FACTORS ASSOCIATED WITH DELAYED TUBERCULOSIS DIAGNOSIS AND PREDICTED POPULATION CASES GENERATED DURING THE DELAYS IN ISIOLO COUNTY, KENYA

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Factors Associated with Delayed Tuberculosis Diagnosis and Predicted Population Cases generated during the Delays in Isiolo County, Kenya

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DECLARATION

This Thesis is my original work and has not been presented for a degree in any other University:

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DEDICATION

This Thesis is dedicated to my brother Jacob Deng Kunjok, my cousin Daniel Akech Thiong, my friends Mama Reita Hutson, Dr. Ken Waxman and Jerry Morse.

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ABBREVIATIONS AND ACRONYMS

AIC	Akaike Information Criterion
AFB	Acid Fast Bacillus
B	Beta Coefficient
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DF	Degree of Freedom
DLTLD	Division of Leprosy, Tuberculosis, and Lung diseases
DNA	Deoxyribonucleic Acid
ERC	Ethical Review Committee
HIV	Human Immunodeficiency Virus
KIRA	Kenya Inter-agency Rapid Assessment
KNH	Kenyatta National Hospital
KNBS	Kenya National Bureau of Statistics
MDGs	Millennium Development Goals
MOH	Ministry of Health
MTB	Mycobacterium Tuberculosis
MTB/RIF	Mycobacterium Tuberculosis and Resistant to Rifampicin
NTP	National Tuberculosis Control Program
NTLD-P	National Tuberculosis and Leprosy Program
OPD	Outpatient Delivery

OR	Odds Ratio
PTB	Pulmonary Tuberculosis
RA	Research Assistant
SDGs	Sustainable Development Goals
SE	Standard Error
UN	United Nations
WHO	World Health Organization

ABSTRACT

Twenty-three (23%) percent of patients who visit a healthcare provider with respiratory symptoms fail to get diagnosed at the first point of contact and could accelerate the transmission of *Mycobacterium tuberculosis* to 10-15 people by a single infected individual annually. The study assessed various factors of delayed Tuberculosis (TB) diagnosis among patients attending the Isiolo County Referral Hospital and predicted the cases generated during the delays in Isiolo County in Northern Kenya. The study employed a cross-sectional mixed methods study design and systematically sampled 172 tuberculosis patients. We subsequently collated their data from January 2018 to January 2019 and abstracted epidemiological and clinical characteristics from their records to serve as our independent variables. The outcome variable was delayed diagnosis dichotomized into <21 days or >21 days and treated as a binary outcome. Pre-tested interviewer-administered questionnaires, focused group discussions, and key informant interview guides were used to collect data. All data were analysed using SPSS for Windows version 20 and R . The number of TB cases was predicted by employing a simple mathematical model. The SIRV-type dynamics model was parameterized using the data collected at the Isiolo County Referral Hospital between January 2018 and January 2019, as well as from the existing published literature. Most (n=89, 57.8%) of the TB diagnoses fell in the category of >21 days delay, which constituted a median of 27.6 and a mean of 37.3, with a standard deviation of 57 days (range 0 to 414 days). Delayed diagnosis associated factors included (i) use of dispensary and private health facilities (OR=4.3, 95% CI: 1.44, 13.14; P= 0.009) and (OR= 4.9, 95% CI: 1.64, 14.73; P= 0.004), (ii) self-employed individuals (OR=21.7, 95% CI: 2.47,190.93; P = 0.006) and employed individuals (OR=9.9, 95% CI: 1.14, 85.80; P= 0.038), (iii) secondary level of education (OR= 0.03, 95% CI: 0.01, 0.21; P=0.000), and tertiary education (OR= 0.033, 95% CI: 0.01, 0.23; P=0.001). The predicted number of TB cases generated by the delayed diagnosis of existing TB cases over a period of 10 years was approximately 2316, with numbers of infectious cases oscillating between two and 23 on any given day. Seventy-five (75%) of the rates of recovery were <0.1 corresponding to a delayed diagnosis of <10 days. Only 9% of these rates were ≥0.2 corresponding to a delayed diagnosis of ≥20 days. The predicted effect of increasing vaccination coverage from the current KDHS 2019 BCG coverage of 94.2% up to 99.2% (by 1% unit), under the same delay periods, reduces the number of TB cases among the susceptible population. The findings in the current study showed a significant delay of more than 21 days with median days of 27.6 in the diagnosis of TB. The health facility of diagnosis, occupation, and education levels, were associated with delayed diagnosis of TB in the current study area. The modelling framework has projected the number of TB cases generated by delayed diagnosis for 10 years at 2316, which is a probable determinant of

the disease endemicity. Therefore, there is a need to increase health education and promotion in the community, to deliberately strengthen healthcare workers' knowledge of symptoms and signs of TB in high-burden settings, and to implement dedicated TB-specific public-private health facility linkages. Prospective studies are needed in order to disentangle the factors and their interactions linked to delay in seeking healthcare (patient delay) or delay in receiving a confirmed diagnosis (health system delays) in settings with a high TB burden.

DEFINITIONS OF TERMS

Acid-fast bacillus	A smear to the microscopic examination of a fluorochrome stain of a specimen
Asymptomatic TB	A positive case of TB in a patient showing no symptoms.
Cardinal signs	Signs and symptoms highly suspicious of Tuberculosis, including cough of greater than two week duration, drenching night sweats, weight loss, hemoptysis, chest pain, swelling of lymph nodes, fever, and fatigue.
Case definition	This is the clinical criteria for determining whether a patient will be included as a case of a delayed diagnostic event of TB in Isiolo Level 4 Hospital.
Case detection	This is the ratio of the number of notified TB cases to the number of incident TB cases in a given year.
Confirmed TB	The patient with probable or suspected TB has laboratory results, including one or more of gene Xpert, microscopy, or culture.
Cross-sectional	A study design in which an investigator look at thr data from a population at one specific point in time
Delayed diagnosis	Doctor or clinical officer makes incorrect diagnoses or fails to diagnose TB on time, which allows the condition to spread to other people.

Diagnosis	The identification of the nature of TB through clinical science and symptoms, physical examination.
Diagnostic errors	Failures to provide timely solutions for a patient's condition.
Drug resistance	When the mycobacterium change after being exposed to anti-tuberculosis and the drug becomes ineffective, and thus the risk of the spread of disease is increased.
Expectorated sputum	Sputum which is coughed up from the throat or lungs. rapid TB diagnosis and rapid antibiotic sensitivity.
End TB strategy	This is a strategy that has been agreed upon by UN member states in order to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035
Extra-pulmonary TB	A type of TB involving organs other than the lungs, e.g., pleura, lymph nodes, abdomen, genital, urinary tract, skin, joints, and bones
GeneXpert	A cartridge-based nucleic acid amplification test for TB
Incidence	The occurrence of new cases of the disease within a single period among a specified population.
Initial contact	The first hospital visit when a patient comes to see a doctor or a clinical officer about their signs and symptoms.

Kenya Vision 2030	This is Kenya's development program, which was initiated in 2008 and is expected to be achieved by 2030, and which includes universal healthcare.
Missed diagnostic events	Represent evidence of a doctor or clinician determining that the patient does not have TB, when in fact the patient does have the disease.
Missed opportunities	These refer to any contact with a healthcare provider by the patients presenting signs and symptoms, and yet which do not result in a TB diagnosis during the initial visit.
Non specific symptoms	A group of symptoms that can be reported by the patient but can not be observed.
Presumptive diagnosis	A diagnosis of TB in the absence of laboratory results.
Probable TB	The patient presents with two or more clinical signs with laboratory diagnosis.
Promulgation	To put a law into effect by official proclamation.
Smear positive TB	This is the presence of at least one acid-fast bacilli (AFB+) in at least one sputum sample.
Smear negative TB	Absence of acid-fast bacilli in the sputum sample.
Suspected TB	The patient presents with one or two clinical signs of TB without laboratory diagnosis.

Sputum smears	The examination of sputum for acid-fast bacilli using microscopy in order to diagnosis tuberculosis.
The Big 4 Agenda	This is Kenyans' government project that includes housing, security, affordable healthcare, and manufacturing, and is expected to be achieved by 2022.
Time interval	Time between the first contact with a healthcare provider and an eventual diagnosis of TB.

CHAPTER ONE

INTRODUCTION

1.1 Background Information

Tuberculosis is a bacterial respiratory infection caused by *Mycobacterium tuberculosis*, and has been ranked seventh among important causes of death worldwide (WHO, 2017). The pathogen infects the lungs (pulmonary TB) in addition to other structural parts of the human anatomy (extrapulmonary TB). Tuberculosis is spread by inhaling bacterial droplets produced by coughing and sneezing (WHO, 2016), and continues to infect millions of people each year (WHO, 2018).

According to the WHO (2017), TB caused the deaths of approximately 1.3 million HIV-negative people globally. The worldwide estimates of those who developed TB, according to the WHO (2017), were 10.0 million. Of these, 5.8 million were men, 3.2 million women, and 1.0 million were children. The WHO recommends adherence to the guidelines developed by national TB programs on diagnosis and treatment (WHO, 2018).

Africa is responsible for 2.5 million of those who fell ill with TB in 2016, which accounts for a quarter of new infections due to TB worldwide and 417,000 TB deaths (WHO, 2016). Even though Sub-Saharan Africa makes up only 12% of the world's total population, it contributes 29% of the 9 million total TB cases and 254,000 deaths (Zumla et al., 2015).

According to the WHO (2017), approximately eighty-five thousand cases of TB were identified, and 67% were confirmed using bacteriology, among the pulmonary cases of TB in Kenya. There is also a rising trend of TB occurrence from a pre-survey assessment of 233 per 100,000 people in 2016, as compared to 558 per 100,000 people in 2017 (WHO, 2017). Kenya is still in the highest-burden index of TB cases. There were approximately 169,000 people who fell ill due to TB in Kenya in 2016, but only 46% (77,376) of these were diagnosed and put on treatment plans (WHO, 2017). Twenty-three percent (23%) of those with TB are undiagnosed at first contact because they are considered asymptomatic and lack the cardinal TB signs, including weight loss, fever, drenching night sweats, and a cough for a duration of more than two weeks (NLTD-P, 2017).

The National Tuberculosis, Leprosy, and Lung Diseases program (NLTD-P) recommends that every person with an inexplicable productive cough lasting more than two weeks be assessed for TB, and those who qualify for sputum submission must present two or possibly three sputum samples for microscopic analysis. A sample taken in the early morning should be used for the examination. However, according to the National Tuberculosis Prevalence Survey (2016), screening following a cough lasting for more than two weeks would have missed 52% of cases. Assessing the symptoms of coughs lasting more than two weeks, fever, drenching night sweats, and weight loss would miss 41% of cases (MOH, 2013). However, confirming suspect cases using sputum smear, culture, and gene Xpert would increase the early diagnosis of TB and reduce delays to diagnose the disease. Diagnostic delay of TB accelerates the transmission of the disease in the community, as an untreated smear-positive patient infects an average of 10-15 people annually, in addition to also negatively impacting treatment outcomes and therefore curtail the “End TB strategy” (WHO, 2015). Early TB diagnosis provides effective control and promotes the prevention of the transmission of the disease to healthy individuals (Creswell et al., 2015). A patient delay occurs due to health-seeking behaviors, inappropriate diagnostic investigations requested by healthcare providers, and limited diagnostic capacities at healthcare facilities (Senkoro et al., 2015).

The interval from the onset of TB-linked symptoms to the diagnosis may contribute to delays in seeking care from healthcare providers and consequently add to the patient's morbidity and mortality burden (Veesa et al.,2018). The passive methods and approach used in low income countries impact case detection rates negatively and many cases are missed annually (Hoj et al.,2016). Kenya depends on passive case detection using standard case definitions upon the patient's presentation to the healthcare provider at the healthcare facility, leading to a delay in diagnosis.

Many factors have been identified to have contributed to the delayed diagnosis of TB worldwide (Veesa et al.,2018). The passive TB detection method is failing and this is attributed to poor health seeking behaviour of patients or health system, accessibility of diagnostic facility, and competence of health provider to detect and investigate TB for early diagnosis and treatment(Veesa et al.,2018) Patients' delay in seeking health care and health system are the factors hindering case detection in resource constrained areas like Isiolo county. The delays attributed to patients and health systems range from weeks to months and failure to detect and treat TB exacerbate disease severity, increases transmission to contacts and prolong suffering (Veesa et al.,2018) In this study, we assessed socio-demographic, socio-economic, and clinical factors; including age, sex, marital status, religion, history of TB in the family, family size, comorbidity, distance to a health facility, type of health facility for diagnosis, income level, self-medication, occupation, place of residence, and level of education of 172 TB patients whose diagnoses were confirmed with microscopy, culture, or Gen Xpert attending Isiolo County Referral Hospital in northern Kenya from January 2018 to January 2019. We aimed to estimate the proportion of people who presented with clinical signs described in the WHO's standard case definitions and determined the time interval between the onset of signs and symptoms to confirmation of TB diagnosis and predicted the cases generated during the delay period.

1.2 Statement of the Problem

Kenya is one of the countries in the top 30 globally with a high TB index. The WHO (2015) report projected that 233 people per 100,000 were living with tuberculosis. However, according to the Kenya Tuberculosis Prevalence Survey's (2016) findings by the NTLD-P, the burden of tuberculosis remains higher, at 558 people with TB per 100,000 people (NTLD-P, 2016), and mortality of 20/ 100,000 population (WHO, 2016). Other burdens of delay in Diagnosis of TB increase disease severity & higher risk of mortality, community transmission (WHO, 2016). Most people ignore their symptoms and only turn to informal care during their recovery. Lack of awareness and suspicion of tuberculosis among both patients and workers at healthcare facilities have contributed to delays in diagnosing TB. It is estimated that 138,105 people fall ill with TB every year in Kenya. In 2015, of the close to 82,000 people who fell ill with tuberculosis, only 60% were diagnosed, which means that 40% of TB cases in Kenya go undiagnosed, and possibly untreated. Due to the prevalence of these undiagnosed and untreated cases of TB, an individual will continue to spread the disease while recovering and can infect an average of 10-15 people annually (NTLD-P, 2016). Factors influencing delayed TB diagnosis are not known in Isiolo County, and Predicted cases generated during the delays in Isiolo County are not estimated. Hence, the reason for carrying out this study at Isiolo County Referral Hospital, which is a rural setting with similar challenges as those in rural settings of Kenya.

1.3.1 Justification of the study

The Sustainable Development Goals (SDGs) targets were set by WHO member states from 2016 through 2035, and endorsed an "End TB strategy." The strategy focuses on the analysis of SDGs targets and indicators in order to change the course of the TB epidemic. Kenya Vision 2030 is in line with this target, and has a clear agenda focused on promoting a high quality of life by 2030 by providing improved quality of health services. Additionally, the Kenyan government's Big 4 Agenda on universal health coverage expected to be achieved by 2022, through quality and excellent healthcare services provided to the people of Kenya, agrees with the TB targets set by SDGs.

The study intends to contribute to the government of Kenya Big 4 Agenda by assessing the factors associated with the delayed diagnosis of tuberculosis. According to the study carried out by the NTLD-P, on the tuberculosis prevalence survey (2016), 80% of the prevalent cases with respiratory symptoms who had previous clinical visits to seek help for their symptoms had not been diagnosed at the initial contact because of a variety of factors. This finding does not conclude that there were missed or delayed opportunities. However, it does portray the bigger picture that a substantial proportion of TB patients with respiratory symptoms seeking care at health facilities are currently being missed, ultimately leading to delayed diagnosis (NTLD-P, 2016).

According to the NTLD-P (2016), testing patients presenting at the health facility with signs and symptoms typical for TB (cough of any duration, hemoptysis, night sweats, weight loss, fatigue, fever, and shortness of breath) increased the rate of diagnosis to 74 percent. These results communicate lost opportunities to diagnose TB taking place in health facilities, and there is a need to assess the various factors contributing to the delayed diagnosis of TB.

Delayed diagnosis of TB patients has been previously reported to be due to patients' delay in seeking care and healthcare providers' delay in making an early and correct diagnosis. Delayed diagnosis of TB is a major problem in the prevention and control of TB, particularly in low-income countries (Gebreegziabher et al.,2016). In Kenya, few studies have been conducted to document the factors leading to delayed diagnosis, and there is insufficient published data on delayed diagnosis in Isiolo County in particular.

1.3.2 Significance of the study

It was essential to establish and estimate the magnitude of delay in order to launch any kind of effective control of TB. Thus, identifying the various delay factors is key in the early diagnosis and treatment of TB patients. A prediction of cases generated during delayed diagnosis informs decision-making in order to increase the suspicion index of clinicians. These findings will be used to devise effective interventions in order to reduce the incidence of delayed diagnosis.

1.4 Objectives

1.4.1 General Objective

To determine Factors Associated with Delayed Tuberculosis Diagnosis and Predicted Population Cases generated during the Delays in Isiolo County, Kenya

1.4.2 Specific Objectives

1. To determine the proportion of presented clinical signs listed in standard TB case definitions prior to diagnostic confirmation among patients attending Isiolo County Referral Hospital, Kenya.
2. To determine the time interval between the first contact with the healthcare system and confirmation of diagnosis among patients attending Isiolo County Referral Hospital, Kenya.
3. To determine factors associated with the delayed diagnosis of TB among patients attending Isiolo County Referral Hospital, Kenya.
4. To predict the number of TB cases in the population generated during delayed TB diagnosis in Isiolo County, Kenya.

1.5 Research Questions

1. What is the proportion of presented clinical signs listed in standard TB case definitions prior to diagnostic confirmation among patients attending Isiolo County Referral Hospital, Kenya?
2. What is the time interval between the first contact with the healthcare system and confirmation of diagnosis among patients attending Isiolo County Referral Hospital, Kenya?
3. What are the factors associated with the delayed diagnosis of TB among patients attending Isiolo County Referral Hospital, Kenya?
4. What is the predicted number of TB cases in the population generated during delayed TB diagnosis in Isiolo County, Kenya?

1.6 Conceptual Framework

The interval from the onset of TB symptoms to diagnosis is generally referred to as delay. This delay is classified as the following two types:

a) delay due to independent factors connected to the patient; which result to patients' delays defined as the time interval in days between the onset of signs and symptoms typical of TB and the first time the patient came into contact with the healthcare provider.

b) and delay due to independent factors connected to health care systems; which caused health systems delays defined as the time interval the patients first consulted with healthcare provider and the time of diagnosis. This study measured the diagnosis delays which was quantified as the delays due to health system and patients' delays from the onset of signs and symptoms to diagnosis of TB. The signs and symptoms in the WHO case definition were used as gold standard that obliged the patients to seek health care.

