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MASTER OF SCIENCE IN FIELD EPIDEMIOLOGY (FETP PROGRAM)

MASTER'S THESIS

FACTORS ASSOCIATED WITH MORTALITY IN TB PATIENTS ON FIRST-LINE TREATMENT IN RWANDA From July 2019 to June 2022

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July 2023

DECLARATION

I, NSHIMIYIMANA Kizito, do hereby declare that this thesis entitled " ***Factors associated with mortality in TB patients on first-line treatment in Rwanda, July 2019- June 2022, Cross-sectional study***", is submitted for a degree of Masters of Science in Field Epidemiology, the University of Rwanda, College of Medicine and Health Sciences in my original research work. It has not previously been submitted elsewhere.

Furthermore, I do declare that a complete list of references has been clearly provided including all the sources of the information quoted or cited.

Date 10/07/2023

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DEDICATION

I dedicate this work to God the Almighty, my creator, source of life, wisdom, knowledge, and power during the FETP Master's program and this research effort.

I also dedicate this work to my whole family, my daughters **ATETE SHIMA Bernice, ILIZA SHIMA Davina, ISARO SHIMA Eloé**, and more especially to my wife **MUKAMANZI Charlotte** who encouraged with enthusiasm and supported me throughout the process.

God bless you abundantly.

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List of abbreviations and acronyms

AFRO	Regional Office for Africa
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment
BMI	Body Mass Index
CFR	Case Fatality Rate
CHWs	Community Health Workers
CI	Confidence Interval
CHMS	College of Medicine and Health Sciences
EAC	Eastern African Community
COR	Crude Odds Ratio
e-TB	Electronic TB Case-based Surveillance System
FETP	Field Epidemiology Training Program
FY	Fiscal Year
TSR	Treatment Success Rate
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
MDR-TB	Multidrug-Resistant Tuberculosis
NTP	National Tuberculosis Program
AOR	Adjusted Odds Ratio
RBC	Rwanda Biomedical Center
SDGs	Sustainable Development Goals
TB	Tuberculosis
UNHLM	United Nations High-Level Meeting
WHO	World Health Organization
<	Less than
>	Greater than
≥	Greater than or Equal to

ABSTRACT

Introduction: Tuberculosis (TB) is a significant cause of mortality worldwide, and Rwanda is no exception. Although the availability of effective treatment, the mortality rate in TB patients remains high. This study aimed to identify factors associated with mortality in TB patients receiving first-line treatment in Rwanda.

Methods: A retrospective cross-sectional study was conducted among adult TB patients aged 15 and above, including those engaged in first-line therapy and registered in health facilities' National electronic individual records (e-TB) between July 2019 and June 2022. Multivariate logistic regression analysis was used to identify significant independent variables retained in an unadjusted model.

Results: Of the 14,451 patients included in the study, 1,262 (8.7%) died during treatment. Death rates were higher in the cohorts of clinically diagnosed (17.1%), and TB/HIV co-infected (16.9%) Several factors were significantly associated with mortality. The risk was higher in patients who were underweight at initial treatment (aOR=1.78, 95% CI: 1.39-2.28), clinically diagnosed with TB (aOR=1.72, 95% CI: 1.27-2.34), not currently on ART (aOR=9.22, 95% CI: 6.39-13.29). Being managed in referral hospitals (aOR=2.58, 95% CI: 1.77-3.76) or district hospitals (aOR=2.18, 95% CI: 1.58-3.01), and not followed up by CHWs (aOR=2.68, 95% CI: 1.92-3.74). Interestingly, being an inmate was found to be a protective factor, with a lower risk of dying from TB compared to those who were not in prison (aOR=0.35, 95% CI: 0.16-0.78).

Conclusion: This study highlights the importance of early diagnosis and treatment of TB, as well as the need for comprehensive healthcare services and follow-up, particularly for patients who are underweight, being not on ART. Additionally, the study provides insight into the potential benefits of prison healthcare systems in managing TB. These findings could inform public health policies and interventions aimed at reducing mortality rates in TB patients in Rwanda and other similar settings.

Keywords: Tuberculosis; Mortality; Risk factors, Rwanda.

0.0. Definition of the key concepts

According to the 2013 revision of the WHO definitions for TB, the following are the standardized definitions of treatment outcomes and TB patient case (1–3).

Cured: "A pulmonary tuberculosis patient with bacteriologically confirmed TB at the start of therapy who was smear or culture-negative in the past month of treatment (C6) and at least once before (C2 or C5).

Treatment completed: A TB patient who had bacteriologically confirmed TB at the start of treatment and finished treatment without evidence of failure but cannot be classified as cured or failed because the tests (smear or culture) were not done in the last month of treatment and at least one before, or because the results are unavailable. A patient who has finished therapy for clinically diagnosed pulmonary or extra-pulmonary tuberculosis.

Treatment failure: A TB patient whose sputum smear or culture is positive at 5 months or later during treatment or patients found to contain a multidrug-resistant MDR strain at any stage throughout multidrug-treatment, whether they are smear-negative or positive".

Died: "A TB patient who dies for any reason before starting or during the course of treatment".

Lost to follow-up: "A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more".

Not evaluated: "A tuberculosis patient for whom no treatment result has been assigned. The patient "transferred out" to another treatment unit for whom the treatment outcome is unknown to the reporting unit. Patient whose treatment was stopped for serious reaction or misdiagnosis".

TB successful treatment: "refers to the sum of cured patients and patients who completed their treatment".

A tuberculosis case or TB patient: "This refers to a patient that has been diagnosed as such by a clinician, regardless if the diagnosis has been confirmed bacteriologically or not".

Drug-susceptible TB patients: It refers to patients who have no indication of rifampicin-resistant strains (not rifampicin-resistant or multidrug-resistant TB).

CHAPTER ONE: INTRODUCTION

1.1. Background

Tuberculosis (TB) is a communicable disease that is a major cause of sickness, one of the world's top 10 causes of death, and the leading cause of death caused by a single infectious agent (4) (5) (6). Tuberculosis is caused by the bacillus Mycobacterium tuberculosis, which is disseminated when people with TB cough, sneeze, or talk, releasing germs into the air. The disease typically affects the lungs (pulmonary tuberculosis), but it can also affect other organs (extra-pulmonary tuberculosis) (1) (5) . *M. tuberculosis* infects almost one-quarter of the global population (7). Tuberculosis affects all sexes and all age groups, however adults are the most often affected. Men accounted 56.5% of the burden, with adult women accounting for 32.5 percent and children accounting for 11%. Several primary factors, namely malnutrition, HIV infection, alcoholism, tobacco use, and diabetes, contribute to the emergence of numerous new cases of tuberculosis (8) (5) (9).

Tuberculosis is a disease of poverty, and those who have it usually face economic difficulties, vulnerability, marginalization, stigma, and discrimination (5). Economic and financial barriers may limit access to health care for TB diagnosis and treatment completion; around half of TB patients and their households face catastrophic total costs as a result of TB sickness (4). Without treatment, the death rate from TB is roughly 50% (10).

