisions. 150 cases and 450 contacts are recruited per year. The inclusion criteria is adults (18years and older) residing in Kawempe and surrounding divisions who present to the NTLP or CWRU-MU clinic with an initial episode of pulmonary tuberculosis and consent to participate in the study.

The exclusion criterion is previous episode of TB and anti-treatment for more than 5 days. Cases are treated with the self administered, standard short regimen of anti-TB therapy comprising of 2 months of Isoniazid, Ethambutol, Rifampicin and Pyrazinamide, and 4 months of Rifampicin and Isoniazid, and followed up monthly during therapy and then quarterly thereafter for a minimum of one year after completion of treatment to check out for cure, treatment failure, relapse, defaulters, multi drug resistant TB and death. Meanwhile the contacts are followed up for about 24 months for any TB infection.

The data from patients, recorded in files, is managed by experienced records personnel and data managers

3.3 Study participants

Target Population

New sputum smear positive, pulmonary tuberculosis adult patients, who completed 8 weeks of anti-tuberculosis treatment.

Accessible Population

New pulmonary tuberculosis, sputum smear positive adult patients, who completed 8 weeks of anti-tuberculosis treatment attending CWRU-MU clinic from 2007 to 2012

Study Population

Eligibility criteria for the cross sectional study design

Inclusion criteria

New pulmonary tuberculosis, sputum smear positive adult patients, who completed 8 weeks of anti-tuberculosis treatment and attending CWRU-MU clinic from 2010 to 2012.

Exclusion

Patients without sputum smear results of the 8 weeks sputum examination.

Eligibility criteria for the case control study design

Case

Definition

A Case was a new sputum smear positive pulmonary tuberculosis patient, who completed 8 weeks of tuberculosis treatment and remained smear positive.

Inclusion criteria

New sputum smear positive, pulmonary tuberculosis adult patients, who completed 8 weeks of anti-tuberculosis treatment, attending CWRU-MU clinic from 2007 to 2012 with a persistent positive sputum smear.

Exclusion criteria

Patients whose medical records could not be traced and those without sputum smear results of the 8 weeks sputum examination.

Control**Definition**

A Control was a new sputum smear positive, pulmonary tuberculosis patient, who completed 8 weeks of tuberculosis treatment and with a converted sputum smear (negative sputum smear).

Three controls were selected for every one case identified.

Inclusion criteria

New sputum smear positive, pulmonary tuberculosis adult patients from Kampala, who completed 8 weeks of anti-tuberculosis treatment, attending CWRU-MU clinic from 2007 to 2012, with a negative sputum smear.

Exclusion criteria

Patients whose medical records could not be traced and lack of a sputum smear result of the 8 weeks sputum examination.

3.5 Sample size Determination

To determine the prevalence of non conversion, the Kish Leslie formula was used to calculate the sample size (Cummings).

$$N = \frac{Z_{\alpha/2}^2 p(1-p)}{d^2}$$

Z is the level of significance at 95%=1.96, p is the estimated prevalence of sputum smear non-conversion=27.7% (13.4-42) (Kuaban, 2009; Banu, 2007) and d is the level of precision=5%.

Therefore N=308 patients.

To determine the factors associated with sputum smear non conversion, the formula for comparing proportions for two groups was used.

$$N = \frac{\left[Z_{\alpha} \sqrt{P(1-P) \left(\frac{1}{q_1} + \frac{1}{q_2} \right)} + Z_{\beta} \sqrt{\left(p_1(1-p_1) \left(\frac{1}{q_1} \right) \right) + \left(p_2(1-p_2) \left(\frac{1}{q_2} \right) \right)} \right]^2}{(p_1 - p_2)^2}$$

N=Total number of subjects

Z_{α} =1.96 at 95%CI.

Z_{β} =0.84

P_1 =proportion of cases with Beijing strain=0.334 and P_2 =proportion of controls with Beijing strain=0.172 (Parwati, etal, 2010).

q_1 =proportion of cases=0.25

q_2 =proportion of controls=0.75

$P=p_1 q_1 + p_2 q_2 =0.2125$

N=283

From the ratio of cases to control 1:3, then the minimum number of cases was 71 and controls 213.

3.4 Sampling Procedure

Sampling frame

A complete list of new pulmonary tuberculosis, sputum smear positive adult patients from Kampala, who completed 8 weeks of anti-tuberculosis treatment, attending CWRU-MU clinic from 2007 to 2012.