The total delay was the dependent variable(outcome) dichotomized into delayed (>21 days) and non-delayed < 21 days).

Patients postponed seeking an early TB diagnosis because of the factors linked to access to healthcare services, socio-demographic and socio-economic factors, awareness of TB symptoms by patients and healthcare providers, human resource factors, and distance from the health facility. A delay is depicted from the onset of symptoms to the detection of TB that defines the delay in diagnosing TB due to socio-demographic, human resource, and facility factors. These factors lead to the inaccessibility of TB services, and hence the delay in diagnosis of TB by the healthcare provider.

Conceptual framework

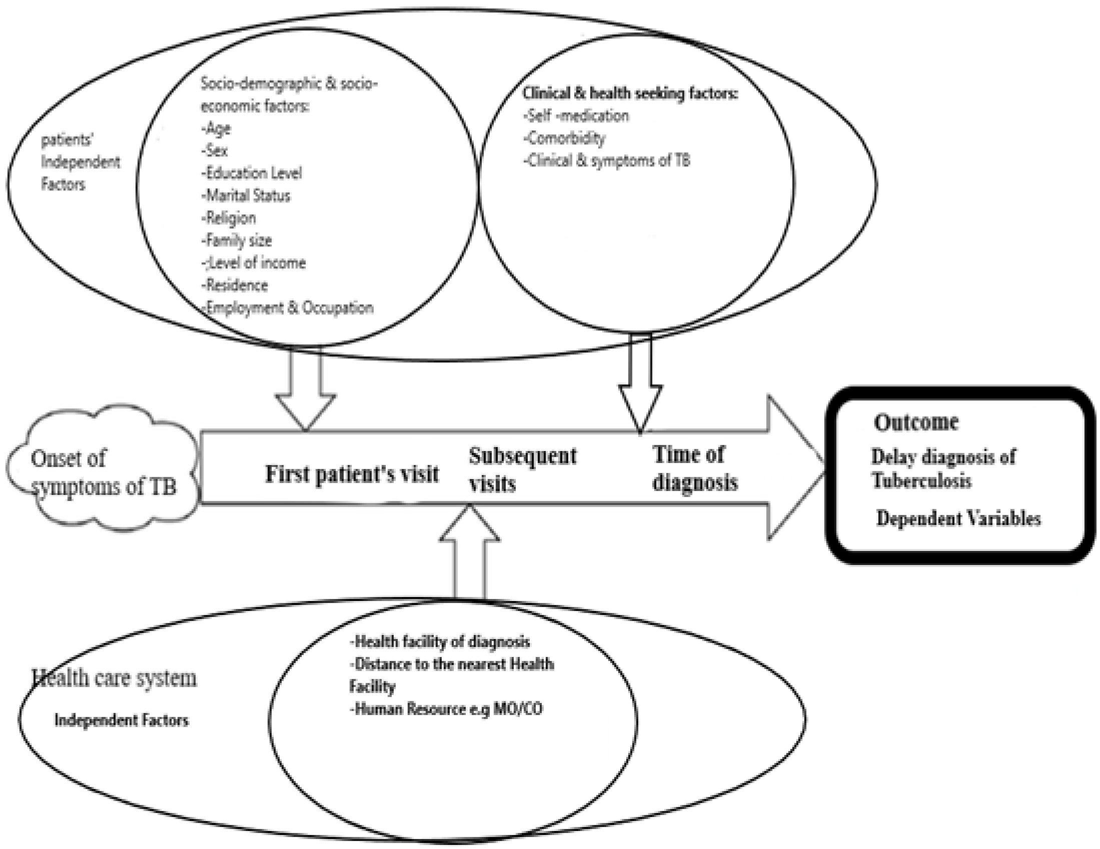

Figure 1.1: The conceptual framework (modified and adapted from Yimer et al.) shows factors associated with the delayed diagnosis of tuberculosis.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Tuberculosis is a transmissible disease that affects many people globally, and it can be cured if identified and treated early. Until the twentieth century, tuberculosis remained the number one cause of death within the developed world, and the disease is still a public health risk in many developing countries. It is calculable that one-third of the worldwide population is presently at risk of developing TB, and that 5-10% of those at risk is going to be vulnerable to have TB at some point or another in their lives. In 2017, almost 40% of TB cases were undiagnosed globally (WHO,2018). In Sub-saharan Africa, 60% of all TB patients initiated care and 50% of patients had a treatment success (Hansen et al., 2017). Most cases are detected passively at the health facility level. However, more aggressive approach has been implemented in recent years to actively search for new cases of TB in the community. Despite this effort to improve diagnosis, detection of TB cases has remained a challenge to low income countries due to a myriad of factors including geographical factors (Murray et al., 2013). Delays in diagnosis of TB increases the prevalence of TB and impedes global effort in achieving elimination of TB by 2030 (Murray et al., 2013). In Kenya, an estimated 40% of TB cases are undiagnosed, and can transmit TB to an average of 10-15 people annually (NTLD-P, 2016).

2.2 The proportion of presented clinical signs

Some symptoms, such as chest pain, were contributing factors for prolonging the delay of diagnosis. Some symptoms have been attributed to a lack of knowledge about TB and its presenting symptoms. People tend to think that cough and fever are the only symptoms, and therefore ignore chest pain, and thus contribute to delayed diagnosis (Laohasiriwong et al., 2016).

Data from NTLD-P (2016) indicates that in Kenya, 38% of TB patients exhibit at least one symptom. The shared symptom was coughing (15%), with 7% of patients having a cough for more than two weeks. The proportions of the commonality of other symptoms from the report were chest pain (19%), drenching night sweats (12%), fatigue (11%), fever (8%), and cough with sputum (5%). However, no data is available regarding the proportion of delayed diagnosis for each symptom and both suspected and probable cases in Kenya (NTLD-P, 2016). Most of the common symptoms were cough, weight loss, and loss of appetite, and these were associated with patient delay (Bojovic et al., 2018). In a study conducted in Tanzania by Said et al. (2017), the delayed diagnosis of TB was more likely among patients who did not have chest pain and who presented with hemoptysis, because patients ignore their symptoms, hence the delays in seeking care.

Patients with a cough for more than two weeks or expectoration are considered to be potential TB cases and should be subjected to smear microscopy or other investigations such as culture and Gene Xpert (Soriano-Arandes et al., 2019). Tuberculosis also may manifest in non-specific signs and symptoms such as irritability, vomiting, poor nutrition, neurological symptoms, respiratory distress, gastrointestinal symptoms, fever, and splenomegaly, which also may cause delayed diagnosis (Soriano-Arandes et al., 2019).

2.3 The time interval

An unacceptable level of delay of ≥30 days has been reported in studies conducted in Ethiopia by Tsegaye et al. (2016). In this study, 53.21% (95% CI: 48.12–58.28%), which was marginally lower than the percentage in a study of Nepal in 2009, indicated that 73% of the studied population faced patient delay. The difference could be because there is a variation in the definition of delay. In a study conducted by Laohasiriwong et al. (2016), the definition of a delayed diagnosis is measured by the time interval between the first appearance of symptoms and when the diagnosis is made during the visit by the patient exhibiting the signs and symptoms of TB.

Miller et al. (2015) demonstrated in their study on missed diagnostic opportunities that a significant percentage of patients had previously visited a healthcare facility where alternative diagnoses were made. Their study indicated that 16% of newly diagnosed TB patients had presented to the clinic at least 30 days before the TB infection was diagnosed. The proportion rose to 26% for patients who had made at least one visit 90 days before the diagnosis was made. A majority of the respiratory-associated visits presented opportunities to diagnose missed cases of TB. Ultimately, the time delays in diagnosing TB exposed the community members, other patients, and healthcare workers to a risk of TB infection (Miller et al., 2015).

A study conducted in Gambia on delays in the diagnosis of TB reported that the median duration from the onset of TB symptoms to diagnosis was 34 days (Owolabi et al., 2020). Fuge et al.(2018) demonstrated that the median delay in TB diagnosis from the first visit to a confirmed case of TB was 30 days.

2.4 Socio-demographic, socioeconomic, and clinical factors associated with delayed TB diagnosis

Sex, age, and marital status are not significantly associated with the delayed diagnosis of TB. However, some studies have shown that females were more likely to be associated with the delayed diagnosis of TB. Some found that a particular age group >45 years of age significantly contributes to delayed diagnosis (Laohasiriwong et al., 2016). The demographic and socio-economic characteristics of patients, including age, sex, residence, religion, education level, signs and symptoms (night sweat, shortness of breath, unexpected weight loss, and other symptoms), visit of diagnosis, occupation, health facility of diagnosis, distance from the health facility, self-medication, comorbidity, and income.

2.4.1 Age

In a study conducted in Australia, persons above 45 years of age were more likely to be diagnosed with TB at a later stage (Bojovic et al., 2018). The same study suggested that this is because older persons were less likely to seek care due to respiratory complaints. The symptom of a cough is less pronounced in the elderly than in the young (Bojovic et al., 2018). Delayed diagnosis of was three times higher in patients younger than 50 years of age than older age (Owolabi et al., 2020).

2.4.2 Sex

Social interactions differ by gender in different societal groups. The identified cases in a male-to-female ratio were said to be 1.6:1 (Banu et al., 2013). Women delayed seeking help for TB symptoms at different stages of the disease more frequently compared to men (Banu et al., 2013). A study by Cai et al.(2015) found no association between gender with delays in TB diagnosis. In other studiea, female gender was associated with TB diagnostic delay (Amar et al.,2016).

2.4.3 Education Level

The educational status of a patient contributes to the delayed diagnosis of TB (Bekana et al., 2017; Deponti et al., 2013). Bekana et al. (2017) found out that individuals with education below the college level had increased chances of a delayed TB diagnosis. Uninformed patients were more likely to miss the diagnosis in comparison to patients who have achieved a college education and above because patients with a college-level education and beyond can access information concerning TB more easily. They were also expected to be more likely to solicit medical care during the early stages of disease development and to access treatment more promptly. Delayed diagnosis of TB has been reported in individuals with a low level of education or awareness. Patients don not identify sigs and symtoms similar to those of TB (Wondawek et al., 2019).

2.4.4 Marital Status

A woman having a low-income level and being married exhibits the factors that are most associated with the delayed diagnosis of TB. This could be due to lack of independence by married women to seek care which are financial and cultural in nature (Amar et al.,2016).

The reason for this might be correlated with a variety of different cultural factors, especially in low-income countries. Unmarried individuals have more opportunities to visit health facilities earlier than married participants (Wondawek et al., 2019). Also, married individuals have certain responsibilities and may not have time to seek treatment as early as possible when compared to their unmarried counterparts. A study from Cameroon also revealed that a high proportion of individuals who are the primary income earner for their families are more likely to delay seeking treatment (Wondawek et al., 2019).

2.4.5 Religion

In a study conducted by Paramasivam et al. (2017) on diagnostic delay and associated factors among patients with pulmonary tuberculosis in Kerala, the majority (75%) of those who experienced a delay of diagnosis were Christians. The reason for the delay may be due to religious beliefs.

2.4.6 Self-medication

The use of prior medication before the TB diagnosis was associated with shorter diagnostic delays (Said et al., 2017). This association can be explained by the fact that patients who did not use medication before their TB diagnosis could not afford any healthcare services, feared the stigma of being known to be sick, or did not have adequate knowledge about the signs and symptoms of TB. Indeed, inadequate lack of awareness about TB and the stigma associated with the diagnosis has previously been associated with longer diagnostic delays (Shete et al., 2015).

2.4.7 Comorbidity

According to a study conducted by Bogale et al. (2017), shorter delays of a confirmed diagnosis of tuberculosis were more common among patients with chronic illnesses, such as HIV. The neglect of particular symptoms of certain non-communicable diseases, such as diabetes and cancer, could lead to disease progression (Jurcev-Savic evic et al., 2013).

2.4.8 Size of the family

In a study conducted by Paramasivam et al. (2017) on diagnostic delay and associated factors among patients with pulmonary tuberculosis in Kerala, India, the delay was observed among patients with ≥five family members and single patients.

2.4.9 Level of income

Some studies found no association of diagnostic delay with the low-income class (Owolabi et al.,2020). In other studies, it was pointed out that level of income is an essential factor in early TB diagnosis (Takarinda et al., 2015). In a study conducted by Fuge et al. (2018), individuals earning less were more likely to delay pursuing a TB diagnosis and treatment than those earning more.

2.4.10 Residence

Many studies have shown that place of residence is a factor that can lead to the delayed diagnosis of TB. Those residing in rural areas have no sophisticated health facilities to provide an early diagnosis of TB (Laohasiriwong et al., 2016). Findings by Chowdhury (2015) have indicated that the missed diagnosis of TB commonly occurs in patients from rural (village) areas when compared to those from urban areas (70.3%). The high rate of delayed TB diagnosis in rural areas has been attributed to the limited knowledge levels and lack of awareness of TB, the unavailability of information on free treatment of the disease, and communication and income constraints among the villagers. The World Health Organization reports that area of residence has proven to be a substantial factor for the delayed diagnosis of TB in several countries. For instance, in Somalia, Pakistan, and Iraq, the relative risk of delayed diagnosis among patients living in suburban areas was 2.2, 2.5, and 3, respectively, when compared to patients living in urban areas. Tsegaye et al. (2016) concluded that area of residence is a substantial risk factor in seeking healthcare leading to missed diagnosis, which subsequently results in the delayed diagnosis of TB. Their study also found that respondents in rural areas with a low household income were 1.7 times more likely to delay seeking healthcare. Tuberculosis patients residing in rural areas were 59% more likely to delay seeking healthcare, thus resulting in diagnostic delay. This finding is consistent with research studies conducted (Wondawek et al., 2019, which contend that there is a variation in seeking healthcare based on area of residence. The reason for this variation is that patients in rural settings were less probable to have access to appropriate health information and well-resourced health facilities.

2.4.11 Employment and occupation

A study conducted by Laohasiriwong et al. (2016) showed that unemployment also leads to a significant level of delay in TB diagnosis. It was observed that delays in diagnosis increased among farmers or people of low socioeconomic status, and more so in people living under the poverty line (Laohasiriwong et al., 2016). Other studies have found out that a likely reason for this is that the self-employed and employed might not want to spend much time in the health facility (Cambanis et al., 2015).

2.4.12 Distance from the nearest health facility

Factors such as distance to urban areas because of a lack of proper healthcare in rural areas may significantly affect rates of TB diagnosis. Findings in a study conducted in Ethiopia correspond positively to this hypothesis. Medical officers and chest specialists who have consistently diagnosed patients had a significantly increased diagnosis delay because most specialized services are located in urban centers (Laohasiriwong et al., 2016). In addition, a longer walking distance to an health facility was associated with patient delay (Cai et al., 2015).

2.4.13 Health facility of diagnosis

Level 1 and 2 healthcare facilities are essential entry points for TB patients seeking diagnosis and care in Kenya. For 27% of patients, public dispensaries are the first point of care. However, only 20% of the dispensaries can conduct microscopy, with the majority of the hospitals referring patients to other equipped facilities (MOH, 2014). Other studies conducted in the Philippines and Ethiopia indicate that community health workers in the public sector are the locus initiation for approximately one-third of the patients (Bersales, 2014; Ethiopia MOH, 2014). Despite this finding, however, the community health workers had no diagnostic equipment; rather, they only have equipment for screening and for collecting sputum specimens.

Hansen et al. (2017) report that over 40% of TB patients initiate care at Level 1 facilities, yet only an average of 39% of the facilities have TB diagnostic capacity.

Nearly 53% of TB patients visit Level 1 facilities in Pakistan, but only 1% of the facilities can carry out smear microscopy (Pakistan Bureau of Statistics, 2012).

2.5 The predicted number of TB cases in the population generated during delayed TB diagnosis

Mathematical modelling has been used extensively in order to assess the effectiveness of various TB interventions on disease outcomes and to predict the scale of activity required to eliminate tuberculosis (Hethcote H. et al., 2000). However, projections of numbers that arise from existing cases would be useful to policymakers as a basis of public health planning. More intuitively, if these numbers are predicted from mathematical models, they can additionally inform context-specific priorities for TB control efforts, including the allocation of resources, or evaluate interventional impacts. Studies in low- and middle-income countries estimate a high number of TB cases with delayed diagnosis of TB (Getnet et al., 2017). Susceptible individuals progress immediately to active infection at a rate beta based on literature that reports that one infected person can affect 10-15 susceptible persons per year on average (WHO, 2015). BCG vaccination may prevent active TB disease in the years following the vaccination (Pienaar, E et al., 2010). This immunity is not normally overwhelmed by infrequent exposure in low endemic settings, and therefore representing vaccination as a complete and permanent immunity in the vaccinated group may be applicable to low endemic TB regions, such as our study site.

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study Site

The study was conducted in Isiolo County (Appendix 5), which is one of the forty-seven counties in Kenya with two ecological zones, namely semi-arid and arid. Isiolo County borders Marsabit to the north; Samburu to the west; Mandera, Wajir, and Garissa to the east; and Tana River, Meru, and Laikipia to the south (KIRA, 2014).

The county was selected according to the TB prevalence of 339 per 100,000 people (KIRA, 2014), making it one of five counties with a high prevalence of tuberculosis.

Table 3.1: Population Statistics of Isiolo County, Kenya Against National Statistics

County	# of Households	Area (sq.km)	Population Density(per.sq.km)	Male	Female	Total Population
Isiolo	58,072	25,350	11	139,510	128,483	268,002
Kenya	12,143,913	580,876.3	82	23,548,056	24,014,716	47,564,296

(Source: KNBS 2019, Census)

3.2 Study design

A cross-sectional mixed study design was conducted, and 172 TB patients were systematically sampled using Yamane's (1967) formula, and their epidemiological and clinical data were collated from January 2018 to January 2019. The data collection was pursued at TB clinics at the Isiolo County Referral Hospital in northern Kenya. The TB patients who were referred from Isiolo County Referral Hospital to their nearest health facility for treatment were contacted for an interview.

3.3 Study Variables

3.3.1 Independent variables

Socio-demographic and socio-economic factors included age, sex, education level, occupation, religion, marital status, family size, income level, and residence. Health-seeking behaviors and other health factors such as self-medication, comorbidity, and family history of TB were also studied. Health system factors, such as distance to the nearest health facility and health facility of diagnosis, which also includes human resource factors and hospital diagnostic capacity, were studied as well.