In 2021, 10.6 million people developed TB worldwide, a 4.5% rise from 10.1 million in 2020, and around 1.6 million died from the illness, including 187,000 HIV-positive people. Furthermore, 54% of HIV-negative TB deaths were males, 32% were women, and 14% were children (4).
Although the decline in the annual number of tuberculosis (TB) fatalities from 2005 to 2019, there was an unfortunate reversal of this trend in 2020 and 2021. As a result, the progress achieved prior to 2019, which included a 14% drop in TB deaths from 2015 to 2019 and a 41% decrease from 2000 to 2019, was compromised by the increases in TB deaths in 2020 and 2021. This means that the progress towards the first milestone of the End TB Strategy, aiming for a 35% reduction in TB deaths between 2015 and 2020, was actually reversed, resulting in a mere 5.9% net reduction in TB fatalities from 2015 to 2021. The global TB targets have not yet been fulfilled owing to an upsurge in TB mortality in 2020 caused by COVID-19 pandemic disruptions in diagnosis and treatment (4) (9).

Nonetheless, the drop in the reported number of TB patients identified in 2020 and 2021 indicates that the number of persons with undiagnosed and untreated tuberculosis has grown. This might lead to an increase in the number of TB fatalities and community spread of infection, followed by an increase in the number of people contracting the disease with some lag time (4).

Geographically, Southeast Asia (45%), Africa (23%), and the Western Pacific (18%) had the largest percentages of TB cases in 2021, while the Eastern Mediterranean (8.1%), the Americas (2.9%), and Europe (2.2%) had the lowest percentages. India (28%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%), and the Democratic Republic of the Congo (2.9%) accounted for more than two-thirds of worldwide TB infections in the same year (4).

In 2021, Rwanda's predicted TB incidence rate was 56 cases per 100,000 people, with 7.3 deaths per 100,000 people. Over the preceding year, mortality climbed progressively from 4.9 in 2019 to 6.2 in 2020. Even so, Rwanda has the lowest mortality rate among the Eastern African Community's countries, with Uganda accounting for 14 deaths per 100,000 population, Burundi 20 deaths per 100,000 population, South Sudan 28 deaths per 100,000 population, and Tanzania 29 deaths per 100,000 population. Kenya has 39 deaths per 100,000 inhabitants, whereas the Democratic Republic of the Congo has 44 deaths per 100,000 people (4).

According to Rwanda's fiscal year report for 2021/2022, 5,538 TB patients were notified, with 98.7% (5,422/5.538) beginning first-line therapy. Children (under 15 years old) made up 271 (5%) of all TB patients diagnosed, while men made up 72.6% and women made up 27.4%. Co-infection with TB and HIV occurred in 14.4% of TB patients.

The unsatisfactory TB treatment outcome resulted in the death of 7.8% (427/5455) of all susceptible TB patients and 12.7% (170/1341) of those clinically diagnosed. TB treatment coverage reported was 71.6% (5,371/7,500) (12).

The case fatality ratio (CFR) is "the estimated proportion of persons who get tuberculosis who die from the disease. It is calculated by dividing the number of TB deaths by the number of new cases in the same year". The most current Rwandan National Strategy called for a 6.5% drop in CFR in FY 2020/2021 and a 6% reduction in FY 2021/2022 compared to 2015, while the End Tuberculosis Strategy calls for a 10% reduction in CFR by 2020 and a 6.5% reduction in CFR by 2025. This implies that all persons should receive timely TB diagnosis and treatment in primary healthcare settings (4) (5).

1.2. Statement of the problem

According to the WHO END Strategy, Rwanda's objective is to eliminate tuberculosis by 2035 by reducing projected TB incidence by 90%. Whereas, End TB milestones were set with the aim of lowering TB incidence by 35% and reducing cases of TB deaths by 55% between 2015 and 2024. The National Strategy called for a 6.5% drop in case fatality rate (CFR) in FY 2020/2021 and a 6% reduction in FY 2021/2022 compared to 2015, while the End Tuberculosis Strategy calls for a 10% reduction in CFR by 2020 and a 6.5% reduction in CFR by 2025. Several studies (27) (34) and reports of TB National program showed that morality hindered the good treatment success outcome, which set at 90% annuals for all drug-susceptible TB patients (1) (12) (13). For example, Rwanda reported in the FY 2021/2022, unfavorable treatment outcome resulted from death, with 7.8% (427/5455) of all susceptible TB patients and 12.7% (170/1341) of those clinically diagnosed (12) (14). Despite substantial efforts made in Rwanda to prevent and control tuberculosis, the fatality rate remains consistently higher among patients on TB drug-susceptible, while the majority of these premature deaths might be averted with early detection and effective treatment (5).

1.3. Justification of the study

Tuberculosis poses a significant public health challenge on a global scale, especially in developing countries. Rwanda as a member of the World Health Assembly has shown its support for the END TB Strategy, a comprehensive initiative aimed at eliminating tuberculosis by the year 2023. However, a significant proportion of people who die from the disease must be lowered from 15% in 2015 to 5% by 2025 (15). No study has been conducted with the aim of determining the factors associated with deaths that often occurred among TB patients on first-line treatment regimens. To this end, It is critical to comprehend the risk factors that lead to tuberculosis mortality so that they may help inform decision-making for the health professionals, policymakers, and program managers during the policy development strategy and its implementation in the respective context of study settings or others countries that we shared the same characteristics. Therefore, this study aims to identify potential risk factors for death in TB patients enrolled in first-line treatment in Rwanda.

1.4. Objectives

1.4.1. Main objectives

The main objective of this study is to determine factors associated with mortality among TB patients receiving first-line therapy in Rwanda.

1.4.2. Specific objectives

- To describe socio-demographic characteristics among TB patients in Rwanda
- To describe clinical factors among TB patients in Rwanda
- To determine the case fatality rate for all TB forms diagnosed in Rwanda
- To identify factors associated with mortality in patients on first-line treatment in Rwanda

1.5. Research question

- What are the socio-demographic characteristics of TB patients in Rwanda?
- What are the clinical factors associated with mortality among TB patients in Rwanda?
- What is the case fatality rate over time for all TB forms diagnosed in Rwanda?
- What are the factors associated with mortality in TB patients in Rwanda?

1.6. Organization of the study

This study was structured into six chapters, with the introduction including the background, statement of the problem, study rationale, research objectives, and research questions. The second chapter is the literature review, which encompasses the theoretical framework, research review, and conceptual framework. The research methodology is the third chapter that describes methods and procedures used in the study to ensure its consistency and reproducibility. The fourth chapter reflects the findings of the study. The fifth chapter is a decision. Finally, the conclusion and recommendations constitute the last chapter, followed by the reference and appendices.

CHAPTER TWO: LITERATURE REVIEW

2.1. Theoretical literature on TB mortality in drug-susceptible TB patients

Tuberculosis (TB) is both preventable and curable. A 6-month medication regimen may effectively cure around 85% of people who get tuberculosis illness; standardized treatment has the added advantage of curtailing onward transmission of infection (4) (5). The multidrug therapy is administered appropriately in two phases. First, the initial or intensive phase includes 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, and the second is a continuous phase that lasts 4 months, in which isoniazid and rifampicin are used (1). Drug provision on a daily basis throughout treatment and Direct Observed Treatment (DOT) is strictly recommended with the aim to optimize treatment adherence and improve TB successful treatment. Therefore, reduced access to TB diagnosis and treatment has increased TB deaths (9). The high mortality among TB patients may represent access constraints to good health care and prompt diagnosis and treatment, but it may also be the result of a lack of government policies and social protection programs (16). Storla et al. examined 58 research on treatment delays in tuberculosis diagnosis and therapy. However, the determinants associated with diagnostic delay were found to be chronic cough or other lung diseases, sputum smear-negative, extra-pulmonary TB, rural residence, poor health care access due to geographical or psycho-social barriers, initial presentation to a governmental low-level health care facility, private practitioner or traditional healer, old age, poverty, drug or alcohol misuse. Additional barriers included poor educational levels, a lack of understanding of Tuberculosis, beliefs that TB is incurable or is caused by bad spirits and concerns about stigma (17) (18).