Unit of study

A patient

Method: All 393 eligible subjects were enrolled into the cross sectional study. Consecutive sampling was used to select the cases (85) and simple random sampling for the controls (255). 3 Controls were selected for every 1 Case.

3.6 Study Variables

Dependent variable

Sputum smear status at 8 weeks of anti-tuberculosis treatment.

Independent variables

Socio-demographics included; sex, age, occupation, marital status, highest level of education and tribe.

Clinical factors included; Tuberculosis strain type, HIV sero-status, Cavitations on chest x-ray, Nutrition status, presence of BCG scar, fever and night sweats.

Social factors included smoking history and alcohol consumption.

3.7 Data collection and Management

Pre-tested structured data extraction forms were used to collect data from the patient's records by trained research assistants, which were then cross checked by the principal investigator for completeness and correctness.

Data were then entered into Epi-data V3.1 by the assistants and then exported to STATA 11 for analysis.

3.8 Data Analysis

Patients' demographics were summarized in percentages.

Bivariate analysis: Characteristics between the cases and controls were compared using the chi-square and Fisher's exact tests. P value < 0.2 was the cut off for a variable to be considered for multivariable analysis. Interaction between significant variables on multivariable was assessed using the chunk test. Confounding of the non significant variables was assessed by comparing the adjusted and unadjusted odds ratios and a difference of more than 10% implied presence of confounding by that variable. Binary logistic regression method was used for the analysis.

3.9 Quality Control

10 Data extraction forms were pre-tested with patients at the clinic and thereafter the necessary adjustments and modifications made. The research team was also trained.

Field and office editing was done to ensure that the collected data is of good quality.

3.10 Ethical Considerations

Approval to carry out the research was sought from the Clinical Epidemiology Unit (CEU), School of medicine research and ethics committee and CWRU-MU research and ethics committee. Approval and waiver of informed consent was obtained.