3.3.2 Dependent variables

The dependent variable was the delayed diagnosis of TB determined by the time between the first contact with the healthcare system and confirmation of diagnosis among TB patients presenting clinical signs listed in standard TB case definitions attending the Isiolo County Referral Hospital.

3.4 Study Population

Tuberculosis patients with confirmed cases and who were above five years of age attending Isiolo County Referral Hospital were allowed to take part in the study.

3.4.1 Inclusion criteria

Participants in the study who fulfilled the following criteria were interviewed:

1. TB patients with confirmed cases who consented to the study;

2. Patients aged five years and above who were in the registries. Parents/ guardians of the children who met the above criteria responded to questions on behalf of their children, signing with parental permission.

3.4.2 Exclusion Criteria

The participants in the TB registry book and laboratory registries who had the following were excluded from the study:

- severely ill TB patients who could not answer the questions;
- and participants with confirmed cases who declined to consent.

3.5 Sample Size Determination

The sample size was calculated using the Yamane (1967) formula:

$$n = \frac{N}{(1+N(e^2))}$$

Where

n- Sample size

N- Population size e- Margin of error

$n = 300/ (1+300(0.05)^2)$

n = 172

We used Yamane's formula for sample size determination, with an error margin of 5% and a confidence coefficient of 95%. With an approximation of the previous population of 300 TB patients, we obtained 172 respondents who were then recruited for the study.

3.6 Sampling techniques

A systematic random sampling technique was used to select participants for the study. The desired sample size of 172 participants was obtained, where an appropriate sampling interval (K) was computed.

K = study population / sample size

The first subject was selected randomly, and the rest were chosen after every k^{th} element. Subject 1 was picked at number 3, and the next subject was picked at $3+k^{th}$ (3+2=5). The subjects were selected until the sample size of 172 was attained. The participants selected had their data abstracted, and they were contacted for an interview in order to collect additional information.

3.7 Data Collection Tools

The researcher and trained research assistant with prior public health experience collected data from hospital registers using a data abstraction form (Appendix 1). The data was collected regarding the socio-demographic, socio-economic, health-seeking behaviors, health system, and clinical characteristics of the patient (Appendix 3) in order to assess objectives 1, 2, 3, and 4 using an interviewer-administered questionnaire, and also a data abstraction form. In addition, qualitative data were collected using a key informant interview guide (Appendix 4) and focused group discussion guides (Appendix 5) in order to assess objective 3. The prediction employed a simple parameterized mathematical model using the data collected at the Isiolo County Referral Hospital between January 2018 and January 2019, as well as from existing published literature.

3.8 Pre-testing of data collection tools

A pre-test for the questionnaire was carried out among TB patients attending Isiolo County Referral Hospital in order to ensure that the contents were appropriate for the respondents. The pre-testing utilized 10% of the questionnaires, and the pre-testing hospital was selected randomly using a lottery system. All assigned numbers of level 4 hospitals were entered into a given group and then chosen at random.

Validity: An expert opinion was sought to reduce questionnaire ambiguity before the development of the final tools. Relevant questions were added from the expert feedback that was subsequently integrated after pre-testing.

Reliability: A test-retest correlation was used to provide scores with repetitive testing with a similar group of participants. Questionnaires were given to the same subjects under similar conditions after some time had passed. Reliability was assessed with correlation scores at a different time—T1 and then T2—in order to ensure that the characteristics being measured did not change over the time interval. The time was long enough yet also short enough in time that the respondents' recollections of taking the test at T1 did not affect the score at T2. The correlation (r) values were strong ($r \geq 0.7$).

3.9 Data collection procedure

The data collection procedure was conducted by a well-trained research assistant who recruited participants with confirmed cases of tuberculosis from the registers at Isiolo County Referral hospital TB clinics between January 2018 and January 2019. Patients who qualified for the selection criteria were offered a chance to take part in this study by answering similar questions in an interviewer-administered semi-structured questionnaire. The consent form was explained to the participants, and they were then asked to sign. The participants were subsequently interviewed for approximately 10-15 minutes, and then the completed questionnaires were checked for errors. Before the participants left, they were given a chance to ask follow-up questions.

The patient's previous number of visits and the time of diagnosis of TB were determined. The date when the patient was first diagnosed, according to the records or participants themselves, was the first date of TB confirmation through the use of sputum smear microscopy, culture, or gene Xpert. The interval between the clinical signs and confirmation of TB indicated the delayed diagnosis of TB. In order to ensure that additional information was collected regarding the various factors associated with delayed diagnosis, the TB patients were interviewed.

For objective 3, additional data were collected using semi-structured questionnaires (Appendix 2) and interviews (Appendices 3 and 4). Part one of the questionnaires included socio-demographic and socio-economic factors that were associated with the delayed diagnosis of TB. Questions were established regarding age, occupation, sex, religion, marital status, residence, occupation, and distance to the health facility, family size, income level, and the education level of the patient. The questionnaires also included questions about health-seeking behaviors, such as self-medication and other health factors, including comorbidity and history of TB in the family. The Key Informant guide (Appendix 3) was used to collect data from healthcare providers, such as medical officers/clinical officers, regarding factors associated with the delayed diagnosis of TB (Objective 3). The focused group discussion guide (Appendix 4) was used to collect data from TB patients regarding factors associated with delayed diagnosis. The data abstraction form (Appendix 1) was also used to obtain data on the patient's first contact with a healthcare provider and the date of confirmation of TB. Recall bias was controlled by aiding participants using a timeline of events to help them remember the date of their initial TB diagnosis.

The abstracted data was used to contact the participants for the interviews. Participants were followed up with and interviewed who were referred from the Isiolo Referral Hospital to their nearby health facility to continue TB treatment after diagnosis (Figure 3.1).

In order to achieve objective 4, we developed a simple mathematical model to assess the number of cases that would be generated by the delayed confirmation of TB. The model was parameterized using the delay data collected at the Isiolo County Referral Hospital between January 2018 and January 2019, as well as from existing published literature.

3.10 Data Management and Analysis

The collected data was coded by assigning a specific value to the different variables. Double data entry was checked and analyzed using the Statistical Package for Social Sciences (SPSS) for Windows Version 20 IBM, 2012. Editing and cleaning were conducted by double-checking the data set in order to correct any erroneous values.

In order to determine the proportion of presented clinical signs (Table.4.2) listed in standard TB case definitions prior to diagnostic confirmation and the time interval (Figure 4.2) between the first contact with the health care system and confirmed diagnoses (specific objective 1 and 2), the data was analyzed using a bivariable analysis to obtain descriptive statistics for socio-demographic and socio-economic factors, as well as the proportions of clinical signs and symptoms of TB, along with their confidence intervals. The output was presented in frequency tables and graphs.

The bivariate analysis was performed in order to obtain descriptive statistics for socio-demographic, socio-economic, and clinical factors (signs and symptoms) at a level of significance of a P-value of 0.2. We used a higher p-value in order to not leave out variables that might turn out to be significant after controlling for confounding. A multivariable regression analysis, which controlled for confounding, was used (Table

4.8) to determine the association between the screened independent variables at a P-value of 0.2 and the dependent variable. The outcome variable was the interval in days between the first health facility contact when suggestive clinical signs of TB were experienced, and the time at which a confirmed diagnosis of TB was made. In order to ensure comparability with other studies, we dichotomized our findings into delay (>21) days and no delay (≤ 21 days) according to the WHO minimum cut-off days of diagnosis. The variables included were those showing association at the p-value of ≤ 0.2 in bivariate (Tables 4.5) analysis. Ultimately, we considered the strength of association to be statistically significant in the multivariable analysis at the level of significance of $P < 0.05$(Table. 4.8). We screened plausible interactions in blocks for statistical significance ($P<0.05$) with TB delayed diagnosis using backward fitting logistic regression interaction (Table 4.10). The parsimonious model was selected, which was run using the backward fitting logistic regression model with a significant association (Table 4.6).

The key informant and focus group discussion data were analyzed through a thematic analysis after the transcription of notes taken during the interviews. The output was narrative and verbatim according to the themes generated.

In the model system, a homogeneous mixing of the population is assumed with SIRV-type dynamics occurring, with hosts being in one of the four compartments, namely Susceptible (S), Infectious (I), Recovered (R), or Vaccinated (V). The parameterized model using the data collected at the Isiolo County Referral Hospital between January 2018 and January 2019, and from the existing published literature, was then evaluated deterministically in 268,002 persons who represented the population of Isiolo County (KNBS, 2019). In order to obtain the infectious period for the model, log-normal, gamma, and Weibull distributions were fitted by the maximum likelihood method, and the best-fitted distribution by Akaike Information Criterion(AIC) was selected. The lognormal distribution best-fitted the empirical distribution of the delay, and estimations for delays were generated for 10 years. The key assumptions for the model included:

(i)The model was a simple without incorporating a lot of data (ii) Infectious period corresponded to delays (iii) The age transmission dynamics was not factored in the model and (iv) Recovery rate was the duration of infectious period.

Table 3.1: Model Parameterization using the data collected at the Isiolo County Referral Hospital between January 2018 and January 2019, and from the existing published literature

Initial values/ Parameter	Value	Source
Population	268,002 (Isiolo population)	KNBS (2019)
The proportion of the population vaccinated	94.2% (BCG coverage- Isiolo County)	KDHS,2014
Transmission rate of susceptible β	0.02739726/365	McIntosh et al 2019
Infectious period γ	Log-normal distribution; 1-409	Model generated (Kunjok et al, 2020)
Transmission rate of vaccinated hosts δ	1.39452E-06	Bowerman, 2004
Recovered hosts become susceptible at rate α	0.85/365	Bowerman, 2004

3.11 Ethical Considerations

Ethical approval was sought University of Eastern Africa, Baraton ethical review committee. Further permission was sought from the Isiolo County Health Department, and also from the hospital. Informed consent was obtained from participants with confirmed cases using consent documents (Appendix 2) for parents/guardians to allow their children to respond to the questions. The assent form (Appendix 2) was also provided for the older children. All consent and assent documents were read aloud to the participants for easy comprehension. Participation was voluntary, and no incentive was given. Participants who wished to pull out from the study at any time were allowed to do so. Confidentiality was observed by coding, and no names were used during the data abstraction and interview process. Also, participants were interviewed in separate and secure rooms, and all records were kept in a secure location. During a focused group discussion, the participants were encouraged to respect and not disclose anything that was discussed during the interview outside the group, and the ground rules were laid out for the participants. The research assistant was also trained on data handling and how to keep information regarding the participants discrete.

CHAPTER FOUR

RESULTS

4.1 Socio-demographic, socio-economic, and health-seeking characteristics among study participants at the Isiolo County Referral Hospital, Kenya 2019

The study utilized a sample of 172 respondents, with 13 participants being relapsed cases, 1 a loss to follow-up following a death, and 4 participants declining to consent, with 154 (89.5%) responses and a median age of 36 years (interquartile range 23-48) and a mean age of 38 years. Regarding the socio-demographic characteristics of the respondents, most (84, or 54.5%) of the respondents were male, 77 (50.0%) were in the age group of 31-to-60, with the least (21, or 13.6%) being those from the age group of more than 60 years. Regarding religion, over one-half of respondents (87, or 56.5%) were Muslims, while 67 (43.5%) were Christians. Sixty-three (97) percent of the study participants had a primary school education, while 43 (28%) had a secondary level of education. Only 14 (9%) had education only at the tertiary level. Over half of the study participants (88, or 57.1%) were married. The distribution of occupation had less than half (52, or 33.8%) being unemployed, and the least number (12, or 7.8%) being casual workers. Income status distribution had equal halves (77, or 50%) living on less than Ksh.5700p.m, and the other half (77, or 50%) more than Ksh.5700p.m. The walking distances to the nearest health facility were distributed with the most (99, or 64.3%) having to walk less than 5km to reach the nearest health facility. Less than half of the study participants (75, or 48.7%) were from family sizes of between 3 and 5 individuals, and 101 (65.6%) came from rural residences, whereas only 53 (34.4%) came from urban residences (Table 4.1). Less than half (56, or 36.4%) of the TB diagnoses were conducted at public hospitals, with a slight difference (54, or 35.1%) observed in TB participants diagnosed at the dispensary, with the least (44, or 28.6%) of the diagnoses being done at private institutions. Regarding participants' self-medication, 107 (69.5%)

asserted to have tried self-medication before TB confirmation. A majority of 113 (73.4%) of the participants had no comorbidities; however, a significant proportion (41, or 26.6%) reported having comorbidities, with most (105, or 68.2%) of the respondents reporting no family history of TB and less than half (49, or 31.8%) with a positive family history of TB (Table 4.1)

Table 4.1: Distribution of socio-demographic, socio-economic , and health-seeking charateristics among study participants at the Isiolo County Referral Hospital, Kenya 2019.

Variable	Variable Code	Frequency n=154	Proportion (%)	95% CI of proportion
Age				
Middle age (31-60yrs)	0	77	50.0	42.1 - 57.9
Young (7-30yrs)	1	56	36.4	28.8 - 44.5
Old (>60yrs)	2	21	13.6	8.6 - 20.1
Sex				
Male	0	84	54.5	46.3 - 62.6
Female	1	70	45.5	37.4 - 53.7
Religion				
Muslim	0	87	56.5	48.3 - 64.5
Christian	1	67	43.5	35.5 - 51.7
Marital status				
Married	0	88	57.1	48.9 - 0.651
Single	1	44	28.6	21.6 -36.4
Widowed	2	13	8.4	4.6 - 14.0
Divorced	3	9	5.8	2.7 - 10.8
Residence				
Rural	0	101	65.6	57.5 - 73.0
Urban	1	53	34.4	27.0 - 42.5
Education				
Primary	0	97	63.0	54.8 - 60.0
Secondary	1	43	28.0	21.0 - 35.7
Tertiary	2	14	9.0	5.1 - 14.8
Visit of Diagnosis				
2nd	0	111	72.1	64.3 -79.0
3rd	1	23	15.0	9.7 - 21.6
1st	2	15	9.7	5.6 - 15.6
4th	3	5	3.2	1.1 - 7.4
Occupation				
Unemployed	0	52	33.8	26.4 - 41.8
self-employed	1	48	31.2	24.0 - 39.1
Employed	2	42	27.3	20.4 - 35.0
Casual labourer	3	12	7.8	4.1 - 13.2
Health Facility of Dx				
Public	0	56	36.4	28.8 - 44.5
Dispensary	1	54	35.1	27.6 - 43.2
Private	2	44	28.6	21.6 - 36.4

Self-Medication				
Yes	0	107	69.5	61.6 - 76.6
No	1	47	30.5	23.4 - 38.4
Comorbidity				
No	0	113	73.4	65.7 - 80.2
Yes	1	41	26.6	19.8 - 34.3
distance from HF				
≤5Km	0	99	64.3	56.2 - 71.8
>5Km	1	55	35.7	28.2 - 43.8
Income				
≤KSh.5700	0	77	50.0	41.8 - 58.2
>KSh.5700	1	77	50.0	41.8 - 58.2
History of TB in Family				
No	0	105	68.2	60.2 - 75.4
Yes	1	49	31.8	24.6 - 39.8
Family size				
3 to 5	0	75	48.7	40.6 - 56.9
6 to 8	1	51	33.1	25.8 - 41.1
>8	2	15	9.7	5.6 - 15.6
0-2	3	13	8.4	4.6 - 14.0

4.2 Proportion of clinical signs and symptoms of TB

Based on the standard TB definition, most (148 respondents, or 96.1%) of the study participants experienced a cough of any duration and felt fatigued (153 participants, or 99.4%). Chest pain (132 participants, or 85.7%) and fever (117 participants, or 76.0%) were noticed to have a significant representation among the study participants. Shortness of breath (143 participants, or 92.9%), night sweats (142 participants, or 92.2%), and unexpected weight loss (147 participants, or 95.5%) were also significant complaints. Apart from the standard TB case definition, a significant representation of 98 (63.6%) of the study participants had other symptoms as well. The majority (111 participants, or 72 .1%) were diagnosed with TB during the second visit, while only 5 (3.2%) were diagnosed with TB at the fourth visit.

The quantitative results were then triangulated with the qualitative result according to the following themes:

Theme 1- Clinical Signs and Symptoms

The experience of the participants in terms of them describing feeling unwell included the symptoms of fever, prolonged cough, weight loss, lack of appetite, and sweating.

Participant explained: "*I had much fever: I could sweat a lot at night, coughing a lot and experienced weight loss.*"

The misconception regarding normal fevers seemingly became consistent among most of the participants, evident by the uniform acceptance of a postulated point by the first participant.

Participant suggested that "*most do think it is a normal fever-like cold/cough and pneumonia or other normal curable diseases*."

The first participant stressed that "*I was coughing a lot and had a sputum production cough."*

Most of the symptoms experienced by the participants were distributed where those with fever were primarily mentioned, whereas other symptoms followed in distribution with prolonged cough being significantly experienced by the participants, whereas weight loss, lack of appetite, and sputum cough being experienced only by a few participants. Upon experiencing these symptoms, some of the participants visited Isiolo county referral Hospital, and others visited the local private clinic.

Another Participant stated, *"I went to Isiolo county referral Hospital, and during the first two visits, they had not taken a sputum sample; they took a sputum sample during the 3rd visit at the facility."*

The key informant interview results on clinical practices in Isiolo county referral hospital showed that clinicians or medical officers did not pay attention to the physical examination, nor did they check on complete history-taking. Only 14.3% of clinical practitioners took into consideration the full understanding of laboratory findings.