On average, 5 to 10% of individuals infected with TB will develop active tuberculosis disease over their lives, typically within the first 5 years after initial infection. The development of TB disease can occur as a result of the infection or later by reactivation of the latent infection due to a weakened immune system (1). To this end, for individuals exhibiting signs or symptoms suggestive of tuberculosis, quick clinical assessment is critical to guarantee early and accurate diagnosis. This should include investigating the patient's medical history and TB risk factors, performing a medical examination, and additional tests (1). However, passive screening of tuberculosis among people attending health facilities with symptoms suggestive of tuberculosis is very important as well as systematic case finding targeting people at high risk of developing TB (1) (12). The high-risk groups (HRG) include prisoners, people living with HIV (PLHIV), diabetes mellitus, underground miners, contacts of TB pulmonary confirmed as index TB cases, all people

≥55 years old, and children under the age of five (13). However, TB screening is based on five symptoms such as cough of more than two weeks and fever, night sweats, weight loss, contact with Tuberculosis Pulmonary Bacteriologically confirmed (TPB +). Regardless duration of symptoms, any presence of symptoms is a subjects of screening for PLHIV.

Community health workers play an essential role in screening by identifying individuals in the community who exhibit TB signs and symptoms and bringing them to the nearest health facility for further evaluation and care. Usage of chest X-rays for screening remains recommendable tool for all but is still a challenge for developing countries with inadequate resources (12). Throughout the epi-reviews and mid-term of 2013-2018 conducted in Rwanda, many weaknesses that may contribute to the under-identification of Tuberculosis (TB) cases have been underlined. Several factors contribute to the suboptimal quality of TB screening and the inadequacy of screening tools in capturing all five screening symptoms. These factors include the underutilization of rapid molecular tests, such as the Xpert test, and chest X-rays (CXR) in all patients suspected of having TB during the diagnostic process. Additionally, there are limitations associated with patient transportation for CXR and the transport of samples for the Xpert test, which can further hinder the detection of TB cases. Another factor that contributes to the under-detection of TB is the delayed transmission of culture and Xpert test results back to the requesting health facility, primarily due to inadequate connectivity systems. These challenges collectively hinder the effectiveness of TB screening and diagnostic processes. Furthermore, a nationwide TB prevalence study done in 2012 revealed low TB awareness on symptoms, and patients delayed as a result of poor health-seeking behavior (13). It is notable that the cause of death can only be established definitively through post-mortem studies (17). The high death rate among individuals with Tuberculosis may be due to difficulties in accessing adequate healthcare, prompt diagnosis, and therapy. Simply giving care to TB patients once they enter the healthcare system may not be enough to prevent early and avoidable deaths (16). Few studies focused on early deaths, there were clarified that death occurred during the 2-month intensive phase of anti-tuberculosis treatment (17). These are critical concerns that call the interventions to mitigate the earliest death due to TB before and/or in foremost months of TB treatment course implying the centered patient care approach.

Apart from the routine lab test used to diagnose *M. tuberculosis* as smear microscopy, culture, and rapid molecular test/Xpert, the WHO also recommended the use of a rapid diagnostic test including

the lateral flow urine lipoarabinomannan assay (LF-LAM), which can provide an early diagnosis of tuberculosis and help to minimize tuberculosis deaths in people living with HIV(5).

2.2. Theoretical framework toward mortality in TB patients with drug-susceptibility

With regard to the factors associated with mortality, the pandemic of the human immunodeficiency virus (HIV) has been demonstrated to constitute a significant danger to global TB control (1) (19), as pathogens for both tuberculosis (TB) and HIV mutually enhance each other's effects and hasten the decline of immune system functionality, leading to unfavorable outcomes (20). Patients with a BMI less than 18.5 are at a greater risk of dying early and relapsing. The factors associated with early mortality are at present not well characterized, and also it is assumed that malnutrition in TB patients further compromises host immunity and predisposes patients to life-threatening nutritional deficiencies and superadded infections (1) (21). The TB verbal death audit conducted in Rwanda and reported in the annual fiscal year of 2019/2020 showed that 64.3% (81/126) and 41.2% (56/136) of patients that died were respectively malnourished and HIV positive. However, 72.7% (88/121) of deaths occurred during the first two months of starting TB therapy (14). TB is the most prevalent opportunistic infection among HIV-infected people, and co-infected people are at a higher risk of dying (22). Some studies from other countries found that advanced age, male gender, HIV co-infection or unknown HIV status, having a negative or missing pre-treatment sputum smear result, being a retreatment patient, treatment by a private provider, and non-adherence during the intensive phase of treatment all increased the risk of death in TB patients (23) (24). Anemia, positive sputum smear, smoking, drug-induced hepatitis, diabetes mellitus, history of prior TB, undernutrition, HIV infection, and poverty were all found to be important explanatory variables for death in TB patients in several studies (5) (25). The combination of homelessness and alcohol and drug use was connected with all causes of mortality (26). In addition, rural inhabitants, HIV co-infection, not getting antiretroviral medication, no Cotrimoxazole prophylaxis, smear-negative TB patients, and no microbiological confirmation were identified as factors in research done in Nigeria.(27) (28).

2.3. Conceptual framework of factors associated with mortality among TB patients on drug susceptibility

The present conceptual framework was made from a literature review, which provides significant factors linked with the dependent variables, mortality. The determinants variables found in the

various countries' studies conducted were characterized into three groups such as socio-demographic, clinical, and behavioral factors (Figure 1).