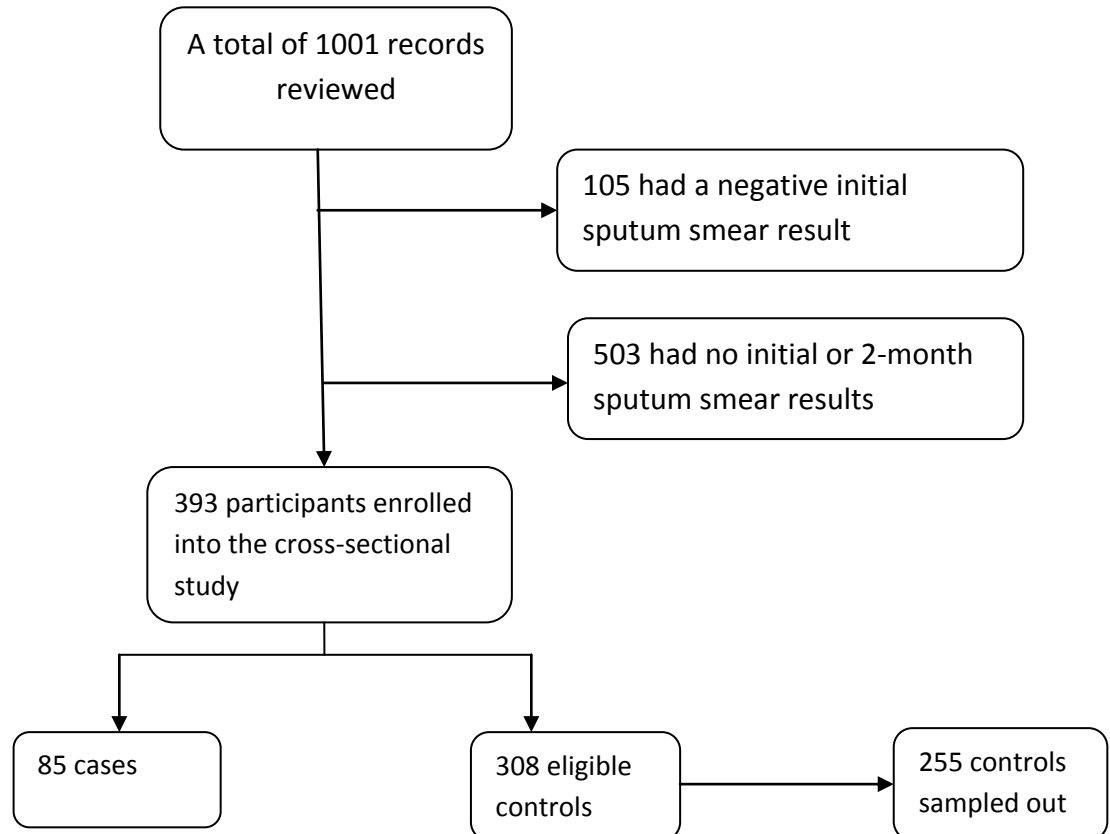
CHAPTER 4

RESULTS

4.0: Introduction

The study was carried out at Makerere University-Case Western Reserve University research (MU-CWRU) collaboration clinic. A total of 393 records of new smear positive pulmonary tuberculosis patients who completed 8 weeks of anti-tuberculosis treatment, and attended the clinic from 2007 to 2012 were studied to determine the prevalence of sputum smear non conversion. Eighty five records of patients who had remained sputum smear positive at 8 weeks and 255 records of patients who had converted to a sputum smear negative were studied to determine the factors associated with sputum smear non conversion.

Figure 2: Study profile of tuberculosis patients attending MUCWRU clinic from 2007 to 2012



4.1: Socio-demographic characteristics of the sample for the cross sectional study

Out of the 393 patient records that were studied, more than a half of the study population (53.4%) was female. Majority (88.3%) were below the age of 40 years. A large percentage (86.7%) of the participants was of Bantu tribe. The highest level of education attained by majority of participants (59.3%) was secondary. The socio-demographic and clinical characteristics of the participants are summarized in Tables 1 and 2.

Table 1: Socio-demographic characteristics of 393 participants attending MUCWRU clinic from 2007 to 2012.

Variable	Frequency(n)	Percentage (%)
Sex		
Female	210	53.4
Male	183	46.6
Age		
<40years	347	88.3
>/=40years	46	11.7
Tribe		
Bantu	341	86.7
Others	52	13.3
Marital status		
Married	218	55.5
Unmarried	175	44.5
Occupation		
Employed	234	59.5
Non-employed	159	40.5
Religion		
Catholics	125	31.8
Anglican	107	27.2
Muslims	96	24.4
Others	65	16.6
Education level		
None	27	6.9
Primary	133	33.8
Secondary	233	59.3

Table 2: Clinical and social characteristics of 393 participants attending MUCWRU clinic from 2007 to 2012.

Variable	Frequency	Percentage (%)
Strain Genotype		
Beijing	0	0
Non-Beijing	393	100
HIV status		
Negative	332	84.5
Positive	61	15.5
Nutrition status		
Normal (BMI \geq 18.5kg/m ²)	255	64.9
Malnutrition (BMI<18.5kg/m ²)	138	35.1
Lung cavities		
No	139	35.6
Present	254	64.4
Cancer		
No	392	99.7
Unknown	1	0.3
Diabetes		
No	388	98.7
Yes	2	0.5
Unknown	3	0.8
Fever		
No	95	24.2
Yes	298	75.8
Night Sweats		
No	159	40.5
Yes	234	59.5
Cough		
No	1	0.3
Yes	392	99.7
Alcoholism		
No	327	83.2
Yes	66	16.8
Smoking History		
Negative	318	80.8
Positive	75	19.2
BCG scar		
Absent	196	49.9
Present	197	50.1

4.2: Prevalence of sputum smear non conversion

Out of the 393 new sputum smear positive pulmonary tuberculosis patients, who completed 8 weeks of anti-tuberculosis treatment and attending MU-CWRU Clinic from 2007 to 2012, sputum smear non conversion was found in 85 (21.6%, 95%CI: 20.8-25.7). Among the HIV positive patients, the prevalence was 24.6% while 21.1% among the HIV negative patients. Participants with ages above 40 years had a higher prevalence of 30.4%, compared to that of participants below the age of 40years which was at 20.2%. The prevalence of sputum smear non conversion among males (23.5%) was slightly higher than that among females (20.0%). The prevalence was also high (30.7) among participants with a positive smoking history compared to those with a negative smoking history whose was at 19.5%. The group specific prevalence of sputum smear non conversion is summarized in Table 3.

Table 3: Prevalence of sputum smear non conversion among 393 participants attending MUCWRU clinic from 2007 to 2012.