Table 4.2: Distribution of the proportion of clinical signs and symptoms among study participants at Isiolo County Referral Hospital, Kenya 2019

Variable	**Variable Code**	**Frequency n=154**	**Proportion (%)**	**95% CI of proportion**
No. of symptoms				
0-1	0	115	74.7	67.0 - 81.3
2 or more	1	39	25.3	18.7 - 33.0
Productive Cough				
Yes	0	148	96.1	91.7 - 98.6
No	1	6	3.9	1.4 - 8.3
Chest pain				
Yes	0	132	85.7	79.2 - 90.8
No	1	22	14.3	9.2 - 20.8
Night sweats				
Yes	0	142	92.2	86.8 - 95.9
No	1	12	7.8	4.1 - 13.2
Shortness of breath				
Yes	0	143	92.9	87.6 - 96.4
No	1	11	7.1	3.6 - 12.4
Unexpected weight loss				
Yes	0	147	95.5	90.9 - 98.2
Fever				
Yes	0	117	76.0	68.4 - 82.5
No	1	37	24.0	17.5 - 31.6
Other symptoms				
Yes	0	98	63.6	55.5 -71.2
No	1	56	36.4	28.8 - 44.5

4.3 Time interval to TB diagnosis

The presentation of clinical signs of TB resulted in the generation of trends on the time interval to TB diagnosis. The majority (89 participants, or 57.8%) of the diagnoses experienced delays (>21 days), with a mean of 37.3 days. Only 42.2% of the diagnoses were not delayed, with a diagnosis being concluded in less than 21 days. The median number of days to TB diagnosis was 27.6 days, with some patients presenting for diagnosis at 0 days and the maximum days being 414 days (Figure 4.2). The majority (44, or 57.1%) of the respondents who delayed seeking diagnosis were of the age group 31-to-44, with most (68, or 88.3%) of them visiting the health facility less than twice. Regarding the sex of the respondents, more than half (50, or 59.5%) experienced delays diagnosis of TB, while 46 (68.7%) were Christians. Those who were married (54, or 61.4%) were more prone to the late diagnosis of tuberculosis. Residing in a rural area had a majority of 62 (61.4%) participants having a delayed TB diagnosis. A majority of 59 (61.0%) of the study participants who had primary school education were inclined toward late diagnosis. The distribution of productive cough had most (86, or 58.1%) predisposed to the delayed diagnosis of TB, while chest pain (77, or 58.3%), sweats (85, or 59.9%), shortness of breath (80, or 55.9%), unexpected weight loss (87, or 59.2%), fever (66, or 56.9%), fatigue (89, or 58.2%) and other symptoms (52, or 53.1%) all having a majority of participants' TB diagnosis being delayed. On the other hand, self-employed and employed participants contributed to majorities of 29 (60.4%) and 32 (76.2%) delays, respectively. The diagnosis of TB also depended on the type of health facility, with private health facility and dispensary yielding most (34, or 77.3%, and 26, or 48.1%) delays, in that order. Self-medication contributed to 58 (54.2%) of the delayed diagnoses of TB, with most (51.0%) of the participants who sought self-medication coming from chemists. A majority of 69 (61.1%) participants had no comorbidity but still delayed seeking a diagnosis, while only 20 (48.8%) who had comorbidity delayed seeking care. Most participants (56, or 56.6%) who delayed getting diagnosed with TB walked a distance of fewer than 5 kilometres, with only 33 (60%) of those who walked a distance of more than 5 kilometers to reach the nearest health facility were delayed. An income of more than Kshs5700 or US$57 per month had 52 (67.5%) cases of TB diagnosed late while having no history of TB in the family contributed to 60 (57.1%) of delayed cases of TB, with those with a history of TB in the family having a lower contribution of 29 (59.1%). Finally, the delayed diagnosis of TB cases was higher 46 (61.3%) among those with a family size of 3-5 members and 6-8 members (29, or 56.9%), respectively (Table 4. 3).

The findings from the quantitative analysis corresponded with the qualitative results about the time interval between the onset of symptoms to confirmation.

Theme 2-Time interval to TB diagnosis

However, the confirmation of TB was prolonged for most of the visits, with the incorrect diagnosis being articulated as pneumonia and symptoms such as chest pain, among other diagnoses. The length of time to confirm the diagnosis for the participants was distributed based on the scale of delay days, with only one participant stating having been diagnosed within the first visit (1 week since the onset of symptoms).

Participant went ahead and explained that *"I had a fever and I was coughing a lot; I was seeking treatment at a local private clinic, and they misdiagnosed me with pneumonia. It took like two months before I could be diagnosed with TB; this is after I went to Isiolo General."*

Other participants also experienced delayed diagnosis, with the last period before the diagnosis being five months.

Another participant stressed that *"I was coughing a lot, a sputum production coughs; I took a step and went to the local private clinic. It took five months before they could diagnose my TB."*

Table 4.3: Distribution of Patients' socio-demographic, socio-economic, and health-seeking behaviour by the time interval to the diagnosis of TB among study participants at Isiolo County Referral Hospital, Kenya 2019

Variable	n=154(%)	Delayed Diagnosis of TB		Visit of Diagnosis	
		<21days	>21 days	<2nd visits	>2nd visits
Total	154(100)	65(42.2)	89(57.8)	134(87.0)	20(13.0)
Age					
Middle age (31-60yrs)	77(50)	33(42.8)	44(57.1)	68(88.3)	9(11.7)
Young (7-30yrs)	56(36.4)	25(44.6)	31(55.4)	47(83.9)	9(16.1)
Old (>60yrs)	21(13.6)	7(33.3)	14(66.7)	19(90.5)	2(9.5)
Sex					
Male	84(54.5)	34(40.5)	50(59.5)	72(85.7)	12(14.3)
Female	70(45.5)	31(44.2)	39(55.7)	62(88.6)	8(11.4)
Religion					
Muslim	87(56.5)	44(50.6)	43(49.4)	75(86.2)	12(13.8)
Christian	67(43.5)	21(31.3)	46(68.7)	59(88.0)	8(12.0)
Marital Status					
Married	88(57.1)	34(38.6)	54(61.4)	77(87.5)	11(12.5)
Single	44(28.6)	21(47.7)	23(52.3)	38(86.4)	6(13.6)
Widowed	13(8.4)	6(46.2)	7(53.8)	12(92.3)	1(7.7)
Divorced	9(5.8)	4(44.4)	5(55.6)	7(77.8)	2(22.2)
Residence					
Rural	101(65.6)	39(38.6)	62(61.4)	87(86.1)	14(13.9)
Urban	53(34.1)	26(49.1)	27(50.9)	47(88.7)	6(11.3)
Education					
Primary	97(63.0)	38(39.1)	59(61.0)	82(84.5)	15(15.5)
Secondary	43(28.0)	16(37.2)	27(62.8)	39(90.7)	4(9.3)
Tertiary	14(9.1)	11(78.6)	3 (21.4)	13(92.8)	1(7.2)
Occupation					
Unemployed	52(33.8)	33(63.5)	19(36.5)	41(78.8)	11(21.2)
self-employed	48(31.2)	19(39.6)	29(60.4)	44(91.7)	4(8.3)
Employed	42(27.3)	10(23.8)	32(76.2)	38(90.5)	4(9.5)

Casual labourer	12(7.8)	3(25)	9(75)	11(91.6)	1(8.3)
Health Facility of Dx					
Public	56(36.4)	27(48.2)	29(51.8)	46(82.1)	10(17.9)
Dispensary	54(35.1)	28(51.9)	26(48.1)	48(88.9)	6(11.1)
Private	44(28.6)	10(22.7)	34(77.3)	40(90.9)	4(9.1)
Self medication					
Yes	107(69.5)	49(45.8)	58(54.2)	93(86.9)	14(13.1)
No	47(30.5)	16(34.0)	31(66)	41(87.3)	6(12.8)
Comorbidity					
No	113(73.4)	44(38.9)	69(61.1)	95(84.1)	18(15.9)
Yes	41(26.6)	21(51.2)	20(48.8)	39(95.1)	2(4.9)
Distance from HF					
≤5Km	99(64.3)	43(43.4)	56(56.6)	88(88.9)	11(11.1)
>5Km	55(35.7)	22(40)	33(60)	46(83.6)	9(16.4)
Income					
≤KSh.5700	77(50)	40(51.9)	37(48.1)	62(80.5)	15(19.5)
>KSh.5700	77(50)	25(32.5)	52(67.5)	72(93.5)	5(6.5)
History TB in Family					
No	105(66.2)	45(42.9)	60(57.1)	95(90.5)	10(9.5)
Yes	49(31.8)	20(40.8)	29(59.1)	39(79.6)	10(20.4)
Family size					
3 to 5	75(48.7)	29(38.7)	46(61.3)	69(92)	6(8)
6 to 8	51(33.1)	22(43.1)	29(56.9)	43(84.3)	8(15.7)
>8	15(9.7)	7(46.7)	8(53.3)	12(80)	3(20)
0-2	13(8.4)	7(53.8)	6(46.2)	10(76.9)	3(23.1)

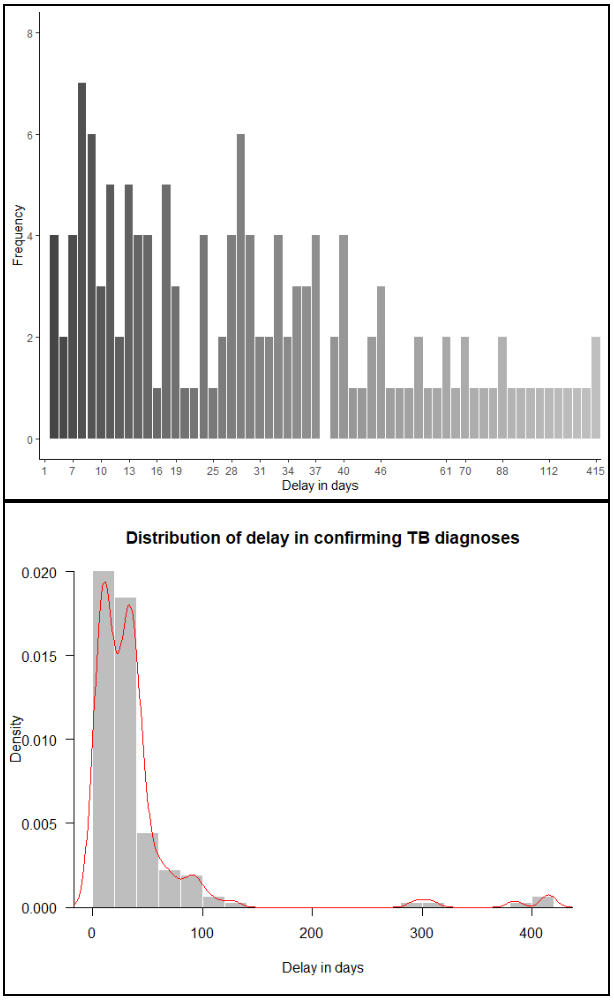

Figure 4.1: Left: A bar plot showing the empirical frequency distribution of the interval in days between first contacts with primary healthcare and confirming TB diagnoses among 154 TB patients at Isiolo County Referral Hospital, 2019. Right: From the same data, a superimposed red line on top of the histogram shows the kernel density.

4.4 Chi-square/Fisher's exact test

A Chi-square/Fisher's exact test was carried out. The variables that showed significant association ($p<0.05$) with delayed TB diagnosis were religion (p=0.021), education (p=0.015), occupation (p=0.001), health facility of diagnosis (p=0.008), and income (0.022), as shown in the table below (Table 4.4). Bivariable and multivariable logistic regression analyses were then carried out in order to determine the strength of association (Table 4.6 and Table 4.8).

Table 4.4: Chi-square table: Relationship between socio-demographic, socio-economic, and health-seeking and clinical factors associated with delayed diagnosis of TB among study participants, Isiolo County Referral Hospital, Kenya 2019.

Variable	Measure	χ^2 Value	df	p (two-tailed)
Age	Chi-Square	0.827	2	0.661
Sex	Fisher's exact test	0.227	1	0.743
Religion	Fisher's exact test	5.739	1	0.021*
Marital status	Chi-Square	1.111	3	0.774
Residence	Fisher's exact test	1.554	1	0.233
Education	Chi-Square	8.395	2	0.015*
Sputum cough	Chi-Square	0.155	1	0.697
Chest pain	Fisher's exact test	0.111	1	0.817
Night sweat	Fisher's exact test	3.192	1	0.125
Shortness of breath	Fisher's exact test	2.803	1	0.120
Weight loss	Fisher's exact test	2.567	1	0.133
Fever	Fisher's exact test	0.155	1	0.710
Fatigue	Fisher's exact test	1.378	1	0.422
Other symptoms	Fisher's exact test	2.473	1	0.130
Visit of diagnosis	Chi-Square	3.074	3	0.380
Occupation	Chi-Square	17.050	3	0.001*
Health facility of diagnosis	Chi-Square	9.733	2	0.008*
Self-medication	Fisher's exact test	1.849	1	0.216
Comorbidity	Fisher's exact test	1.860	1	0.119
Distance to the health facility	Fisher's exact test	0.171	1	0.735
Income	Fisher's exact test	5.990	1	0.022*
TB in family	Fisher's exact test	0.057	1	0.862
Family size	Chi-Square	1.248	3	0.742

*** Significant at $p< 0.05$**

4.5 Interpretation of Bivariate analysis

4.5.1 Positively associated factors to delay the diagnosis of TB

With reference to middle-aged individuals (31-60 years), the young (7-30 years) and the old (>60 years) were 1.5 times (95% CI: 0.544-4.132; p=0.433) and 1.6 times (95% CI: 0.565-4.605; p=0.372), respectively, more likely to have a delayed TB diagnosis. However, this was not statistically significant. Compared to being of Muslim faith, being Christian had 2.2 odds (95% CI: 1.152-4.361) of having delayed diagnosis, and this finding was statistically significant (p=0.017). With reference to being married, single individuals were protective towards a delayed TB diagnosis (OR= 0.787, 95% CI: 0.197-3.138). However, this was not statistically significant (P=0.734). Widowed and divorced individuals were 1.14 times (95% CI: 0.270-4.825; P=0.857) and 1.07 times (95% CI: 0.194-5.913; P=0.937), respectively, more likely to have a delayed diagnosis of TB. However, this was not statistically significant. Compared to the primary level of education, having only a secondary level of education (OR= 0.176, 95% CI: 0.046-0.671) or tertiary education (OR= 0.162, 95% CI: 0.039-0.668), respectively, were protective towards the delayed diagnosis of TB, and this was statistically significant (p=0.011 and p=0.012, in that order. Compared to having a productive cough, having unproductive cough had 0.72 odds of delayed diagnosis of TB (95% CI: 0.141-3. 692), and this was not statistically significant (p=0.695). Compared to having shortness of breath, having no shortness of breath unexpectedly had 3.5 odds (95% CI: 0.739-16.9881) of having a delayed diagnosis of TB, and this was not statistically significant (p=0.114). Compared to having a fever, having no fever was 1.2 times more likely to result in a delayed diagnosis of TB (95% CI: 0.550-2. 452). However, this was not statistically significant (p=0.694). Compared to having other symptoms, having no other symptoms was 1.7 times more likely to result in a delayed diagnosis of TB (95% CI: 0.872-3.403), and this was not statistically significant (p=0.117). With reference to the second visit for diagnosis, being diagnosed at the third and first visits were 2.8 times

(95%CI: 0.306-26.158; p =0.359) and 2.5 times (95% CI: 0.246-26.851; p=430), respectively, more likely to result in a delayed TB diagnosis. However, this was not statistically significant. But being diagnosed at the fourth visit was 6 times (95% CI: 0.532-67.649) more likely to result in a delayed diagnosis, and this was not statistically significant (p= 0.147). Concerning unemployed individuals, self-employed individuals were 5.2 times (95% CI: 1.255-21.629) and employed individuals were 1.9 times (95% CI: 0.471-8.2015) more likely to have a delayed diagnosis of TB, and the former was statistically significant (p=0.023); however, the latter was not statistically significant (p=0.354). With reference to being diagnosed at the public health facility, being diagnosed at a dispensary and private health facilities were 3.2 times (95% CI: 1.315-7.7621) and 3.7 times (95% CI: 1.512 -8.866), respectively, more likely to result in a delayed TB diagnosis, and this was statistically significant (p=0.10 and p=0.004). Compared to individuals who had self-medication, individuals who did not have self-medication were 1.6 times (95% CI: 0.802-3.340) more likely to have a delayed diagnosis of TB, and this was not statistically significant (p=0.176). With reference to having a walk distance of ≤5km from the health facility, individuals covering a distance of >5km were 1.2 times (95% CI: 0.589-2.251) more likely to have a delayed diagnosis of TB. However, this was not statistically significant (p=0.679). Individuals with an income level of >kshs.5700 were 2.2 times (95% CI: 1.170- 4.324) more likely to have a delayed diagnosis of TB compared to individuals who had an income level of ≤ Kshs.5700, and this was statistically significant (p=0.015). Compared to having a history of TB in the family, having no family history of TB resulted in being 1.1 times (95% CI: 0.546-2.165) more likely to have a delayed TB diagnosis. However, this was not statistically significant (p=0.811).

4.5.2 Negatively associated factors to delay the diagnosis of TB

With reference to being male, being female was protective towards a delayed TB diagnosis (OR=0.855, 95% CI: 0.450-1.626). However, this was not statistically significant (p=0.634). Concerning residing in a rural area, residing in an urban area was protective towards a delayed TB diagnosis (OR= 0.653, 95% CI: 0.334-1.278), and this was not statistically significant (p=0.214). Regarding experiencing chest pain, having no chest pain decreased the occurrence of delayed diagnosis of TB (OR=0.857, 95% CI: 0.346-2.125), and this was not statistically significant (p=0.739). Compared to having night sweats, experiencing no night sweats unexpectedly had 0.335 odds (95% CI: 0.096-1.166) of having a delayed diagnosis of TB, and this was not statistically significant (p=0.086). Compared to having unexpected weight loss, experiencing no unexpected weight loss had 0.276 odds (95% CI: 0.052-1.469) of having a delayed diagnosis of TB, and this was not statistically significant (p=0.131). Being a casual laborer was protective (OR= 0.938, 95% CI: 0.212-4.148) towards having a delayed diagnosis of TB, and was not statistically significant (p=0.932). Compared to individuals having comorbidity, not having comorbidity was a protective factor (OR=0.607, 95% CI: 0.296-1.247) towards having a delayed diagnosis of TB. However, this was not statistically significant (p=0.174). With reference to family size of 3-to-5 individuals, a family size of 6-to-8 (OR=0.540, 95% CI: 0.165-1.7681), family size of >8 (OR =0.650, 95% CI: 0.191-2.209), and a family size of 0-to-2 (OR =0.750, 95% CI: 0.169-3.325) were all protective towards having a delayed diagnosis of TB, respectively, and this was not statistically significant (p=0.309, p=0.490 and p=0.75).

Table 4.5: Bivariate table: Distribution of socio-demographic, socioeconomic, health-seeking behaviours, and clinical characteristics among TB patients, Isiolo County Referral Hospital, 2019 Kenya.