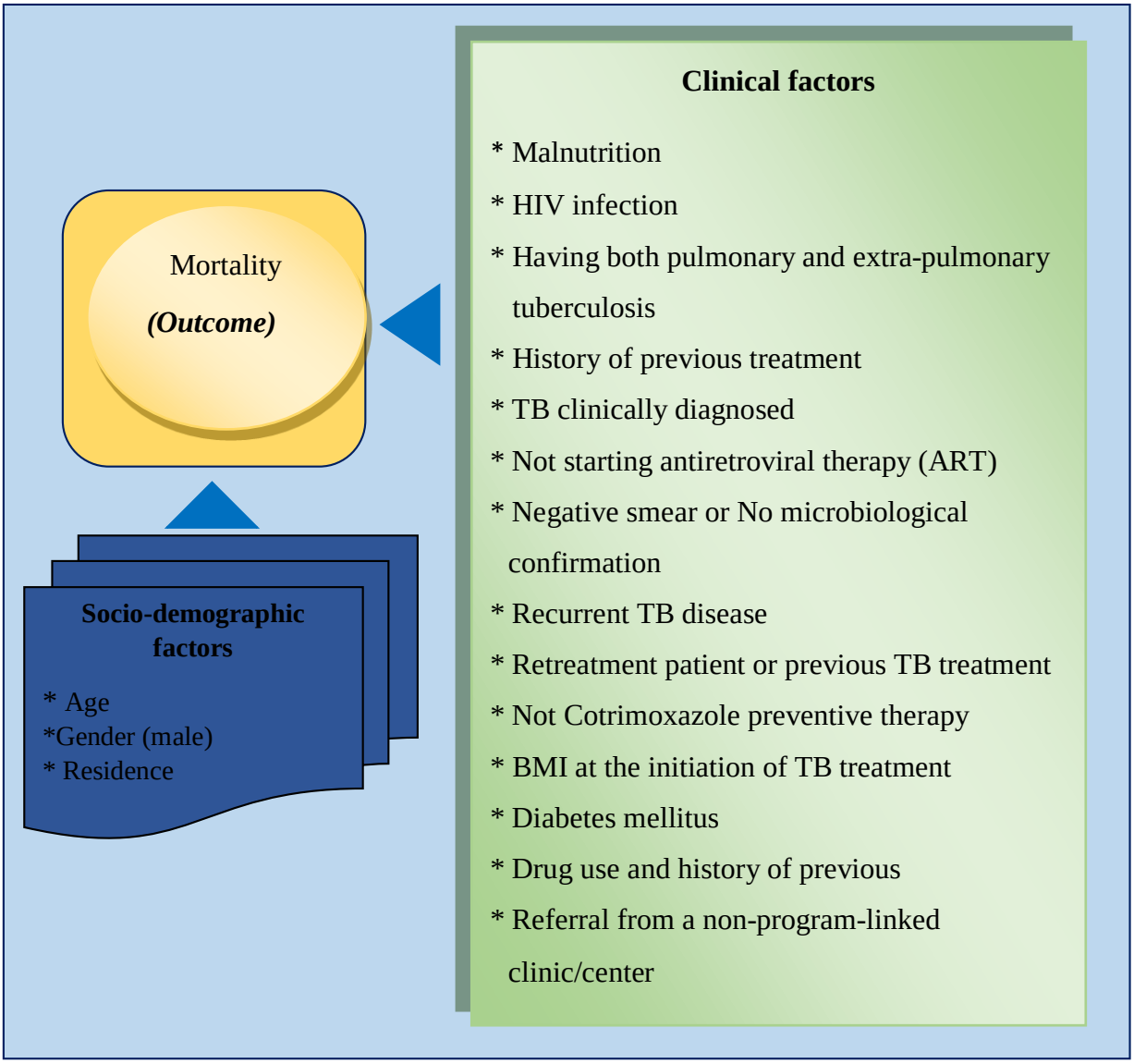


Figure 1 . Conceptual framework of factors associated with mortality in TB patients

CHAPTER THREE: RESEARCH METHODOLOGY

3.1. Study setting

This study was based on data gathered from public and private health institutions across the country, where TB cases were recorded into the electronic TB case-based surveillance system (e-TB) between July 2019 and June 2022. These healthcare primary settings accounted for 565 health facilities of which 52 are hospitals (8 referrals, 40 District, 4 Provincial Hospitals) and 513 health centers.

3.2. Study design

A retrospective observational cross-sectional study was conducted using quantitative methods to investigate potential factors associated with mortality among TB patients who are drug-susceptible.

3.3. Study population

The study population consisted of TB patients who were receiving first-line treatment regimens and had their cases registered in the computerized TB case-based surveillance system used by health facilities across the country.

3.3.1. Inclusion criteria

The study included all adult TB patients aged 15 years old and above who started first-line therapy and had their treatment results documented in an electronic TB case-based surveillance system in compliance with National TB Program guidelines.

3.3.2 Exclusion criteria

The study specifically excluded TB patients under the age of 15, those with multidrug-resistant (MDR-TB), treatment failures, loss to follow-up, and individuals whose outcomes were reported as “not evaluated” in an electronic TB case-based surveillance system. Consequently, these groups were not included in the analysis or considered in the study’s results.

3.4. Sampling and sample size

This study selected all TB patients reported in three consecutive fiscal year (FY) reports in the period starting July 2029 to June 2022. Therefore, the sample size was nationally representative of

all health facilities, which reported TB patients in an electronic case-based surveillance system. Indeed, apart from the removal of inconsistent or unreliable information, the sample size holds all TB patients reported by the National TB Program whether any participant meets inclusion criteria regardless of their health conditions. The total number of study subjects accounted for 14,451 TB patients.

3.5. Study variables

The duration of treatment for the patient with TB drug susceptibility is six months. The outcome of interest is death, which refers to all tuberculosis patients who died for whatever cause before or during treatment, while alive people included those who were successfully treated either declared "cured" or those who have "completed" treatment. Nevertheless, different independent variables were a subject of analysis such as socio-demographic characteristics, gender (male/female), age, residence, etc., and clinical features. The clinical factors include the people who received nutrition support (Yes/No), BMI (underweight: 18.5 kg/m2, normal: 18.5-24.9, overweight: 25-29.9, obese: 30 and above), special high-risk groups (TB contacts, diabetes, inmates, miners), patients receiving follow up by community health workers (Yes/No), TB confirmation method (bacteriological, clinical), and previous TB (new/recurrent). Additionally, we also considered the HIV status (HIV negative, HIV positive, HIV unknown), Site of TB disease (pulmonary /extra-pulmonary), sputum smear control at month two (C2) (positive, negative, not done), initiated on CTX (Yes/No), and initiated antiretroviral (Yes/No).

3.6. Data collection method

Accessing the Ministry of Health's National electronic health management information, individual instance, and a line list was established with data elements related to the independent variables and outcome of interest. The data was collected by combining the data elements, the organizational unit respecting the structural level of the health system, and the selection of the period starting in July for the financial year. The secondary data were extracted from the e-TB system to an Excel spreadsheet for data cleaning. The study population was refined by excluding TB patients who did not meet the predefined inclusion criteria. These individuals were subsequently dropped from the study, ensuring that the final analysis only included patients who fulfilled the specified criteria. Furthermore, the treatment category/regimen as variable was useful to specify and categorize the people enrolled on first-line either on the second line treatment throughout the e-TB system. Thus, those who were on the first-line treatment and met all the requirements were retained for the study.

The quality of data in the electronic system is linked to the data checking and validation process organized and conducted quarterly across the country by the National TB program in close collaboration with District hospital to ensure the accuracy and reliability of the data regularly uploaded into the electronic system.

3.7. Data analysis procedure

The cleaned data was exported to the STATA 14.0 software package for further analysis. The frequency and proportions were used to describe the socio-demographic characteristics and clinical factors of the study participants. A bivariate logistic regression was performed to assess the association between each explanatory variable and the outcome of interest, mortality. Thereafter, the multivariate logistic regression model was computed to control all significant variables retained in bivariate analysis. Adjusted odds ratio, and confidence interval of 95%, and a p-value of less than 0.05 were considered statistically significant.

3.8. Ethical considerations

Ethical clearance and approval were obtained from the Institutional Review Board (IRB) of the University of Rwanda, College of Medicine and Health Sciences (CMHS/IRB/126/2023). A confidentiality agreement between the principal investigator and Rwanda Biomedical Center was agreed upon on data use and the privacy of patient information. Names and other identifier of patients were encrypted during the analysis process and the full dataset is locked with a password to ensure confidentiality during and after the study, therefore, the principal investigator is the only person to access data.

CHAPTER FOUR: RESULTS

4.1. Univariate analysis

4.1.1. General characteristics of study participants

Throughout the National TB electronic case-based surveillance system, 16,798 patients with tuberculosis were reported in the country from FY 2019/2020 to FY 2021/2022. Of these, 15,956 (95%) depicted TB patients with their treatment outcome evaluated in the e-TB system. Considering the study's exclusion criteria, only 14,451 patients enrolled on TB first line treatment were retained as study participants. A total of 896 (5.6%) children aged under 15 years old, 342 (2.1%) individuals lost to follow-up, 132 (0.8%) treatment failures, and 137 (0.9%) with TB drug-resistance were excluded from the study due to not meeting the conditions (Figure 2).