Variable	Total (N)	Frequency(n)	Percentage (%)	95%CI
Overall	393	85	21.6	20.8-25.7
Sex				
Female	210	42	20.0	14.6-25.4
Male	183	43	23.5	17.3-29.7
Age				
<40years	347	71	20.2	15.9-24.4
>/=40years	46	14	30.4	16.9-43.9
HIV status				
Negative	332	70	21.1	16.7-25.5
Positive	61	15	24.6	13.7-35.5
Nutrition status				
Normal	255	51	20.0	14.9-24.9
Malnutrition	138	34	24.6	17.4-31.9
Alcohol use				
Yes	66	17	25.8	15.1-36.4
No	327	68	20.8	16.4-25.2
Smoking history				
Negative	318	62	19.6	15.2-24.0
Positive	75	23	30.7	20.1-41.2
BCG				
Present	197	36	18.3	13.5-26.0
Absent	196	49	25.1	18.9-31.3

4.3: Socio-demographic characteristics of Cases and Controls.

Table4: Socio-demographic characteristics of Cases and Controls.

Variable	Cases, n (%)	Controls, n (%)	P-value
Sex			
Male	43(49.4)	111(43.5)	0.258
Female	42(50.6)	144(56.5)	
Age			
Below 40 years	70(82.4)	228(89.4)	0.087
>=40years	15(17.7)	27(10.6)	
Tribe			
Bantu	72(84.7)	226(88.6)	0.461
Non-Bantu	6(7.1)	17(6.7)	
Others	7(8.2)	12(4.7)	
Marital status			
Married	48(56.5)	142(55.7)	0.900
Unmarried	37(43.5)	113(44.3)	
Occupation			
Employed	49(57.7)	150(58.8)	0.849
Non-employed	36(42.3)	105(41.2)	
Religion [†]			
Catholics	27(31.8)	85(33.3)	0.705
Anglican	22(25.9)	72(28.2)	
Muslims	24(28.2)	54(21.2)	
Adventists	2(2.4)	5(2.0)	
Others	10(11.8)	39(15.3)	
Education level			
None	5(5.9)	20(7.8)	0.395
Primary	34(40.0)	82(32.2)	
Secondary	46(54.1)	153(60.0)	

† Evaluated by Fisher's Exact test

**Significant at 5%level of significance*

None of the socio-demographic factors was significantly different between the cases and controls.

4.4: Factors associated with sputum smear non conversion

Table 5: Unadjusted Association between the socio-demographic factors and sputum smear non conversion among 340 participants attending MU-CWRU clinic from 2007-2012.

Variable	Odds Ratio	95%CI	p-value
Sex			
Male	1.00		
Female	0.75	0.46-1.23	0.258
Age			
Below 40 years	1.00		
Above/=40years	1.81	0.91-3.59	0.090*
Tribe			
Bantu	1.00		
Non-Bantu	1.11	0.42-2.91	0.836
Others	1.83	0.69-4.83	0.221
Religion			
Adventists	1.00		
Anglican	0.76	0.14-4.21	0.757
Catholic	0.80	0.15-4.38	0.801
Muslim	1.11	0.20-6.14	0.904
Others	0.64	0.11-3.80	0.625
Education			
None	1.00		
Primary	1.66	0.58-4.78	0.349
Secondary	1.20	0.43-3.80	0.727
Marital status			
Married	1.00		
Un married	0.97	0.59-1.59	0.900
Employment status			
Employed	1.00		
Unemployment	1.05	0.64-1.72	0.849
Alcohol use			
Non user	1.00		
User	1.27	0.68-2.37	0.457
Smoking history			
Negative	1.00		
Positive	1.73	0.97-3.08	0.062*

*p-value less than 0.2 (included in multivariate analysis)

Non-conversion=1, conversion=0

Table6: Unadjusted association between clinical factors and sputum smear non conversion among 340 participants attending MU-CWRU clinic from 2007-2012.

Variable	Odds Ratio	95% CI	p-value
HIV Status			
Negative	1.00		
Positive	1.61	0.81-3.16	0.169*
Nutrition Status			
Normal nutrition	1.00		
Malnutrition	1.16	0.70-1.92	0.560
BCG scar			
Absent	1.00		
Present	1.09	0.67-1.80	0.710
Lung Cavities			
None	1.00		
Present	0.93	0.56-1.56	0.792
Fever			
No	1.00		
Yes	1.33	0.72-2.46	0.368
Night Sweats			
No	1.00		
Yes	1.08	0.66-1.79	0.751

* *p-value less than 0.2 (included in multivariate analysis)*

1-nonconversion, 0-conversion

Age OR: 1.81(p=0.090), history of smoking OR: 1.73 (p=0.062) and HIV status OR:1.61(p=0.169) were the factors considered for multivariable analysis. Sex was also considered for multivariable analysis because literature shows a strong association between sex and sputum smear nonconversion.