Variable	Variable Code	B	S.E.	Wald	df	Sig.	OR	95% CI for OR	
								Lower	Upper
Age									
Middle age (31-60yrs)	0	Ref.							
Young (7-30yrs)	1	.405	.517	.615	1	.433	1.500	.544	4.132
Old (>60yrs)	2	.478	.535	.797	1	.372	1.613	.565	4.605
Sex									
Male	0	Ref.							
Female	1	-.156	.328	.227	1	.634	.855	.450	1.626
Religion									
Muslim	0	Ref.							
Christian	1	.807	.340	5.648	1	0.017*	2.241	1.152	4.361
Marital status									
Married	0	Ref.							
Single	1	-.239	.706	.115	1	.734	.787	.197	3.138
Widowed	2	.132	.736	.032	1	.857	1.141	.270	4.825
Divorced	3	.069	.872	.006	1	.937	1.071	.194	5.913
Residence									
Rural	0	Ref.							
Urban	1	-.426	.342	1.546	1	.214	.653	.334	1.278
Education									
Primary	0	Ref.							
Secondary	1	-1.739	.684	6.470	1	0.011*	.176	.046	.671

Tertiary	2		-1.823	.724	6.342	1	0.012*	.162	.039	.668
No. of symptoms										
0-1	0		Ref.							
2 or more	1		-.076	.374	.041	1	.840	.927	.445	1.931
Sputum Cough										
Yes		0	Ref.							
No		1	-.327	.833	.154	1	.695	.721	.141	3.692
Chest pain										
Yes		0	Ref.							
No		1	-.154	.463	.111	1	.739	.857	.346	2.125
Night sweats										
Yes		0	Ref.							
No		1	-1.093	.636	2.953	1	.086*	.335	.096	1.166
Shortness of breath										
Yes		0	Ref.							
No		1	1.265	.800	2.503	1	.114*	3.544	.739	16.988
Yes		0	Ref.							
No		1	-1.288	.853	2.278	1	.131*	.276	.052	1.469
Fever										
Yes		0	Ref.							
No		1	.150	.381	.154	1	.694	1.162	.550	2.452
Other symptoms										
Yes		0	Ref.							
No		1	.544	.347	2.452	1	.117*	1.723	.872	3.403
Visit of Diagnosis										
2nd		0	Ref.							
3rd		1	1.041	1.135	.841	1	.359	2.831	.306	26.158

1st	2	.944	1.197	.623	1	.430	2.571	.246	26.851
4th	3	1.792	1.236	2.101	1	.147*	6.000	.532	67.649
Occupation									
Unemployed	0	Ref.							
self-employed	1	1.651	.726	5.167	1	.023*	5.211	1.255	21.629
Employed	2	.676	.729	.859	1	.354	1.966	.471	8.205
Casual labourer	3	-.065	.759	.007	1	.932	.938	.212	4.148
Health Facility of Dx									
Public	0	Ref.							
Dispensary	1	1.152	.448	6.608	1	.010*	3.166	1.315	7.621
Private	2	1.298	.451	8.274	1	.004*	3.662	1.512	8.866
Self-Medication									
Yes	0	Ref.							
No	1	.493	.364	1.834	1	.176*	1.637	.802	3.340
Comorbidity									
No	0	Ref.							
Yes	1	-.499	.367	1.844	1	.174*	.607	.296	1.247
Distance from HF									
≤5Km	0	Ref.							
>5Km	1	.141	.342	.171	1	.679	1.152	.589	2.251
Income									
≤KSh.5700	0	Ref.							
>KSh.5700	1	.810	.334	5.902	1	.015*	2.249	1.170	4.324
History TB in Family									
No	0	Ref.							
Yes	1	.084	.351	.057	1	.811	1.087	.546	2.165
Family Size									
3 to 5	0	Ref.							

6 to 8	1	-.615	.605	1.036	1	.309	.540	.165	1.768
>8	2	-.430	.624	.476	1	.490	.650	.191	2.209
0-2	3	-.288	.760	.143	1	.705	.750	.169	3.325

The twelve (12) variables showing an association with delayed TB diagnosis in bivariable regression analysis at $p \leq 0.2$ denoted with * were religion, education, night sweats, shortness of breath, unexpected weight loss, other symptoms, visit of diagnosis, occupation, health facility of diagnosis, self-medication, comorbidity, and income. These variables were entered into the backward-fitting multivariable logistic regression analysis. Multivariable regression analysis controlled for confounding and this model began with a step in which all of the selected variables were included. The analysis then systematically removed variables with higher p values until a final model was reached. In our case, seven steps were automatically performed, and the p values are displayed in the Table below (Table 4.8).

Theme 3 -Factors for delayed diagnosis of TB

The sixth Participant reported, *"If you have customers, there will be no time to go the hospital because my children require schools and will be going to school."*

The experience encountered by TB patients in order to access diagnosis and treatment included issues with the distance to the health center and the lack of experienced personnel to advise on future actions (counselling services).

On the hand another participant said, *"Most of us live far away from the health centre; therefore, it becomes a problem for us to access the medical centre, and as well, I thought mine was just normal fever."*

Table 4.6: Parsimonious model table: Association between Sociodemographic, socioeconomic, health-seeking behaviours, and clinical factors with delayed TB diagnosis among study participants, Isiolo County Referral Hospital, Kenya 2019.

Variable	Variable level	Step1	Step2	Step3	Step4	Step5	Step6	Step7
Religion	Religion (1)	.044	.043	.065	.087	.066	.050	.040
Education								
	Education (1)	.000	.000	.000	.000	.000	.000	.000
	Education (2)	.001	.001	.001	.001	.001	.001	.001
Night sweats	Night sweats (1)	.071	.060	.072	.063	.079	.078	.071
Shortness of breath	Shortness of breath (1)	.215	.217	.275	Removed	Removed	Removed	Removed
Weight loss	Weight loss (1)	.202	.194	.199	.187	Removed	Removed	Removed
Other symptoms	Other symptoms (1)	.177	.171	.134	.096	.076	.048	.037
Visit of diagnosis	Visit of dx (1)	.431	.397	Removed	Removed	Removed	Removed	Removed
	Visit of dx (2)	.597	.573	Removed	Removed	Removed	Removed	Removed
	Visit of dx (3)	.229	.211	Removed	Removed	Removed	Removed	Removed
Occupation								
	Occupation (1)	.015	.015	.008	.008	.006	.006	.003
	Occupation (2)	.056	.058	.036	.040	.038	.045	.045
	Occupation (3)	.573	.581	.474	.513	.490	.549	.488
Health facility								
	H. facility (1)	.025	.026	.011	.009	.009	.016	.007
	Health facility (2)	.007	.007	.006	.005	.004	.008	.007
Self –medication	Self –med (1)	.706	Removed	Removed	Removed	Removed	Removed	Removed
Comorbidity	Comorbidity (1)	.082	.084	.079	.112	.167	Removed	Removed
Income	Income (1)	.104	.092	.091	.101	.119	.134	

We then selected the most appropriate (parsimonious) model that we intended to discuss, not necessarily the one with all p values significant. We chose step 5 so that we could discuss not only the statistically significant variables but also other important ones such as income and comorbidity, even if they were not significant. The full model from the analysis is shown below (Table 4.6).

4.7 Interpretation of multivariate analysis

4.7.1 Positively associated factors to delay the diagnosis of TB

Compared to being of Muslim faith, being Christian had 2.3 odds (95% CI: 0.949-5.337) of having a delayed diagnosis, and this was not statistically significant (p=0.066). Compared to having other symptoms, having no other symptoms was 2.2 times (95% CI: 0.918-5.444) more likely to have a delayed diagnosis of TB, and this was not statistically significant (p=0.076). Concerning unemployed individuals, self-employed individuals were 21.7 times (95% CI: 2.471-190.927; P= 0.006) and employed individuals were 9.9 times (95% CI: 1.136-85.798; p=0.038), respectively, more likely to have a delayed diagnosis of TB. Being a casual laborer was 2.2 times (95% CI: 0.239-19.705) more likely to result in a delayed diagnosis of TB. However, this was not statistically significant (p=0.490). With reference to being diagnosed at a public health facility, being diagnosed at a dispensary and private health facilities was 4.3 times (95% CI: 1.437-13.144) and 4.9 times (95% CI: 1.642-14.728), respectively, more likely to have a delayed TB diagnosis, and this was statistically significant (p=0.009 and p=0.004). With reference to individuals with an income level of ≤ kshs.5700, individuals with income of > Kshs.5700 were 2.0 times (95% CI: 0.834- 4.920) more likely to have a delayed diagnosis of TB, and this was not statistically significant (p=0.119).

4.7.2 Negatively associated factors to delay the diagnosis of TB

With reference to the primary level of education, having only a secondary level of education (OR= 0.032, 95% CI: 0.005-0.214) or tertiary education (OR= 0.033, 95% CI: 0.005-0.232), respectively, were protective towards the delayed diagnosis of TB. However, this was statistically significant (p=0.011 and p=0.012) in that order. Compared to experiencing night sweats, having no night sweats resulted in being 0.238 times (95% CI: 0.48-1.179) less likely to have a delayed diagnosis of TB, and this was not statistically significant (p=0.079). Compared to individuals having comorbidity, not having comorbidity was protective (OR=0.515, 95% CI: 0.201-1.320) towards having a delayed TB diagnosis. However, this was not statistically significant (p=0.167).

Table 4.7: Multivariate table: Association between socio-demographic, socioeconomic, health-seeking behaviours, clinical characteristics, and delayed diagnosis of TB among patients at Isiolo County Referral Hospital, Kenya 2019.

Variable	Variable Code	B	S.E.	Wald	P	OR	95% CI of OR	
							Lower	Upper
Religion								
Muslim	0	Ref						
Christian	1	.811	.441	3.389	.066	2.250	.949	5.337
Education								
Primary	0	Ref						
Secondary	1	-3.445	.972	12.566	.000	.032	.005	.214
Tertiary	2	-3.400	.990	11.792	.001	.033	.005	.232
Night Sweats								
Yes	0	Ref						
No	1	-1.435	.816	3.092	.079	.238	.048	1.179
Other Symptoms								
Yes	0	Ref						
No	1	.804	.454	3.138	.076	2.236	.918	5.444
Occupation								
Unemployed	0	Ref						
Self-employed	1	3.078	1.109	7.705	.006	21.723	2.471	190.927
Employed	2	2.290	1.103	4.308	.038	9.872	1.136	85.798
Casual worker	3	.776	1.125	.476	.490	2.172	.239	19.705
Health Facility								
Public	0	Ref						
Dispensary	1	1.469	.565	6.773	.009	4.346	1.437	13.144
Private	2	1.593	.560	8.102	.004	4.918	1.642	14.728
Comorbidity								
No	0	Ref						
Yes	1	-.663	.480	1.909	.167	.515	.201	1.320
Income								
≤KSh.5700	0	Ref						
>5700	1	.706	.453	2.428	.119	2.025	.834	4.920

4.8 Model interpretation

4.8.1 Interactions negatively associated with delayed diagnosis

With reference to middle age (31-60 years), an interaction of middle age and a visit to a public facility was protective against delayed TB diagnosis (OR=0.138; 95% CI: 0.019-0.983; p=0.048). Compared to the male sex, an interaction of being male and being unemployed was protective against a delayed TB diagnosis (OR=0.043; 95% CI: 0.003-0.559; p=0.016). Compared to visiting a public facility, visiting a public facility and being married was protective towards a delayed TB diagnosis (OR=0.391; 95% CI: 0.168-0.911; p=0.030). Compared to living in a rural area, living in a rural area and being unemployed was protective towards a delayed TB diagnosis (OR=0.013; 95%CI: 0.000-0.333; p=0.009). With reference to having fever alone, having fever and a lower level of income (≤ KSh. 5700) was protective against a delayed TB diagnosis (OR=0.017; 95% CI: 0.000-0.801); p=0.038). Compared to having other symptoms in addition to TB signs, having those signs and self-medicating at the same time was protective against a delayed TB diagnosis (OR=0.002; 95% CI: 0.000-0.162; p=0.006). Compared to not having comorbidities only, having no comorbidities and a lower income (≤ KSh. 5700) at the same time was protective against a delayed TB diagnosis (OR=0.000; 95% CI: 0.000-0.069; p=0.005).

4.8.2 Interactions positively associated with delayed diagnosis

Compared to primary education alone, an interaction of primary education and being male would lead to a 16 times higher chance of a delayed TB diagnosis (OR=16.2; 95% CI: 1.101-237.526; p=0.042). Concerning the male gender alone, males who did not have TB in the family were 16.6 times more likely to have a delayed TB diagnosis (OR=16.587; 95% CI: 1.176-234.047; p=0.038). Compared to being Muslim alone, Muslims who also lived in rural areas were 141 times more likely to have a delayed TB diagnosis (OR=141.252; 95% CI: 1.275-15,646.305; p=0.039). Compared to those with primary education, those with primary education who also resided in rural areas were 119 times more likely to have a delayed TB diagnosis (OR=119.440; 95% CI: 2.444-5836.133; p=0.016). With reference to those living in rural areas, those living in rural areas and who were self-medicating were 16.3 times more likely to have a delayed TB diagnosis (OR=16.252; 95% CI: 1.824-144.764; p=0.012). Compared to those with 0-1 TB symptoms, those with 0-1 TB symptoms who also had other atypical symptoms were 34.7 times more likely to have a delayed TB diagnosis (OR=34.686; 95% CI: 1.194-1007.309; p=0.039). With reference to those with no comorbidities, those with no comorbidities and who were also unemployed were 225 times more likely to have a delayed TB diagnosis (OR=225.346; 95% CI: 7.145-7106.987; p=0.002). Compared to those who were married, those who were married and who also had fever were 129 times more likely to have a delayed TB diagnosis (OR=128.995; 95% CI: 1.820-9142.568; p=0.025).

Finally, in this interaction model, the only single factor that was significantly associated with a delayed TB diagnosis in the multivariable model that still showed a statistically significant association with delayed TB diagnosis was education, which was still protective toward a delayed TB diagnosis (OR=0.047; 95%CI: 0.002-0.988; p=0.049).

Table 4.8: Parsimonious interaction model table: Socio-demographic, socioeconomic, health-seeking behaviour factors associated with delayed TB diagnosis, Isiolo County Referral Hospital, Kenya 2019.

Interaction	B	S.E.	Wald	df	Sig.	OR	95%CI of OR	
							Lower	Upper
Age * Health-facility	-1.984	1.003	3.908	1	.048	.138	.019	.983
Education * Sex	2.783	1.371	4.122	1	.042	16.173	1.101	237.526
Sex * Occupation	-3.148	1.309	5.780	1	.016	.043	.003	.559
Sex * TB-in-family	2.809	1.350	4.325	1	.038	16.587	1.176	234.047
Religion * Residence	4.951	2.402	4.248	1	.039	141.252	1.275	15646.305
Marital status * Fever	4.860	2.174	4.997	1	.025	128.995	1.820	9142.568
Education * Residence	4.783	1.984	5.810	1	.016	119.440	2.444	5836.133
Residence * Occupation	-4.379	1.673	6.854	1	.009	.013	.000	.333
Residence * Self-medication	8.248	2.883	8.183	1	.004	3819.218	13.418	1087080.254
Fever * Income	-4.051	1.953	4.300	1	.038	.017	.000	.801
Other symptoms * Self-medication	-6.489	2.381	7.429	1	.006	.002	.000	.162
No. symptoms * Other symptoms	3.546	1.719	4.257	1	.039	34.686	1.194	1007.309
Comorbidity * Occupation	5.418	1.761	9.466	1	.002	225.346	7.145	7106.987
Comorbidity * Income	-8.790	3.122	7.927	1	.005	.000	.000	.069
Education	-3.067	1.559	3.873	1	.049	.047	.002	.988

*Refers to interactions between independent variables with the delayed diagnosis of TB

4.9 The predicted number of TB cases generated by delayed diagnosis in Isiolo County: the SIRV Model

Empirical frequency distribution of the interval in days between the first contact with primary healthcare facility and confirmed TB diagnoses among 154 TB patients ranged between 1 to 415 days (Figure 4.3)**.** Seventy-five (75%) percent of the rates of recovery were <0.1, corresponding to a delayed diagnosis of <10 days. Only 9% of these rates were ≥0.2, corresponding to a delayed diagnosis of ≥20 days (Figure 4.4). The predicted number of TB cases generated by delayed diagnosis and the treatment of existing TB cases over a period of 10 years was approximately 2316, with numbers of infectious cases oscillating between two and 23 on any given day (Figure 4.5). The predicted effect of increasing vaccination coverage from the current KDHS 2019 BCG coverage of 94.2% up to 99.2% (by 1% unit) under the same delay periods reduces the TB cases among the susceptible population (Figure 4.6).

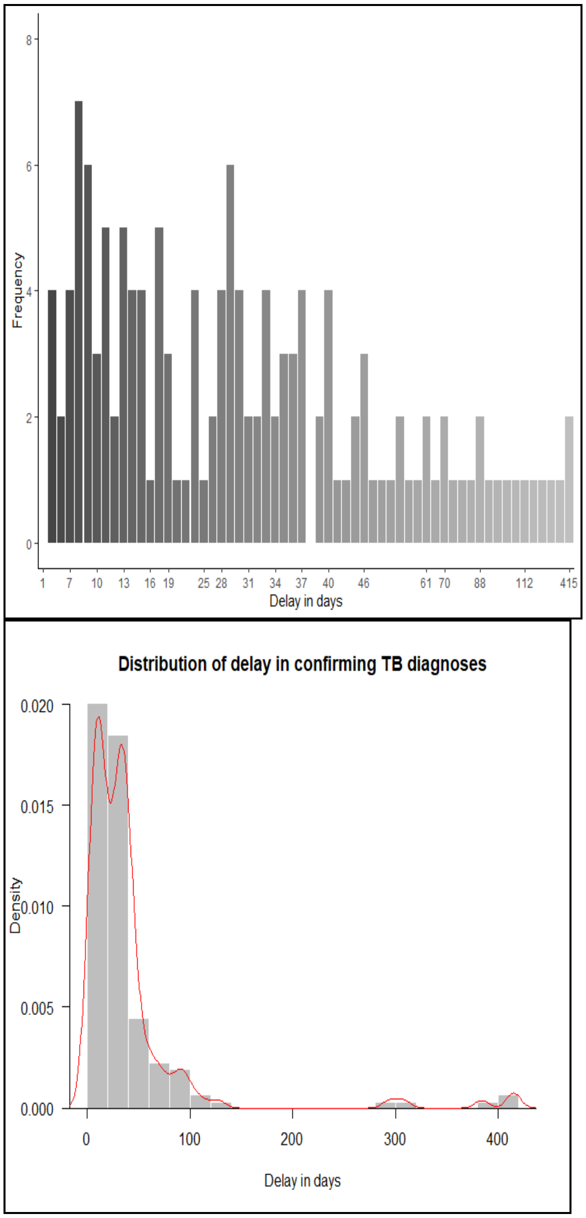

Figure 4.2: Distribution of delay in TB diagnosis among study participants at Isiolo County Referral Hospital, Kenya, 2019. Right: From the same data, a superimposed red line on top of a histogram represents the kernel density.