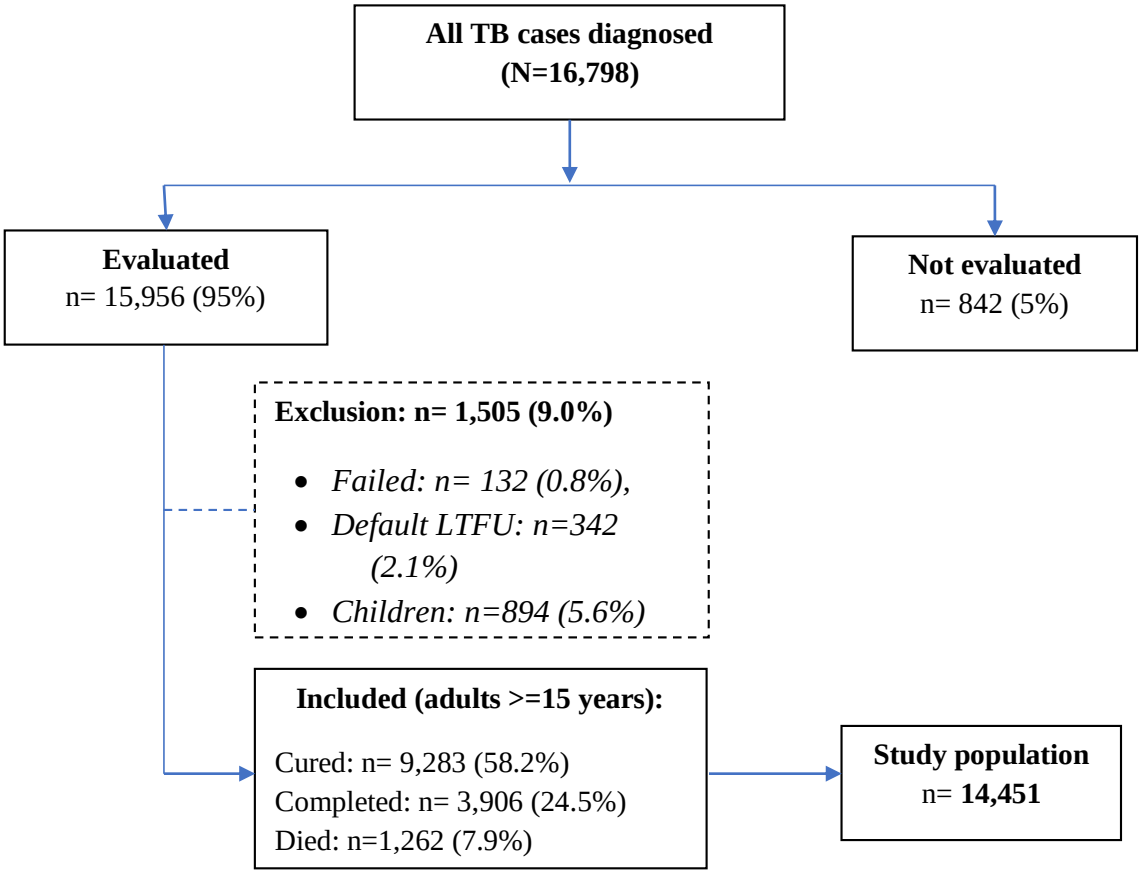


Figure 2: Flowchart of recruitment of study participants

4.1.2. Participants' socio-demographic characteristics

As shown in Table 1, the majority of patients with drug-susceptible tuberculosis were between the ages of 15 and 34 (40.8%) and 35 to 54 (41.0%). Male patients (72.4%) outnumbered female patients (27.6%). The mean age of the subjects was 40.3 (SD +15 years). Most study participants were reported in Kigali City (29.4%), followed by Eastern Province (24.4%), Southern Province (22%), Western Province (15.9%), and the least (8.3%) in Northern Province (Figure 3). At the health facility level, the results indicate that predominant proportion of TB patients were notified through health centers (62.5%, n=9029) and 21.9% (n=3169) in the district hospitals. At initial treatment, 42.7% of TB patients who enrolled in first-line treatment had a body mass index (BMI) less than 18.5 kg/m2. Those who worked in mining represented 1.1% while 13% were inmates treated for tuberculosis.

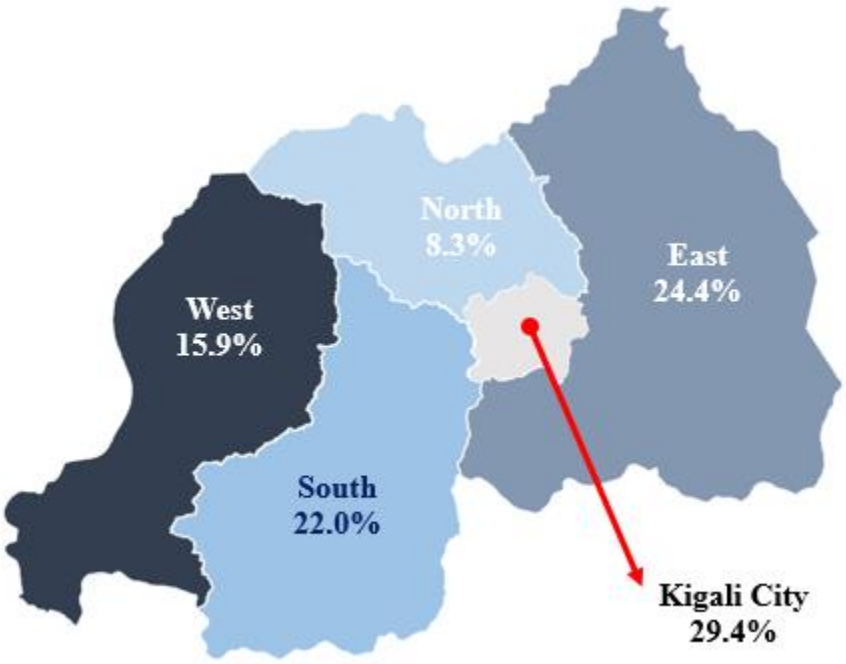
Table 1: Socio-demographic characteristics of TB patients enrolled on first-line treatment

Attribute	Frequency (n=14,451)	Percentage (%)
Gender		
Male	10463	72.4
Female	3988	27.6
Age (Years)		
15-34	5900	40.8
34-54	5924	41
55+	2627	18.2
Health Facility Level		
Health Centres (HC)	9029	62.5
District Hospital (DH)	3169	21.9
Referral Hospitals (CHUs, RH,PH)	2253	15.6
Body Mass Index (BMI)		
BMI less than 18.5	7702	42.7
Normal BMI (18.5-24.9)	6169	53.3
Overweight (>25)	580	04.0
Working in Mining		
No	14293	98.9
Yes	158	1.1
Prisoners		
Yes	1845	13
No	12571	87
Health care providers		
No	14367	99.4
Yes	84	0.6
Health community workers		

No	14357	99.3
Yes	94	0.7

** CHUs: Teaching Hospital, RH: Referral Hospitals, PH: Provincial Hospital*

Figure 3 . Distribution of study participants by residence



4.1.3. Clinical characteristics of the study participants

Based on the clinical characteristics of the study participants, Table 2 provides key insights. The majority of TB patients, accounting for 91.3% (13,194/14,451), were newly diagnosed with tuberculosis. Out of all the patients, 83% had pulmonary tuberculosis. Among the diagnosed cases, bacteriologically confirmed represented 78%, while clinically diagnosed cases accounted for 22%. In terms of TB high-risk groups (HRG), the study found that 9.2% (1,332/14,451) of the study participants were contacts of TPB+, with 0.5% being contacts of MDR-TB, and 0.7% having diabetes mellitus. Additionally, 17.5% of people are infected with both TB and HIV. Notably, a significant number of PLHIV were initiated on antiretroviral treatment, with 92.8% (2359/2542) receiving ART. Furthermore, 73% (1855/2542) of these patients received Cotrimoxazole during their TB treatment course.