Table7: Multivariable analysis of the factors associated with sputum smear non conversion among 340 participants attending MUCWRU clinic from 2007 to 2012.

On multivariable analysis, factors found to be significantly associated with sputum smear non conversion at 5% level of significance included sex OR: 0.56(p=0.047) and Smoking history OR: 2.11(p=0.038). There was no significant interaction between sex and smoking history (p=0.565)

Age was found to be a confounder for smoking history at 10% cut off level for confounding.

Multivariable results are summarized in table7 below.

Variable	Odds Ratio	95%CI	p-value
Sex			
Male	1.00		
Female	0.56	0.31-0.99	0.047*
Age			
<40years	1.00		
>/=40years	1.53	0.73-3.17	0.257
HIV status			
Negative	1.00		
Positive	1.44	0.72-2.86	0.298
Smoking history			
Negative	1.00		
Positive	2.10	1.04-4.27	0.038*

**significant at 5% level*

1-nonconversion, 0-conversion

Table 8: Final model of the factors associated with sputum smear non conversion among 340 participants attending MUCWRU clinic from 2007 to 2012.

The factors found to be associated with sputum smear non conversion were sex (OR= 0.54, 95%CI 0.30-0.96), Smoking history (OR= 2.18, 95%CI 1.08-4.40), while age was found to be a confounder.

Variable	Odds Ratio	95%CI	p-value
Sex			
Male	1.00		
Female	0.54	0.30-0.96	0.036*
Age			
<40years	1.00		
>=40years	1.52	0.73-3.15	0.265
Smoking history			
Negative	1.00		
Positive	2.18	1.08-4.40	0.029*

1-nonconversion, 0-conversion

CHAPTER 5

DISCUSSION

5.0: Introduction

The current study employed cross sectional and case-control study designs to determine the prevalence and factors associated with sputum smear non conversion at 8 weeks of anti-tuberculosis treatment among new pulmonary tuberculosis patients attending the MU-CWRU Clinic from 2007 to 2012.

5.1: Socio-demographic characteristics of the participants.

The current study revealed that most of the participants (53.4%) were female. This result may be explained by the fact that women have better health seeking habits than men. In addition, the larger proportion of women in the general population as compared to men might also explain the result. The large (88.1%) representation of participants below the age of 40 years may be explained by the large proportion of young people in the general population of Uganda. The current study also revealed that most of the participants (86.7%) were from the Bantu tribe. This may be due to the fact that the clinic where the study was carried out is the central region, where the predominant tribe is Bantu.

Objective one

5.2: Prevalence of sputum smear non conversion at 8 weeks of treatment

The current study showed that the prevalence of sputum smear non conversion at 8 weeks of anti-tuberculosis treatment among new pulmonary tuberculosis patients was 21.6%. Studies done by Kayigamba (2012) in Rwanda and Bawri (2008) in India showed lower prevalences of 18% and 16% respectively. This difference could be explained by the fact that the study done in

Rwanda included participants from various health facilities around the country, unlike the current study that was based on a highly selective population of referred patients hence subject to selection bias. Bawri's lower prevalence may be due to random error as a result of the small sample size (100) that was used. The study also revealed that the prevalence of sputum smear non conversion among HIV positive and HIV negative patients was 24.6%, 95%CI 13.7-35.5 and 21.1%, 95%CI 16.7-25.5 respectively. A study done by Bwire and colleagues (1999) in south Eastern Uganda found that the proportion of non conversion among HIV positive and HIV negative tuberculosis patients was 22% and 24% respectively, a result similar to the one in the current study. Participants with ages above 40 years had a higher prevalence of 30.4%, compared to that of participants below the age of 40 years which was at 20.2%. This difference may be explained by the reduced immunity associated with increasing age, which may delay sputum clearance off the bacilli.

Objective two

5.3: Factors associated with sputum smear non conversion at 8 weeks of treatment

Sex

The current study revealed that men were two times likely to remain sputum smear positive compared to women. Women have better health seeking habits for example early seeking of medical attention leading to early diagnosis and hence, a better treatment outcome than men. Similar findings have been reported in a study done in Tanzania (Kidola, 2009) in which men are about 2 times more likely to persist with a positive sputum smear than women.