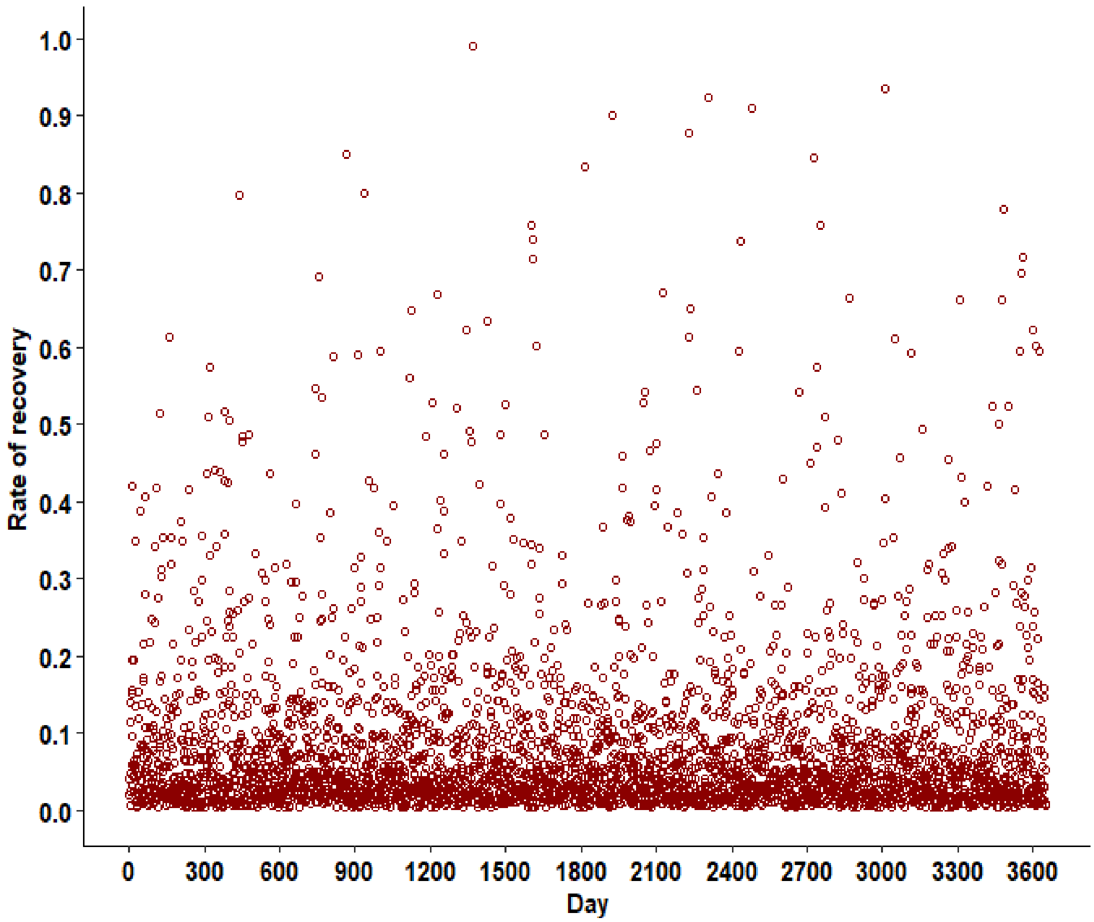

Figure 4.3: A scatterplot of the daily rate of recovery and delayed TB diagnosis, Isiolo County, Northern Kenya, 2019.

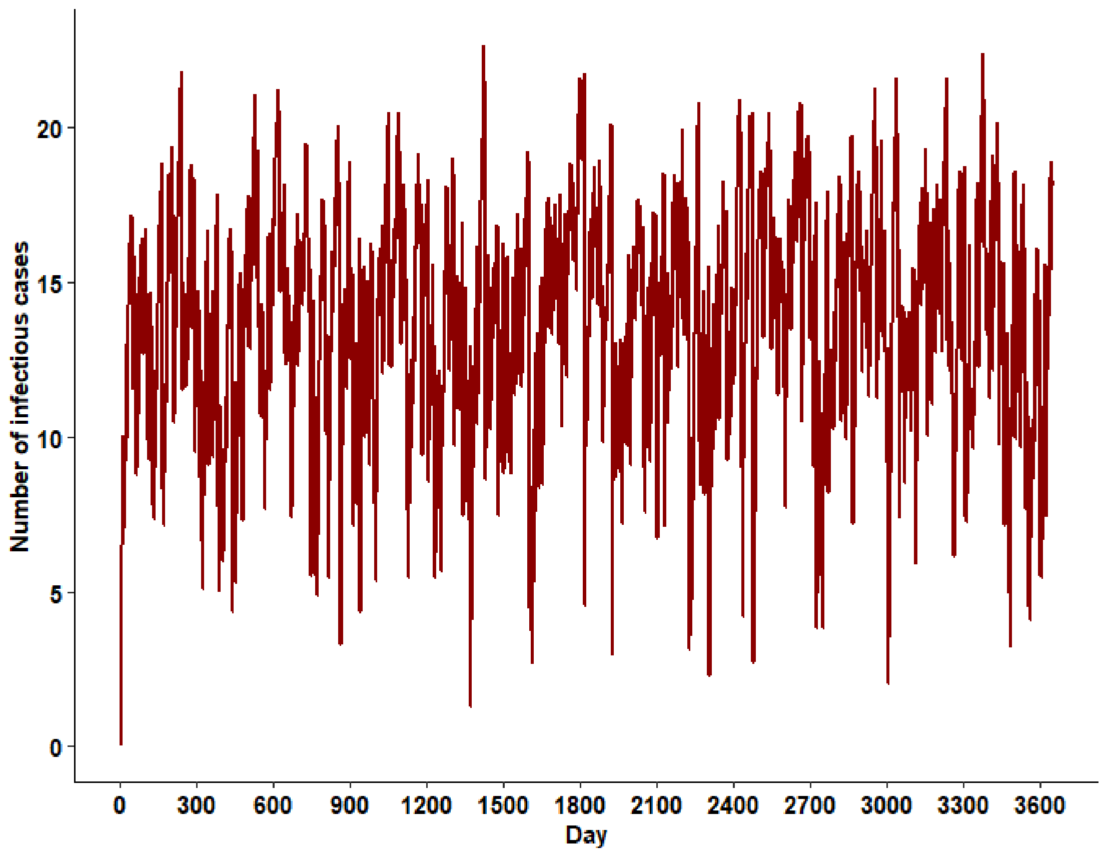

Figure 4.5: Daily TB cases in the population generated by the delayed TB diagnosis, Isiolo County, Kenya, 2019.

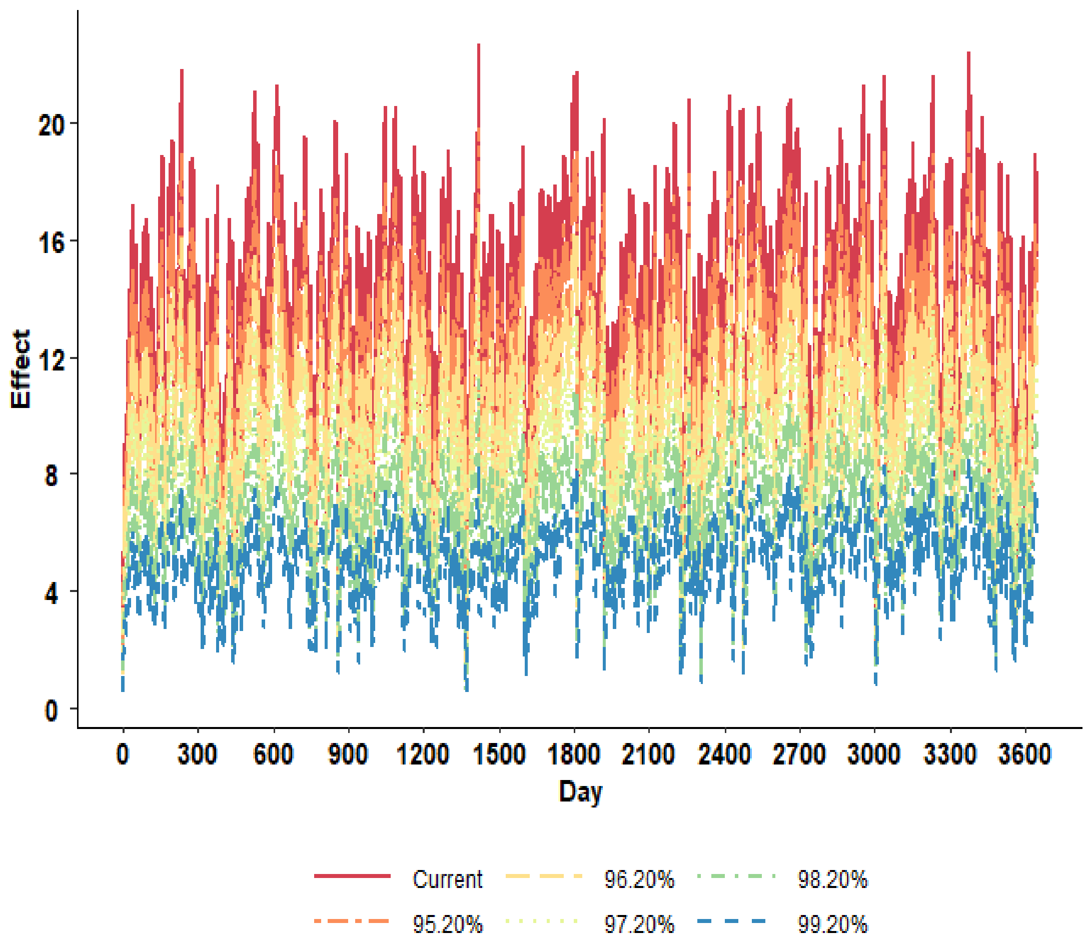

Figure 4.6: The predicted effect of increasing vaccination coverage, Isiolo County, Kenya, 2019.

CHAPTER FIVE

DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

5.1 Discussion

5.1.1 Clinical signs listed in standard TB case definitions

The major clinical signs discussed in this study included a cough lasting for more than three weeks, fatigue, chest pain, fever, shortness of breath, night sweats, and unexplained weight loss. Most of the study participants also had other non-specific symptoms as well.

The proportion of presented clinical signs listed in standard TB case definitions prior to diagnostic confirmation among TB patients attending the Isiolo County referral Hospital was determined. The study revealed that clinical signs including coughs that lasted any duration, sputum coughs, chest pains, night sweats, shortness of breath, weight loss, fever, and fatigue were the most common clinical signs among the patients. According to Fogel (2015), the most common clinical manifestation of tuberculosis includes severe cough, fever, chest pains, fatigue, and weight loss. These findings are similar to the case definitions of TB, which include signs such as pain in the chest, coughing of blood or sputum, a cough that lasted three weeks or longer, fatigue, sweating at night, fever, and lack of appetite (CDC, 2019). Similarly, Herchline et al. (2019) also noted clinical signs including persistent coughs lasting more than three weeks, chest pains, sweating at night, coughing up blood or sputum, weight loss, lack of appetite, and fatigue. Our findings matched previous reports by Bojovic et al. (2018), which revealed that most of the common symptoms were cough, weight loss, and loss of appetite, and were associated with patient delay. In the current study, these findings were associated with the delayed diagnosis of tuberculosis.

However, in a multivariable analysis, none of these were statistically significant. In a similar study conducted in Tanzania Said et al. (2017) found that the delayed diagnosis of TB was more likely among patients who did not have chest pain and who presented with hemoptysis. The likely explanation for this is that TB patients regarded these symptoms as not particularly dangerous.

Theme 1: Signs and symptoms of TB

In the triangulated quantitative focused group findings, the participants described the experience of feeling unwell, including the symptoms of fever, prolonged cough, weight loss, lack of appetite, and sweating. Symptoms such as cough, fever, and night sweats were regarded as non-serious by the participants, and they thought that they would improve with time and never associated the symptoms with TB (Paz-Soldan et al., 2014). This current study matched these findings, as most participants thought that what they were experiencing was a normal fever and would go away over time.

Patients with more than two weeks of cough or expectoration are considered to be potential TB cases and should be subjected to smear microscopy or other investigations, such as culture and Gene Xpert (Amar et al.,2016). It is suggested that clinicians and doctors have seemed to lack focus when the patient presented with their complaints at the outpatient department.

Another study utilized a multicentre retrospective cross-sectional study in order to capture the clinical presentation and outcomes associated with tuberculosis. A total of 134 patients were included in the study, from which 94.0% of the patients were diagnosed with the condition. The clinical manifestations of the disease included irritability, vomiting, poor nutrition, neurological symptoms, respiratory distress, gastrointestinal symptoms, fever, and splenomegaly (Soriano-Arandes et al., 2019). The current study also had non-specfic symptoms such as vomiting, and inexperienced clinicians and doctors in health facilities with inadequate diagnostic capacities could miss and consequently contribute to the delayed diagnosis of tuberculosis.

5.1.2 The time interval between the first contact with the healthcare system and confirmed diagnoses

The second objective of the study was to determine the time interval between the first contact with the healthcare system and confirmed diagnoses among TB patients presenting with the clinical signs listed in standard TB case definitions attending the Isiolo County referral Hospital ,Kenya. The median time interval between the first symptoms of TB and sought medical advice was 27.6 days, with some patients presenting for diagnosis at 0 days, and the maximum number of days being 413. Most (57.8%) of the diagnoses experienced delays of >21 days. The WHO (2017) recommends a minimum delay of 3 weeks since the first experiences of symptoms of TB. The current study findings match the results of a study conducted in the urban district of Dar es Salam, Tanzania, which reported a median diagnostic delay of 3 weeks (Said et al., 2017), and a systematic review and meta-analysis conducted in Asia to evaluate the health-seeking behaviors and extent of patient delays among the TB patients in which a median patient delay of 20 days was determined (Cai et al., 2015). The current study findings were also consistent with those of a study by Lusignani et al. (2013), who reported a 30-day mean patient delay. The median days reported by Belay et al. (2012) in the Afar Region of Ethiopia was 33.5 days, which was slightly different from the current findings. The difference was noted in a study conducted by Santos et al. (2018), which reported a median delay of 64 days in Huambo, Angola. The average delay (28.4 days) in low-income and middle-income countries is much less, while high-income countries have reported delay of TB diagnoses of 3-26 weeks (Sreeramareddy et al., 2009). The delay in this current study is due to health facility of diagnosis, education level and income level. The reasons for these differences in median delay days noteably middle and high oncome countries could be attributed to better health services in high-income countries and inadequate healthcare services and low- or middle-income countries, respectively. The study area is located in Kenya which has been classified as a low income country and could explain why most patients were diagnosed with TB late, an indication that suggesting level of education, diagnostic capcity of the health facility and income level.

In the focused group discussion, however, confirmation of TB was prolonged for most of the visits, with the wrong diagnosis being attributed to pneumonia and other symptoms such as chest pains, among other diagnoses. The length to confirm the diagnosis for the participants was distributed based on the scale of delay days, with only a few participants having been diagnosed earlier. This is suggesting the delay period could be prolonged in other instances.

5.1.3 Factors associated with the time interval between first contact with the healthcare system and confirmed diagnosis of TB

We also determined various factors associated with the delayed diagnosis of TB between the first clinical signs and symptoms and confirmed diagnoses. The bivariate analysis conducted revealed that the twelve (12) variables showing association with delayed TB diagnosis at $p \leq 0.2$ were religion, education, night sweats, shortness of breath, unexpected weight loss, other symptoms, visit of diagnosis, occupation, health facility of diagnosis, self-medication, comorbidity, and income. We then selected the most appropriate (parsimonious) model, which was entered into the multivariable analysis model at the $p < 0.05$. In this study, other important factors such as income and comorbidity were intended for discussion even if they were not significant. The study revealed that level of education was associated with the delayed diagnosis of tuberculosis.

Primary education level was associated with longer diagnostics delays, and a higher level of education was a protective factor of delayed diagnosis TB; secondary level

(OR: 0.035; 95% CI: 0.005-0.214; P < .001) and tertiary level (OR: 0.033; 0.005-0.232; P < .001). The association may be attributed to the awareness of patients higher level of education about the signs and symptoms of the disease. The current study finding was similar to that of a study conducted by Getnet et al. (2017), which showed that uneducated patients were highly likely to suffer delay in tuberculosis diagnosis. The implication of this is lack of awareness among patients with low level of education could be a barrier to early TB diagnosis.

In this study, we evaluated the health facility of diagnosis of TB, and it is associated with delayed diagnosis. We found that being diagnosed at the dispensary (OR: 4.346; 95% CI: 1.437- 13.144; P ≤ .009) and private health(OR: 4.918; 95% CI: 1.642-14.728; P ≤ 0.004) facilities were associated with the late diagnosis of TB. Private health facilities were more highly associated with the delayed diagnosis of TB compared to public health facilities due to the accessibility of government healthcare providers to diagnostic microscopy centers, as well as a greater awareness of TB diagnostic processes (Paramasivam et al., 2017). Private healthcare providers do not have strong linkages with the government health system. A general lack of training of healthcare providers in the private sector contributes to delays in diagnosis, which could be due to frequent changes of doctors (Paramasivam et al., 2017). The likely reason in the current study could be inexperience of health care providers in private health facilities. This is confounded by the lack of weak referrals to health facilities with better diagnostic capacities.

An interaction of being of middle age (31-60 years) and having visited a public health facility was protective against delayed TB diagnosis in our study. Visiting a public health facility and being married was also protective toward a delayed TB diagnosis. The study revealed that women were more likely to delay in the diagnosis of tuberculosis, with factors such as an area of residence and the transition from private to public health facilities playing as key factors (Mistry et al., 2016). However, diagnoses at the dispensary and private health facilities were associated with delayed TB diagnosis in this study, which is suggestive of a lack of adequate diagnostic capacity, whether in private or public health facilities, contributing to delayed TB diagnosis.