The current study findings indicate that 81.8% (11,817/14,451) of patients enrolled in first-line treatment did not receive nutritional support during their TB treatment course. Additionally, only 41.1% (5,945/14,451) of patients were followed-up in the community by CHWs through Directly Observed Treatment, Short-course (DOTS).

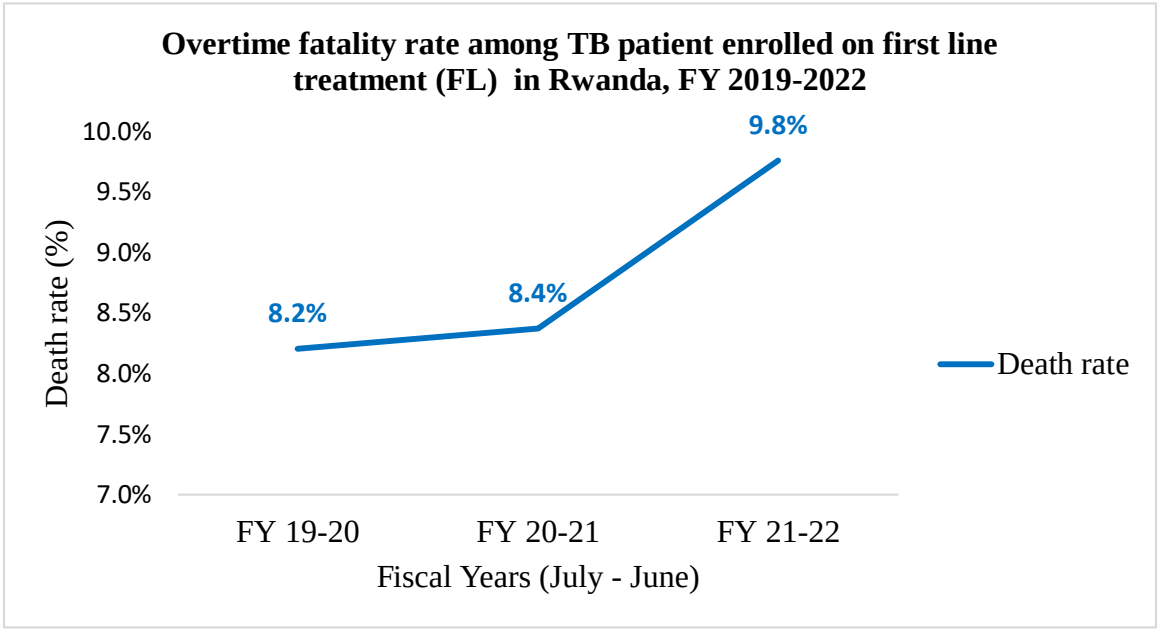
Table 2: Clinical characteristics of TB patients on first-line treatment in Rwanda

Attribute	Frequency (n=14,451)	Percentage (%)
Contact TPB+		
No	13119	90.8
Yes	1332	9.2
Contact MDR-TB		
No	14376	99.5
Yes	75	0.5
Diabetic Mellitus		
No	10023	69.4
Yes	108	0.7
Unknown	4320	29.9
History of HIV (n=2,576)		
People living with HIV (PLHIV)	1889	73.3
Newly tested-positive	687	26.7
Method of confirmation		
Bacteriologically confirmed	11270	78.0
Clinically diagnosed	3181	22.0
Site of Disease		
Pulmonary	12057	83.4
Extra-pulmonary	2394	16.6
Previously treatment history		
TB case newly treated	13194	91.3
Retreated TB cases	1257	8.7
Start immediately TB treatment		
No	143	1.0
Yes	14308	99.0
Currently on ART (n=2,542)		
Yes	2359	92.8
No	183	7.2
Currently on Cotrimoxazole (n= 2,542)		
Yes	1855	73
No	687	27
Nutrition Support		
Yes	2634	18.2
No	11817	81.8
Followed by CHW		
Yes	5945	41.1
No	8506	58.9

4.1.4. Prevalence of mortality among the study participants

The overall prevalence of mortality among TB patients enrolled in first-line treatment in Rwanda was found to be 8.7% (1262/14,451) from July 2019 to 2022. Figure 3 illustrates the proportions of case fatality rates (CFR) over time among the research individuals who received first-line treatment. Moreover, an upward trend in the CFR was observed over time, with an increase of 1.4% in the death rate from FY 2020-2021 to FY 2021-2022 compared to the previous fiscal year, where a slight increase of 0.2% was observed. Furthermore, Tables 4 and 5 provide noteworthy findings regarding specific subgroups exhibiting higher mortality rates. For example, individuals with comorbidities like diabetes mellitus experienced a death rate of 19.4%. Similarly, clinically diagnosed TB patients had a death rate of 17.1%.Patients with co-infection of TB/HIV had a death rate of 16.9%, while patients with extra-pulmonary TB accounted for 14.8%. Elderly individuals aged 55 years and above had a death rate of 15.1%. Those treated at district and referral hospitals had mortality rate of 15.4% and 15.5% respectively. Additionally, individuals with BMI lower than 18.5 kg/m2 had a mortality rate of 11.7%.

Figure 4 : Fatality rate over time among TB patients enrolled in first-line treatment, from July 2019 to June 2022



4.1.5. Distribution of mortality rate per district among TB patient on first-line treatment

In regard of table 3, it shows that mortality rate remains high in all provinces and some districts. The majority of the death occurred in the district of Nyarugenge (11%), Rwamagana (10%), Kicukiro (10%), Gasabo (8%), Huye (7%), and Ngoma (4%). Other remains districts are less than or equal to 3%. With aggregation of districts within district in terms of the rates, we demonstrated that death are distributed as follows: South province with 9% (286/3178), Kigali City with 8.8% (373/4255), Eastern province 8.7% (307/3522), Northern province 8.6% (104/1204), and then the Western province accounted for 8.4% (192/2292). Considering sub-district levels, a majority of them, specifically more than 53% (24 out of 45), exhibited a high case fatality rate. This range of case fatality rates varied from 8.7 to 22%, with the average being 12%. Notably, a significant contribution to the national rate of 8.7% can be attributed to specific district hospitals' catchment areas. These areas include Masaka (9.7%), Rwamagana (9.6%), Nyarugenge (8.6%), Kibagabaga (8.5%), and Kabutare with 7.3% (Appendix.2).