Smoking history

Participants with a positive smoking history were about 2 times more likely to have a positive sputum smear result at the end of 2 months of anti-tuberculosis treatment. Individuals with a positive smoking history are likely to have a radiologically extensive disease, which some studies have associated with sputum smear non conversion (Guller et al, 2007). Siddiqui (2010) found similar results in which smokers were 4.42 times more likely not to convert to a negative sputum smear. This magnification of the effect may be due to the small sample size (53) that was used. Visser and colleagues (2012) also found that a positive smoking history was associated with sputum smear conversion in South Africa (aHR=0.32, 95%CI 0.1-1.02)

HIV sero-status

HIV sero-positivity was not found to be significantly associated with the non conversion of positive sputum smears after two months of anti-tuberculosis treatment in this study.

This result is in agreement with those of several studies which have shown that HIV positive patients co-infected with pulmonary tuberculosis do not show delayed sputum conversion.

Bwire and colleagues (1999) found that HIV was not a principal factor in delaying sputum smear conversion among tuberculosis patients at St. Francis hospital Buluba (OR=0.9, 95%CI 0.6-1.5)

Age

Age above or equal to 40 years was a confounder for a positive smoking history. Other studies have found age to be an independent predictor of non conversion of the positive smears at 8 weeks of treatment. Singla et al observed in his study that patients aged over 60 years had an almost six times greater risk of remaining sputum positive after two months of treatment than patients aged 21-40 years, while patients aged 41-60 years were twice as likely to remain

sputum positive. Kuaban (2009) also found age above or equal to 40 year to be significantly associated with sputum smear non conversion (OR=2.72, 95%CI 1.41-5.22, P=0.003).

5.4: Limitations of the Study

The sample size was not adequate for the case control study based on Beijing strain and assumed 17.2% of cases and 33.4% of controls had Beijing strain. Such distribution was not found.

The participants were a selective population of referred patients and this might have introduced selection bias in the results.

Assessment of non conversion could have had misclassification on the outcome and thus distorting the true effect measures.

Lack of data on pre-treatment bacillary load, drug resistance and adherence to treatment was another limitation.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

- Non conversion of positive sputum smears after the initial two months of anti-tuberculosis treatment in Kampala is high with about one in every five patients remaining smear positive.
- Non conversion of sputum smears after the initial two months of anti-tuberculosis treatment is considerably high among male patients and those with a positive smoking history.

6.2 Recommendations

- Tuberculosis patients especially of male sex and with a positive smoking history should be given a fully supervised treatment and counseling for the entire duration of chemotherapy so as to prevent default from treatment and improve treatment outcomes.
- A larger study, prospective in nature should be carried out to determine the effect of Mycobacterium tuberculosis genotype on sputum smear non conversion.
- A large study involving various health centers should also be carried out to substantiate the findings of this current study.

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DATA EXTRACTION FORM

PREVALENCE AND FACTORS ASSOCIATED WITH NON CONVERSION OF POSITIVE SMEARS AT 8 WEEKS OF ANTI-TUBERCULOSIS TREATMENT AMONG NEW SMEAR POSITIVE PULMONARY TUBERCULOSIS PATIENTS IN KAMPALA.

Name of Research Assistant.....

Participant's ID No.....

(Write in bold or circle where appropriate)

Socio-demographic characteristics	Response
1. Sex	0. Male, 1. Female
2. Age(years)	
3. Religion	0. Protestant, 1. Catholic, 2. Moslem, 3. Others (specify)
4. Tribe	0. Bantu, 1. Non Bantu, 2. Unknown
5. Marital status	0. Single, 1. Married, 2. Separated/divorced/widowed.
6. Occupation	
7. Highest level of education	0. None, 1. Primary, 2. Secondary, 3. Tertiary
8. Division of Residence	0. Kawempe, 1. Makindye, 2. Rubaga, 3. Nakawa, 4. Central.

Clinical Factors	Response
9.The strain of tuberculosis	
10.HIV Serostatus	0. Negative, 1. Positive, 2. Unknown
11.Nutritional factors	Height(m) Weight(kg) BMI(kg/m ²)
12 Presence of cavities on Chest X-Ray	0. No, 1. Yes
13.Presence of co-morbidities Diabetes Cancer	0. No, 1. Yes 0. No, 1. Yes
14. Presence of BCG scar	0. No, 1. Yes
Social characteristics	Response
13. Smoking Status	0. Non smoker, 1. Smoker
14. Alcohol Use	0. Non user, 1. User