This current study revealed that self-employed (OR: 21.723; 95% CI: 2.471-190.97; $P \leq .006$) and employed (OR: 9.872: 95% CI: 1.136- 85.798; $P \leq .038$) individuals had a likelihood of a delayed diagnosis of TB. The likely reason is that they do not want to spend much time going to the health facility for care due to their competing priorities. An interaction of being male and being unemployed was protective against delayed TB diagnosis. This association is explained by the fact that the unemployed male had more time to spend in seeking healthcare than his employed counterparts. Living in rural areas and being unemployed was protective towards delayed TB diagnosis, and this is contrary to a study conducted by Cai et al. (2015), which revealed that unemployment is a predictor of delayed TB diagnosis.

The current study discusses factors that were not significant at $P < .005$ but yet important in the contribution for delayed diagnosis of TB when they interact with other factors. Longer tuberculosis diagnosis delays were highly likely to be experienced by patients who resided in rural areas. Those living in rural areas and who were self-medicating were more likely to have a delayed TB diagnosis. Also, Muslims who also lived in rural areas were more likely to have a delayed TB diagnosis as well. The reasons for this might be related to misconceptions among the Muslim community and the lack of capacity to diagnose TB in rural health facilities.

In this study, a case with no comorbidities and a lower-income status (≤ KSh. 5700 or US$57 per month) at the same time was protective against a delayed TB diagnosis. The likely explanation for this is that those who sought care at public health facilities were lower-income because these health care services were either subsidized or free of charge. Higher-level public health facilities had a functional capacity to diagnose TB in due time. Another explanation could be that those with no comorbidities and who were also unemployed would have a higher chance of seeking care early enough due to a lack of work commitments. According to Bogale et al. (2017), and Jurcev-Savic evic et al.(2013) shorter delays of diagnosis of tuberculosis were more common among patients with chronic illnesses such as HIV.

This study revealed that individuals with an income of > Kshs.5700 or US$57 per month were more likely to have a delayed diagnosis. Individuals of higher economic levels were more inclined to seek healthcare from private health facilities. However, it has been noticed previously that level of income is an essential factor in early TB diagnosis. In some previous studies individuals earning less were reported to more likely to delay seeking TB diagnosis and treatment than those earning more (Terefe et al., 2018 & Takarinda et al., 2015).

In Montenegro, the National tuberculosis control program 2013-2017 postulated that delayed TB diagnosis was due to lack of awareness and suspicion of tuberculosis by clinicians and doctors in private health facilities (Montenegro Ministry of Health, 2012). This explains the reasons for delay in individuals with higher income levels seeking care in private health facilities.

Theme 2: Factors for delayed diagnosis of TB

The qualitative findings from the current study indicated that most of the TB patients had their first contact at a private clinic or primary healthcare facility. This is similar to findings in a study conducted by Hanson et al. (2017), which showed that most TB patients initiated care in low-level health facilities that did not have TB diagnostic capacity. Private practitioners in rural areas have inadequate knowledge and limited diagnostic capacity and are often only motivated to generate income. They treat and hold the patient, continually depriving them of a referral to the relevant facility for better diagnosis (Mbuthia et al., 2018). Most participants sought care at primary care facilities and private clinics where there were no TB diagnostic services available (Mbuthia et al., 2018). This study indicated most TB patients had their first contact at private clinics or a primary healthcare facility. This is similar to findings in a study conducted by Hanson et al. (2017), which showed most TB patients initiated care in low-level facilities that did not have TB diagnostic capacity.

In a qualitative study conducted by Gebreweld et al. (2018), patients mentioned the high costs of reaching the health facility as the reason for delaying seeking TB care because they were unemployed, and their family depended on them. In this study, most participants indicated that they did not have time to seek care for their symptoms because they were committed to their business in order to provide for their children's school fees, for example, among other expenditures.

In the current study, most participants provided reasons for their delayed diagnosis of TB with regards to distance to the nearest healthcare facility. Some participants had to walk for a distance of more than 5 kilometres in order to reach the facility. This matched the results of a qualitative study conducted by Demissie et al. (2013) stating that some patients around Asmara still encountered difficulty accessing the healthcare facility. Some participants covered a distance of approximately 2 hours in a single day just to reach the healthcare facility (Demissie et al., (2013).

5.1.4 SIRV Prediction Model

The study predicted a relatively low number of TB cases (n=2316) generated by the delayed diagnosis over 10 years. Studies in low- and middle-income countries estimate a high number of TB cases with delayed diagnosis (Getnet et al., 2017). Unexpectedly, we predicted low cases of TB due to delayed diagnosis. This suggests that perhaps our study area was an area of low TB burden. However, there is also a sustained transmission of TB.

These predictions underscore a key finding: Optimizing vaccination to 99% coverage with the same delay period suppresses the generation of new cases in ways that are feasible to eliminate the infection. Normally, the properties of mathematical models are a function of the distributions used. As a standard practice, therefore, more realistic distributions should be implemented, which is the justification for assessing the different distributions in this study. The empirical data was well approximated by a lognormal distribution and was straightforward enough to build more realistic infectious period distributions. In this study, the choice of lognormal distribution produced disease endemicity. The predicted number of TB cases generated by the delayed diagnosis of existing TB cases over a period of 10 years was relatively low **(n=2316)**. Although relatively low, there is predicted persistent transmission of TB in Isiolo County. Transmissions in such scenarios are predicted to be endemic.

Increasing diagnostic sensitivity clinically and laboratory

Our predictions illustrate the importance of addressing the persistent transmission of TB, achievable by fast-tracking the rate at which individuals with TB are diagnosed and initiated on treatment. Strengthening the supply side of primary health care provision should enable disease elimination. Our findings emanated from known low TB burden areas because of the sparse population with low contact rates, which concurs with a modelling study conducted by Mathema et al. (2017).

Assessing vaccination effectiveness

The predicted effect of vaccination in this study falls within the magnitude of impact required for the global “End TB Strategy, 2035” and underscores the emphasis and sustenance of the standard policy in Kenya that fulfills WHO recommendations for BCG at birth. These predictions have demonstrated the importance of increasing coverage. A trade-off policy between increasing coverage or reducing delayed diagnosis is a complex situation to grapple with. Our predictions suggest that vaccination falls within the magnitude of impact required for the End TB goals underscoring the emphasis and sustenance of the standard policy in Kenya that fulfills WHO recommendation for BCG at birth. Though achieving 100% BCG coverage at birth is difficult, the predictions have shown the importance of increasing coverage. The BCG vaccination coverage in Isiolo County was reported to be 94.2 % (KDHS, 2014) which could be significant in reducing transmission. Nonetheless, these predictions need to be interpreted with caution as current BCG vaccines are not entirely effective in preventing tuberculosis, particularly in adolescents and adults. Furthermore, the presence of strains resistant to multiple drugs constraints the use of vaccines. Our study agrees with previous modelling studies which asserted that continuous vaccination of new-borns curtails transmission (Lietman et al., 2000). Vaccinating the susceptible population was predicted to slow the increase of infections and contain the prevalence of disease for at least ten years (Pienaar et al., 2010). Pienaar et al. (2010) predicted vaccination to have a significant effect on the sudden increase in cases after 4 years in a study to model transmission and Intervention strategies of TB. This strategy reduces the rates of flow into the infectious sub-population and increase case finding for diagnosis and treatment (Pienaar et al., 2010). The empirical data was well approximated by a lognormal distribution. Given that a lognormal distribution with an integer shape parameter could be used to fit empirical infectious period data, it was straightforward to build more realistic infectious period distributions into compartment models. In this case, the use of lognormal distribution produced disease endemicity.

Limitations of the study

The current study did not classify the delay into patients and health system delays. In addition, the delay period was estimated from the patients memory of first date of signs and symptoms onset which could overestimate or underestimate the delay days. To minimize this, the events of calendar was used to estimate the date of onset. Lastly, due to the focused objective that we pursued, the model findings had certain limitations related to data gaps regarding health systems, and to the characteristics of TB. The framework was simplified leaving out many aspects of the disease transmission dynamics. Notwithstanding the fact that the findings are not representative of other county settings, the modelling framework did not incorporate other reasons for delays including patient-related, pre-health system delays, or the more granular delay to treatment following diagnosis. Some of the parameters we used as inputs into the model were from other settings or global averages estimated from regions with different scale of transmission of TB. Lastly, we assumed that regardless of the cause of delay, all had the same levels of infectiousness.

5.2 Conclusion

In conclusion, the study established that major signs and symptoms included productive cough, chest pain, night sweats, shortness of breath and unexpected weight loss which patients and health care providers did not prioritise. In addition, a significant delay of more than 21 days with the median of 27.6 days in the diagnosis of TB was established. The main factors associated with delay of TB diagnosis were health facility of diagnosis, occupation, and education levels. To address these factors could accelerate reductions in local control and the incidence of tuberculosis. The modelling framework used in this study projects that 2,316 TB cases would be generated by delayed diagnosis for 10 years, which is a probable determinant of the disease endemicity, which if addressed, would translate to long-term benefits in the public health especially amongst vulnerable and poor populations..

5.3 Recommendations

From the foregoing discussion and conclusions, the researcher recommends that there be :

1. Increase health education promotion in the community in order to improve health-seeking behaviors, thus reducing the extent of delays.
2. Deliberate the strengthening of health care workers' suspicion index of TB diagnosis in high burden settings through continuing medical education on TB, which will enhance early diagnosis.
3. Strengthening and implementing public-private health facility linkages to improve the early diagnosis of TB.
4. Strengthen TB clinical and laboratory diagnosis systems to reduce delays in diagnosis.
5. Areas of further study:
6. Prospective studies are needed in order to disentangle determinants and their interactions linked to delays in seeking healthcare (patient delay) or delays in receiving a confirmed diagnosis (health system delays) in high-burden TB settings.

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APPENDICES

Appendix I: Data Abstraction Form

Study Title: Factors Associated with Delayed Tuberculosis Diagnosis and Predicted Population Cases generated during the Delays in Isiolo County, Kenya

Initials of the research Assistant---------------------------

3. Patient Study ID # ___ ___ ___ ___

4. Date of abstraction __ __/__ __/__ __

   Day mo yr

5. Date of Birth__ __/__ __/__ __

   Day mo yr

6. Sex ☐ Male ☐ Female

7. Hospital Visit Date ___ ___/ ___ ___/___ ___

   Day mo yr

8. Reason for Visit ☐ Symptoms ☐ Other--------------------------------

Dummy table for objectives 1 and 2

Please tick in as appropriate

		TB Clinical Signs and Symptoms							
Patient's number of visit	**Cough of any duration**	**Night sweat**	**Fever**	**Weight loss**	**Fatigue**	**Hemoptysis**	**Lymph node swelling**	**Chest pain**	**Total count**
1									
2									
3									
4									

9. Sputum examination

	Sputum examination		
Patient's number of visits	**Culture**	**Microscopy**	**GeneXpert**
1			
2			
3			
4			

Appendix II: Informed consent

Study Title: Factors Associated with Delayed Tuberculosis Diagnosis and Predicted Population Cases generated during the Delays in Isiolo County, Kenya

My name is **____________________** from Jomo Kenya University of Agriculture and Technology. I want to gather information from you, which will assist us in evaluating whether you have had delayed diagnostic events preceding confirmed tuberculosis diagnosis symptoms.

Purpose of Study: The primary purpose is to define delayed diagnostic events preceding confirmed tuberculosis diagnosis. The study will also determine the proportion of presented clinical signs in the suspected and probable TB case definitions before confirmation among TB patients, the factors associated with delayed diagnosis , and predict the number of TB cases generated from the delayed diagnosis of TB. This information will be precious to TB's early diagnosis and treatment at Isiolo county referral hospital. A questionnaire will be administered to you. Questions concerning tuberculosis will be asked, and you will offer your replies.

Risks: There are no foreseeable risks to participating in this study.

Benefits: There will no immediate benefit to the participant. Your participation will support us in understanding delayed diagnosis and associated factors concerning TB in Isiolo county referral Hospital. The information obtained will support the county government and partners in order to devise policies for the early identification and treatment of TB.

Compensation: You will not receive any payment for participating in this study.

Confidentiality: Necessary measures will be set aside to preserve confidentiality so that threats of revealing your personal information will be completely reduced. The data you have provided will be kept and held in secret. The data will be stored in a computer, and the hard disk with passwords and hard copies will be kept safely.

Your participation is voluntary: You are free to drop out of this study without any punishment.

Subject: If any question arises during the study, please interact with **Dr. John Gachohi** at 0727671796, or **Kunjok David Majuch**. P.O.Box 62000-00200, JKUAT. Telephone Number: 0721678781.

I ____ have read/been read the information presented above and had the chance to query, and all were responded to acceptably. I hereby give consent for my participation as clarified to me.

Study Participant's number:
______________________Sign:__________________Date_________

Research Assistant:
____________________Sign:_________________________Date___________

Appendix III: Assent Form for Children Above Five Years of Age

Study Title: Factors Associated with Delayed Tuberculosis Diagnosis and Predicted Population Cases generated during the Delays in Isiolo County, Kenya

Investigator(s):---

We are conducting a research study about

Factors Associated with Delayed Tuberculosis Diagnosis and Predicted Population Cases generated during the Delays in Isiolo County l, Kenya

Permission has been granted to undertake this study by the University of Eastern Africa-Baraton protocol number **REC: UEAB/05/042019**.

This research study is a way to learn more about people. At least 50 children will be participating in this research study with you.

If you decide that you want to be part of this study, you will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 10 minutes and will cover topics such as reasons for visiting your healthcare provider.

Not everyone who takes part in this study will benefit. A benefit means that something good happens to you. We think these benefits might be early diagnosis and treatment among the community.

When we are finished with this study, we will write a report about what was learned. This report will not include your name or the fact that you were a participant in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that is okay, too. Your parents know about the study as well.

If you decide that you want to be in this study, please sign your name below.

I ________________________________ want to take part in this study.

______________________________ ______

(Sign your name here) (Date)

Appendix IV: Parental Permission for Children's Participation in Research

Study Title: Factors Associated with Delayed Tuberculosis Diagnosis and Predicted Population Cases generated during the Delays in Isiolo County, Kenya

Introduction

The purpose of this form is to provide you (as the parent of a cross-sectional) information that may affect your decision as to whether or not to let your child participate in this research study. The person performing the research will describe the study to you and answer all your questions. Read the information below and ask any questions you might have before deciding whether or not to give your permission for your child to take part. If you decide to let your child be involved in this study, this form will be used to record your permission.

Purpose of the Study

The primary purpose is to define delayed diagnosis of TB. The study will also determine the proportion of presented clinical signs in the in the standard case difintion before the confirmation among TB patients, as well as the factors associated with delayed diagnosis, and predict the number of TB cases generated during delayed diagnosis. This information will be important to TB's early diagnosis and treatment at Isiolo county referral Hospital. A questionnaire will be administered to you. Questions concerning tuberculosis will be asked, and you will offer your replies.

What is my child going to be asked to do?

If you allow your child to participate in this study, they will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 10 minutes. The interview will cover topics such as the reasons for visiting your healthcare provider.

Your child will be audio-recorded at some point.

What are the risks involved in this study?

There are no foreseeable risks to participating in this study.

What are the possible benefits of this study?

Your child will receive no direct benefit from participating in this study; however, this study will help determine reasons for delayed TB diagnosis.

Does my child have to participate?

No, your child's participation in this study is voluntary. Your child may decline to participate or to withdraw from participation at any time. Withdrawal or refusing to participate will not affect their relationship. You can agree to allow your child to be in the study now and change your mind later without any penalty.

What if my child does not want to participate?

In addition to your permission, your child must agree to participate in the study. If your child does not want to participate, they will not be included in the study, and there will be no penalty. If your child initially agrees to be in the study, they can change their mind later without any penalty.

Will there be any compensation?

Neither you nor your child will receive any payment for participating in this study.

How will my child's privacy and confidentiality be protected if s/he participates in this research study?

Your child's privacy and the confidentiality of his/her data will be protected by using specific codes and securing personal information in a secure place.

If it becomes necessary for my institution to review the study records, information that can be linked to your child will be protected to the extent permitted by law. Your child's research records will not be released without your consent unless required by law or court order. The data resulting from your child's participation may be made available to other researchers in the future for research purposes not detailed within this consent form. In these cases, the data will contain no identifying information that could associate it with your child or with your child's participation in any study.

If you choose to participate in this study, your child audio-recorded. Any audio recordings will be stored securely, and only the research team will have access to the recordings. Recordings will be kept for one year and then erased.

Who to contact with questions about the study?

Prior, during, or after your participation, you can contact **Kunjok David Majuch** at **0721678781** or send an email to **davidmajuch@gmail.com** for any questions, or if you feel that you have been harmed in any way. This study has been reviewed and approved by the University of Eastern Africa-Baraton at **+254 719 617 586 or + 254 731 793 934**.

Who should I contact with questions concerning my rights as a research participant?

For questions about your rights or to express any dissatisfaction with any part of this study, you can contact, anonymously if you wish, the Jomo Kenyatta University of Agriculture and Technology at 067-5870005, or by email: info@jkuat.ac.ke.

Signature

You are deciding to allow your child to participate in this study. Your signature below indicates that you have read the information provided above and have decided to allow them to participate in the study. If you later decide that you wish to withdraw your permission for your child to participate in the study, you may discontinue his or her participation at any time. You will be given a copy of this document.

____

Printed Name of Child

___________________________________ __________________

Signature of Parent(s) or Legal Guardian Date

___________________________________ __________________

Signature of Investigator Date

Appendix V: Questionnaire

Study Title**:** Factors Associated with Delayed Tuberculosis Diagnosis and Predicted Population Cases generated during the Delays in Isiolo County, Kenya

1. Initials of the research Assistant---------------------------
2. Patient Study ID # ----------------------------
3. What is your age? --------------------------------------
4. What is your Sex?

   ☐ Male

   ☐ Female
5. What is your religion?

   Christian ☐

   Muslim ☐

   Other ☐

   Please mention-------------------------------
6. What is your marital status?

   Single ☐

   Married ☐

   Divorced ☐

   Widowed ☐
7. What is your residence?

   Urban ☐

   Rural ☐
8. What is your occupation?