Table 3: Proportion and rate of death per district within the Province, July 2019 to June 2022

Geographical location	Completed	Cured	Died	Total	Proportion (%)	Death rate
Eastern Province	**768**	**2447**	**307**	**3522**	**24%**	**8.7%**
Bugesera District	60	261	22	343	2%	6.4%
Gatsibo District	37	286	23	346	2%	6.6%
Kayonza District	83	273	35	391	3%	9.0%
Kirehe District	106	216	26	348	2%	7.5%
Ngoma District	58	263	49	370	4%	13.2%
Nyagatare District	106	209	31	346	2%	9.0%
Rwamagana District	318	939	121	1378	10%	8.8%
Kigali City	**1386**	**2496**	**373**	**4255**	**30%**	**8.8%**
Gasabo District	296	831	107	1234	8%	8.7%
Kicukiro District	442	722	123	1287	10%	9.6%
Nyarugenge District	648	943	143	1734	11%	8.2%
North Province	**253**	**847**	**104**	**1204**	**8%**	**8.6%**
Burera District	36	74	9	119	1%	7.6%
Gakenke District	40	102	13	155	1%	8.4%
Gicumbi District	35	161	33	229	3%	14.4%
Musanze District	105	319	28	452	2%	6.2%
Rulindo District	37	191	21	249	2%	8.4%
Southern Province	**644**	**2248**	**286**	**3178**	**23%**	**9.0%**
Gisagara District	50	317	22	389	2%	5.7%

Huye District	200	554	92	846	7%	10.9%
Kamonyi District	61	234	43	338	3%	12.7%
Muhanga District	50	429	26	505	2%	5.1%
Nyamagabe District	109	144	26	279	2%	9.3%
Nyanza District	102	232	40	374	3%	10.7%
Nyaruguru District	23	51	9	83	1%	10.8%
Ruhango District	49	287	28	364	2%	7.7%
West Province	**855**	**1245**	**192**	**2292**	**15%**	**8.4%**
Karongi District	85	207	35	327	3%	10.7%
Ngororero District	49	75	23	147	2%	15.6%
Nyabihu District	82	87	12	181	1%	6.6%
Nyamasheke District	91	146	40	277	3%	14.4%
Rubavu District	308	450	37	795	3%	4.7%
Rusizi District	188	201	31	420	2%	7.4%
Rutsiro District	52	79	14	145	1%	9.7%
Total	**3906**	**9283**	**1262**	**14451**	**100%**	**8.7%**

4.2. Bivariate logistic regression analysis

4.2.1. Relationship between individual characteristics and mortality among TB patients on first-line treatment

The bivariate logistic regression analysis between each variable from individual socio-demographic and clinical characteristics against the outcome of interest revealed a significance with a p-value less than 0.05 and associated with mortality among TB patients undertaken first-line treatment regimen as shown in Table 4-5. However, the patients between 35-54 years old were 1.63 times more likely to have the risk of dying (COR=1.63, 95% CI: 1.41-1.88), and those older than 55 years old were 2.99 times more likely to die (COR=2.99,95% CI: 2.57-3.48), both compared to patients aged between 15-34 years. Women had 26% higher odds of dying with TB (COR=1.26, 95% CI: 0.08-0.10) compared to men. The study indicates that the individuals with a BMI below 18.5 kg/m2 at the moment of TB diagnosis were almost 2 times more likely to have the risk of dying from tuberculosis (COR=1.94, 95% CI: 1.72-2.19) compared to patients with normal body mass index (BMI:18.5-24.9). The likelihood of mortality was 3.02 times higher among TB patients clinically diagnosed (COR=3.02, 95% CI: 2.68-3.06) compared to those who had TB bacteriologically confirmed. It showed that the risk of death among individuals with extra-pulmonary TB was 2.14 times more likely (COR=2.14, 95% CI: 1.88-2.44) compared to patients with pulmonary tuberculosis. According to the analysis of the previous treatment history, patients newly diagnosed had a 1.26 times higher risk of dying (COR=1.26, 95% CI: 1.01-1.58), compared

to those who had received treatment for recurrent tuberculosis. Patients who had contact with a TB index case or TB bacteriologically confirmed had 62% lower odds of dying from tuberculosis (COR=0.38, 95% CI: 0.29-0.51) compared to patients who did not have contact with a TB index case patient. Prisoners had 32% reduced odds of dying from TB (COR=0.68, 95% CI: 0.56-0.83) compared to non-prisoners.

About commodity, the study revealed that the risk of dying among patients with diabetes mellitus was 2.51 times more likely (COR=2.51, 95% CI: 1.55-4.06) compared to patients without diabetes. Of the patients co-infected with both TB and HIV, those who had not started anti-retroviral treatment (ART) were 9.39 times more likely to have a higher risk of dying (COR=9.39, 95% CI: 6.83-12.90) than those who had started ART. The patients who were also not currently on Cotrimoxazole prophylactic therapy (CTX) had 1.39 times more likely to have a risk of dying (COR=1.39, 95% CI: 1.11-1.74) compared to co-infected TB/HIV patients put on CTX. According to the health care settings, patients who sought care at district hospitals had 3.68 times higher odds of dying from TB (COR=3.68, 95% CI: 3.21-4.23) compared to patients who sought care at primary health care centres. This was also observed for the patients who sought care at referral hospitals (COR=3.71, 95% CI: 3.19-4.31), where the risk of dying was 3.71 more likely compared to those who followed up at health centers. The patients who were not followed up with by community health workers (CHWs) during the TB treatment course were 3.25 times more likely to have a risk of dying (COR=3.25, 95% CI:2.81-3.75) compared to those who did not.

Table 4 : Bivariate logistic regression analysis of socio-demographic factors associated with mortality among TB patients first-line treatment in Rwanda

Attributes	Outcome		Bivariate			p-value
	Dead (%)	Alive (%)	COR	95% CI		
	n= 1,262	n= 13,189		Lower	Upper	
Gender						
Male	858 (8.2%)	9605 (91.8%)	**Ref**			
Female	404 (10.1%)	3584 (89.9%)	1.26	0.08	0.10	**<0.0001**
Age (Years)						
15-34	332 (5.6%)	5568 (94.4%)	**Ref**			
35-54	510 (8.8%)	5262 (91.2%)	1.63	1.41	1.88	**<0.0001**
55 and above	420 (15.1%)	2359 (84.9%)	2.99	2.57	3.48	**<0.0001**
Health Facility Level						
Health Centres (HC)	425 (4.7%)	8604 (95.3%)	**Ref**			

District Hospital (DH)	488 (15.4%)	2681 (84.6%)	3.68	3.21	4.23	**<0.0001**
Referral Hospitals	349 (15.5%)	1904 (84.5%)	3.71	3.19	4.31	**<0.0001**
Body Mass Index (BMI)						
Normal BMI (18.5-24.9)	493 (6.4%)	7208 (93.6%)	**Ref**			
BMI less than 18.5	723 (11.7%)	5446 (88.3%)	1.94	1.72	2.19	**<0.0001**
Overweight (18.5 and above)	46 (7.9%)	535 (92.1%)	1.26	0.92	1.72	0.154
Residence (Province)						
East	307 (8.7%)	3215 (91.3%)	**Ref**			
North	104 (8.6%)	1100 (91.4%)	0.99	0.78	1.25	0.933
Kigali City	373 (8.8%)	3882 (91.2%)	1.01	0.86	1.17	0.939
South	286 (9%)	2892 (91%)	1.04	0.87	1.23	0.684
West	192 (8.4%)	2100 (91.6%)	0.96	0.79	1.16	0.651
Health care providers						
No	1260 (8.8%)	13107 (91.2%)	**Ref**			
Yes	2 (2.4%)	82 (97.6%)	0.25	0.06	1.03	0.056
Health community workers						
No	1259 (8.8%)	13098 (91.2%)	**Ref**			
Yes	3 (3.2%)	91 (96.8%)	0.34	0.11	1.08	0.069
Mining						
No	1254 (8.8%)	13039 (91.2%)	**Ref**			
Yes	8 (5.1%)	150 (94.9%)	0.55	0.27	1.13	0.105
Prisoners						
No	1142 (9.1%)	11429 (90.9%)	**Ref**			
Yes	120 (6.4%)	1760 (93.6%)	0.68	0.56	0.83	**<0.0001**