   Employed ☐

Unemployed ☐

Casual laborer ☐

9. What is your highest level of education?

No schooling ☐

Primary, incomplete ☐

Primary, complete ☐

Secondary school, not complete ☐

Secondary school, complete ☐

Tertiary ☐

10. When was your hospital Visit date? ___ ___/ ___ ___/___ ___

Day mo yr

11. What is your reason for visiting the hospital?

☐ Symptoms

☐ Other__________________

a. Cough of any duration: Yes ☐ No ☐

b. Sputum Cough Yes ☐ No ☐

c. Chest pain Yes ☐ No ☐

d. Night sweats: Yes ☐

No ☐

e. Shortness of breath: Yes ☐

No ☐

f. Unexpected weight loss: Yes ☐

No ☐

g. Fever: Yes ☐

No ☐

h. Fatigue: Yes ☐

No ☐

i. Other symptoms---

12. Upon what visit were you diagnosed?

1st ☐

2nd ☐

3rd ☐

4th ☐

13. Have you had a sputum examination for these symptoms?

Yes ☐

No ☐

If yes, which one?

a. Culture ☐

b. Gene expert ☐

c. Microscopy ☐

If no, did you return again to see your doctors with the same signs and symptoms?

Yes ☐

No ☐

Were the results negative or positive?

a. Culture: Negative ☐ Positive ☐
b. Microscopy: Negative ☐ Positive ☐
c. Gene Xpert: Negative ☐ Positive ☐

Health Facility and Patient health-seeking Behaviors

14. Which type of health facility did you go to when TB was diagnosed?

Public Hospital ☐

Dispensary ☐

Private Institution ☐

15. What were the reasons for not seeking care earlier?

Symptoms will go away ☐

Shortage of money ☐

Common causes ☐

16. a. Did you ever try to self-medicate yourself once you noticed the TB symptoms?

Yes ☐

No ☐

b. If yes, in 16(a), where did you go for self-medication?

Chemist ☐

Tradition healers ☐

Other………………

17. Do you have any other illnesses apart from TB (comorbidities)?

Yes ☐

No ☐

18. What are your reasons for the consultation?

Illness got worst ☐

Advised by family members ☐

Enlightened through a community awareness ☐

19. What is the walking distance from your home to the nearest healthcare facility?

>5km ☐

<=5km ☐

20. What is your income status?

>kshs5700/month ☐

<kshs5700/month ☐

21. Has anyone in your family ever had TB?

Yes ☐

No ☐

22. a. Are you the head of this family?

Yes ☐

No ☐

b. What is your family size?

0 – 2 ☐

3 – 5 ☐

6 – 8 ☐

Above 8 ☐

Appendix VI: Focused Group Discussion and in-Depth Interview Guide

(Adapted from Mbuthia et al., 2018)

Study Title: Factors Associated with Delayed Tuberculosis Diagnosis and Predicted Population Cases generated during the Delays in Isiolo County, Kenya	Date (dd/mm/yy)	Interview number

To be completed by the interviewer

1.0 Introduction

This dialogue is meant to survey the fundamental elements related to the diagnosis of tuberculosis. It will emphasize topical themes that are basic to the diagnosis of TB. This incorporates both human resource and health facility factors.

In-depth interview guide

1.1 Tell me about the experiences you have had since you began feeling unwell from tuberculosis (TB). Probes: "When did you come to suspect that you had TB? What moves did you make when you began encountering TB manifestations (the health-seeking practices in chronological order)? How long did you take from symptom onset to diagnosis?"

1.2 For what reason do individuals delay before seeking TB treatment from the health facility? Probe: "What blocked you from getting TB treatment instantly?"

In-depth interview guide in Kiswahili language (English translation)

2.1 Nieleze kwa kina uliyoyapitia baada ya kupata ugonjwa wa kifua kikuu. (Jinsi ulivyo kuja kushuku ulikuwa na ugonjwa wa kifua kikuu, hatua ulizozichukua kutafuta matibabu, uliyoyapitia kabla ya utambuzi wa ugonjwa, Ilikuchukua muda gani kujua ulikuwa unaungua kifua kikuu,

2.2 Kwa wa nini watu huchukua muda kabla ya kwenda hospitalini wanapo pata dalili za kifua kikuu? (Kwa upande wako nini kilikuzuia kupata matibabu ya kifua kikuu kwa haraka?

3.0 Focus group discussion guide

3.1 Tell me about the experience TB patients encounter in order to get TB diagnosis and treatment.

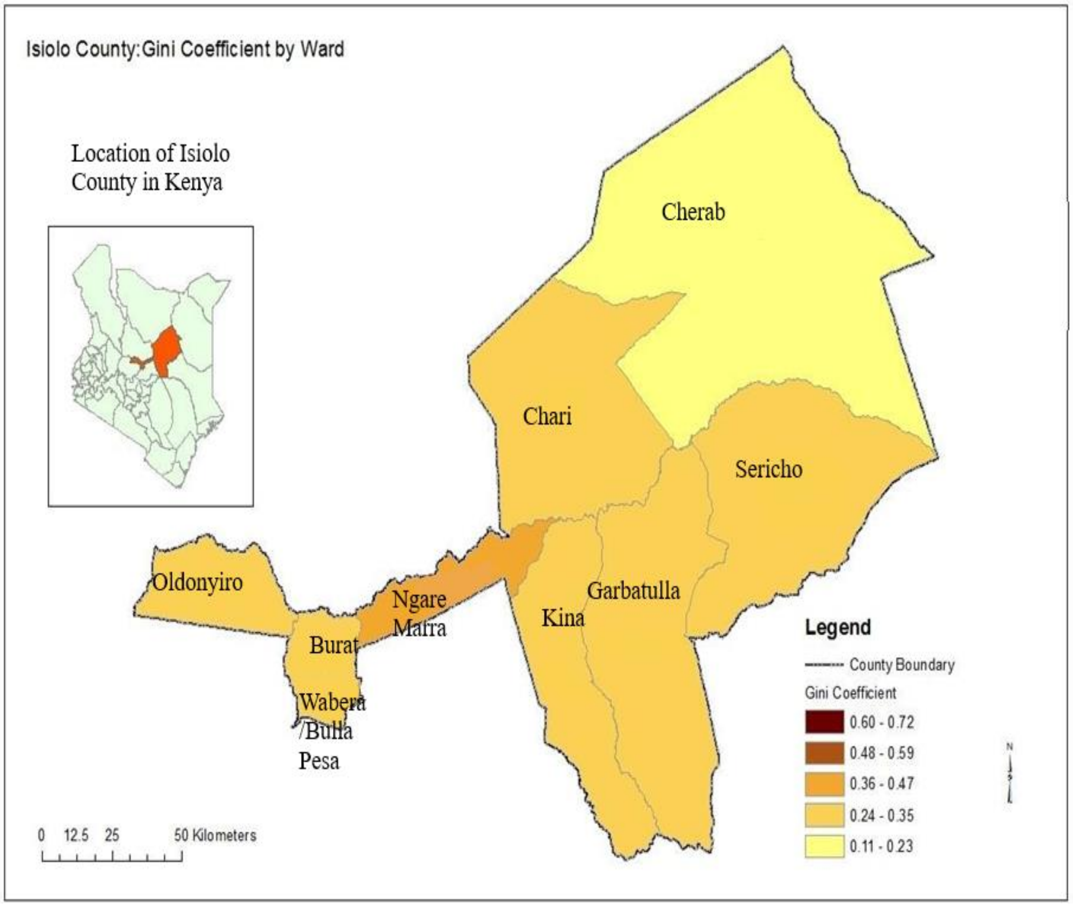
3.2 Do TB patients look for treatment promptly from the health facility when they suspect that they have TB? Why?

Focus group discussion guide in Kiswahili language (English translation)

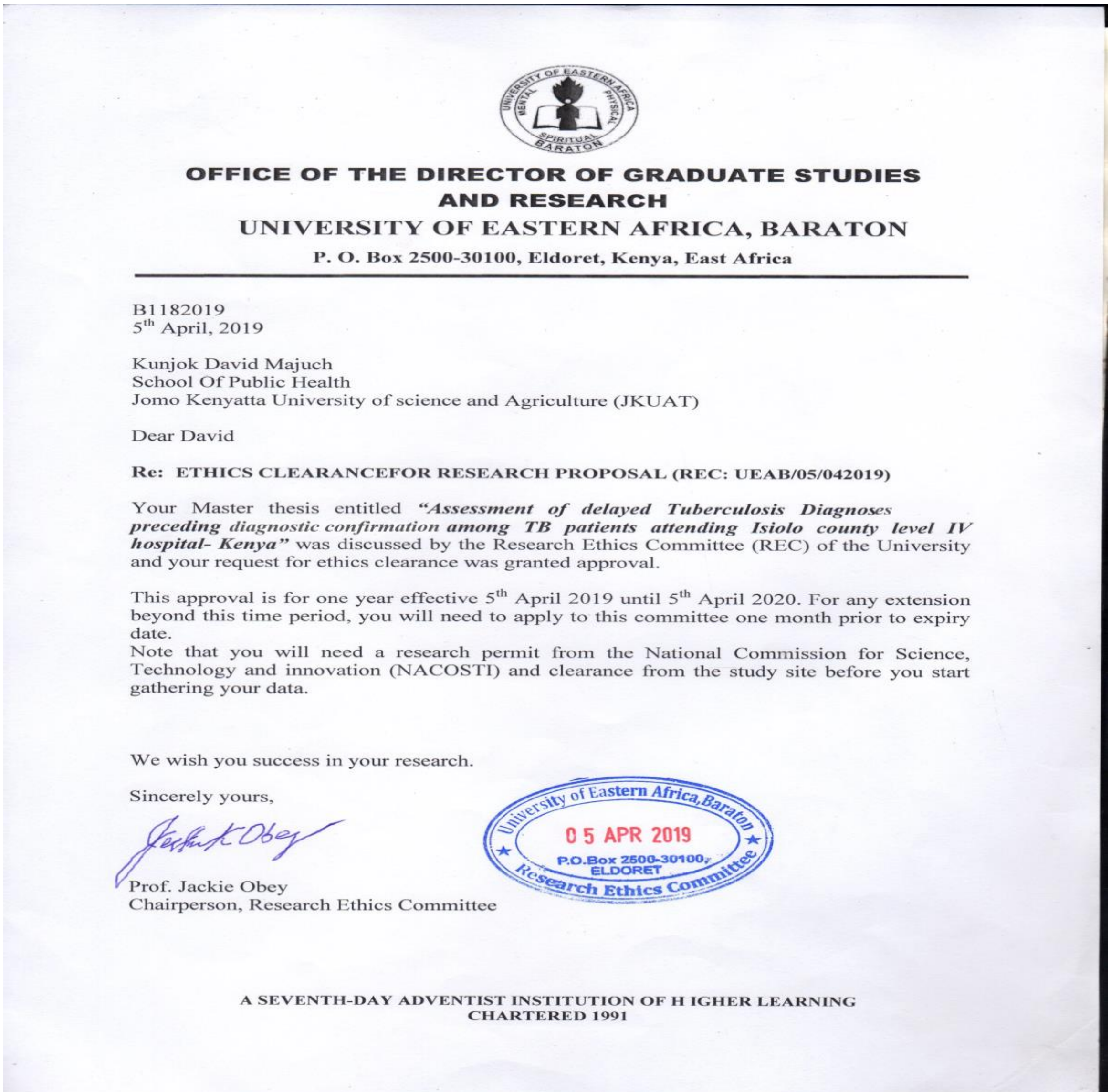
a) Mtu anapoungua huu ugonjwa wa kifua kikuu, anapitia yapi katika hii jamii?

b) Je, wagonjwa wa kifua kikuu hutafuta matibabu mara moja kutoka kituo cha afya wanaposhuku wako na ugonjwa wa kifua kikuu?

Appendix VII: Map Showing the Location of Isiolo County in Kenya



Appendix VIII: Ethical Review Committee Approval Letter



OFFICE OF THE DIRECTOR OF GRADUATE STUDIES AND RESEARCH

UNIVERSITY OF EASTERN AFRICA, BARATON

P. O. Box 2500-30100, Eldoret, Kenya, East Africa

B1182019
5th April, 2019

Kunjok David Majuch
School Of Public Health
Jomo Kenyatta University of science and Agriculture (JKUAT)

Dear David

Re: ETHICS CLEARANCEFOR RESEARCH PROPOSAL (REC: UEAB/05/042019)

Your Master thesis entitled ***"Assessment of delayed Tuberculosis Diagnoses preceding** diagnostic confirmation **among TB patients attending Isiolo county level IV hospital- Kenya"*** was discussed by the Research Ethics Committee (REC) of the University and your request for ethics clearance was granted approval.

This approval is for one year effective 5th April 2019 until 5th April 2020. For any extension beyond this time period, you will need to apply to this committee one month prior to expiry date.
Note that you will need a research permit from the National Commission for Science, Technology and innovation (NACOSTI) and clearance from the study site before you start gathering your data.

We wish you success in your research.

Sincerely yours,

Prof. Jackie Obey
Chairperson, Research Ethics Committee

University of Eastern Africa, Baraton
05 APR 2019
P.O.Box 2500-30100, ELDORET
Research Ethics Committee

A SEVENTH-DAY ADVENTIST INSTITUTION OF H IGHER LEARNING
CHARTERED 1991

Appendix IX: Letter of Research Authorization

NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY AND INNOVATION

Telephone:+254-20-2213471,
2241349,3310571,2219420
Fax:+254-20-318245,318249
Email: dg@nacosti.go.ke
Website : www.nacosti.go.ke
When replying please quote

NACOSTI, Upper Kabete
Off Waiyaki Way
P.O. Box 30623-00100
NAIROBI-KENYA

Ref. No. **NACOSTI/P/19/46686/29732**

Date: **11th September, 2019**

David Majuch Kunjok
Jomo Kenyatta University of
Agriculture and Technology
P.O. Box 62000-00200
NAIROBI.

RE: RESEARCH AUTHORIZATION

Following your application for authority to carry out research on ***"Assessment of delayed Tuberculosis diagnoses preceding diagnostic confirmation among TB patients attending Isiolo County Level Four Hospital, Kenya"*** I am pleased to inform you that you have been authorized to undertake research in **Isiolo County** for the period ending **27th May, 2020.**

You are advised to report to **the County Commissioner, the County Director of Education and the County Director of Health Services, Isiolo County** before embarking on the research project.

Kindly note that, as an applicant who has been licensed under the Science, Technology and Innovation Act, 2013 to conduct research in Kenya, you shall deposit **a copy** of the final research report to the Commission within **one year** of completion. The soft copy of the same should be submitted through the Online Research Information System.

GODFREY P. KALERWA MSc., MBA, MKIM
FOR: DIRECTOR-GENERAL/CEO

Copy to:

The County Commissioner
Isiolo County.

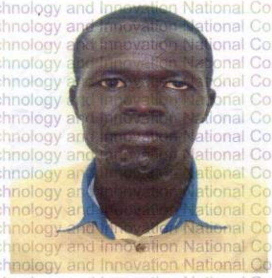
Appendix X: Research permit

THIS IS TO CERTIFY THAT:
MR. DAVID MAJUCH KUNJOK
of JOMO KENYATTA UNIVERSITY OF AGRICULTURE AND TECHNOLOGY , 6200-200 Nairobi,has been permitted to conduct research in *Isiolo County*

on the topic: *ASSESSMENT OF DELAYED TUBERCULOSIS DIAGNOSES PRECEDING DIAGNOSTIC CONFIRMATION AMONG TB PATIENTS ATTENDING ISIOLO COUNTY LEVEL FOUR HOSPITAL, KENYA*

for the period ending:
27th May,2020

Permit No : NACOSTI/P/19/46686/29732
Date Of Issue : 11th September,2019
Fee Recieved :Ksh 1000



....
Applicant's Signature

....
Director General
National Commission for Science, Technology & Innovation

Appendix XI: Letter of introduction

JOMO KENYATTA UNIVERSITY
OF
AGRICULTURE AND TECHNOLOGY
COLLEGE OF HEALTH SCIENCES (COHES)

TEL: 067-52181-4 Extn. 2226 FAX: 067-52030 Email : director @itromid.jkuat.ac.ke

JKU/2/159/075

23RD APRIL, 2019

MEDICAL SUPERINTENDENT
ISIOLO COUNTY
P. O. BOX 42 - 60300
ISIOLO

The Incharge
Medical Superintendent
Isiolo Level 4 Hospital
Isiolo County

Dear Sir/Madam

RE: INTRODUCTION LETTER FOR KUNJOK DAVID MAJUCH: HSH315-0030/2017

The bearer of this letter is a student pursuing **Master of Science in Epidemiology** in the School of Public Health at the College of Health Sciences (COHES), Jomo Kenyatta University and Technology (JKUAT). As part of his Master's thesis he is required to collect data for his research topic on **"Assessment of Delayed Tuberculosis Diagnoses Preceding Diagnostic Confirmation among TB Patients Attending Isiolo County Level Four Hospital, Kenya"**

We highly appreciate your assistance in this endeavor and look forward to your continued support.

Yours faithfully,

JKUAT
www.jkuat.ac.ke
Box 62000-00200, NAIROBI

PROF. GIDEON KIKUVI
COD, ENVIRONMENTAL HEALTH AND DISEASE CONTROL

COD, ENVIRON. HEALTH
& DISEASE CONTROL

Setting Trends in Higher Education, Research and Innovation

Appendix XII: Publication

Research | Volume 38, Article 51, 18 Jan 2021 | 10.11604/pamj.2021.38.51.21508

Assessment of delayed tuberculosis diagnosis preceding diagnostic confirmation among tuberculosis patients attending Isiolo county-level four-hospital, Kenya

David Majuch Kunjok, John Gachohi Mwangi, Susan Mambo, Salome Wanyoike

Corresponding author: David Majuch Kunjok, Jomo Kenyatta University of Agriculture & Technology (JKUAT), Nairobi, Kenya

Received: *11 Jan 2020* - ***Accepted:*** *31 Dec 2020* - ***Published:*** *18 Jan 2021*

Domain: Infectious diseases epidemiology

Keywords: Kenya, Isiolo, tuberculosis, delayed diagnosis, level four hospital, diagnostic confirmation

Cite this article: *David Majuch Kunjok et al. Assessment of delayed tuberculosis diagnosis preceding diagnostic confirmation among tuberculosis patients attending Isiolo county-level four-hospital, Kenya. Pan African Medical Journal. 2021;38:51. [**doi**: 10.11604/pamj.2021.38.51.21508]*

Available online at https://www.panafrican-med-journal.com/content/article/38/51/full