Table 5: Bivariate logistic regression analysis between clinical characteristics and mortality in TB patients on first-line treatment in Rwanda

Variables	Outcome		Bivariate			p-value
	Dead (%)	Alive (%)	COR	95% CI		
	n= 1,262	n= 13,189		Lower	Upper	
Contact TPB+						
No	1212 (9.2%)	11907 (90.8%)	**Ref**			
Yes	50 (3.8%)	1282 (96.2%)	0.38	0.29	0.51	**<0.0001**
Contact MDR-TB						
No	1259 (8.8%)	13117 (91.2%)	**Ref**			
Yes	3 (4%)	72 (96%)	0.43	0.14	1.38	0.157
Diabetic Mellitus						
No	880 (8.8%)	9143 (91.2%)	**Ref**			
Yes	21 (19.4%)	87 (80.6%)	2.51	1.55	4.06	**<0.0001**
unknown	361 (8.4%)	3959 (91.6%)	0.95	0.83	1.08	0.408

Method of confirmation						
Bacteriologically confirmed	719 (6.4%)	10551 (93.6%)	**Ref**			
Clinically diagnosed	543 (17.1%)	2638 (82.9%)	3.02	2.68	3.40	**<0.0001**
Site of Disease						
Pulmonary	907 (7.5%)	11150 (92.5%)	**Ref**			
Extra-pulmonary	355 (14.8%)	2039 (85.2%)	2.14	1.88	2.44	**<0.0001**
Previously treatment history						
Retreated TB cases	90 (7.2%)	1167 (92.8%)	**Ref**			
TB case newly treated	1172 (8.9%)	12022 (91.1%)	1.26	1.01	1.58	**0.039**
History of HIV						
Newly tested Positive	305 (16.2%)	1583 (83.8%)	**Ref**			
People living with HIV	124 (19%)	530 (81%)	1.21	0.96	1.53	0.099
Currently on Cotrimoxazole						
Yes	289 (15.6%)	1566 (84.4%)	**Ref**			
No	140 (20.4%)	547 (79.6%)	1.39	1.11	1.74	**0.004**
Currently on ART						
Yes	320 (13.6%)	2039 (86.4%)	**Ref**			
No	109 (59.6%)	74 (40.4%)	9.39	6.83	12.90	**<0.0001**
Nutrition Support						
Yes	225 (8.5%)	2409 (91.5%)	**Ref**			
No	1037 (8.8%)	10780 (91.2%)	1.03	0.89	1.20	0.701
Followed by CHW						
Yes	240 (4%)	5705 (96%)	**Ref**			
No	1022 (12%)	7484 (88%)	3.25	2.81	3.75	**<0.0001**

4.3. Multivariate logistic regression analysis

4.3.1. Factors associated with death in TB patients receiving first-line therapy in Rwanda

The modeling with multivariate logistic regression analysis controlled for the significant independent variables retained in the bivariate analysis. Potential predictors for mortality include patients who were underweight or had a BMI below 18.5 at initial diagnosis of TB (aOR=1.78, 95% CI: 1.39-2.28), having a TB clinical diagnosis (aOR=1.72, 95% CI: 1.27-2.34), and not currently being started on ART (aOR=9.22, 95% CI: 6.39-13.29). Additionally, being managed in the referral hospitals (aOR=2.58, 95% CI: 1.77-3.76) as well as in the district hospitals (aOR=2.18, 95% CI: 1.58-3.01), and not followed up with by CHWs (aOR=2.68, 95% CI: 1.92-3.74) were significantly associated with mortality in the full adjusted model (Table 6). Particularly for inmates, the risk of dying from tuberculosis was 65% lower for individuals in prison (aOR=0.35, 95% CI: 0.16-0.78) compared to those who were not in prison, this was obviously a protective factor.

Table 6 : Multivariate logistic regression analysis

Variables	AOR	(95% CI)	p-value
Gender			
Male	**Ref**		
Female	0.91	(0.71-1.16)	0.445
Age (Years)			
15-34	**Ref**		
35-54	0.90	(0.69-1.17)	0.428
55 and above	1.13	(0.78-1.65)	0.524
Health Facility level			
Health Centers (HC)	**Ref**		
District Hospital (DH)	2.18	(1.58-3.01)	**<0.0001**
Referral Hospitals (CHU, RH, PH)	2.58	(1.77-3.76)	**<0.0001**
Body Mass Index (BMI)			
Normal BMI (18.5-24.9)	**Ref**		
BMI less than 18.5	1.78	(1.39-2.28)	**<0.0001**
Overweight (18.5 and above)	0.89	(0.48-1.64)	0.709
Prisoners			
No	**Ref**		
Yes	0.35	(0.16-0.78)	**0.010**
Contact TPB+			
No	**Ref**		
Yes	1.17	(0.63-2.20)	0.617
Diabetic Mellitus			
No	**Ref**		
Yes	1.21	(0.35-4.13)	0.763
Unknown	0.91	(0.70-1.19)	0.502
Method of Confirmation			
Bacteriologically confirmed	**Ref**		
Clinically diagnosed	1.72	(1.27-2.34)	**<0.0001**
Site of disease			
Pulmonary	**Ref**		
Extra pulmonary	1.06	(0.75-1.50)	0.748
Previously treatment history			
Retreated TB cases	**Ref**		
TB case newly treated	1.27	(0.87-1.85)	0.211
Currently on Cotrimoxazole			
Yes	**Ref**		
No	1.29	(0.98-1.70)	0.067
Currently on ART			
Yes	**Ref**		
No	9.22	(6.39-13.29)	**<0.0001**
Followed by CHW			
Yes	**Ref**		
No	2.68	(1.92-3.74)	**<0.0001**

AOR: Adjusted Odds Ratio, CI: Confidence Interval, Ref: Reference Group

CHAPTER FIVE: DISCUSSION

This study, which used national routine surveillance data captured in individual electronic case-based systems with 14,451 study participants from July 2019 to June 2022, showed that the overall death rate among TB drug-susceptible patients in Rwanda was 8.7%. It was found to be extremely higher among patients with comorbidities, where diabetes accounted for 19.4%, co-infection TB/HIV patients for 16.9% (429/2542), clinically TB diagnosed (17.1%), elderly aged 55 years and above (15.1%), and extra-pulmonary (14.1%). As well, TB patients with BMI less than 18.5 kg/m2 (11.7%) and patients who received their treatment at referral hospitals and district hospitals had a higher death rate, at 15.5% and 15.4% respectively, compared to those who received follow up at health centers (4.7%) or in the community (4%). Moreover, death rates above the national average were observed in the most of sub-districts or hospitals' catchment areas at 51.1% (23/45). Of these, death rates ranged from 8.8% to 22% (Appendix.2). Therefore, particular attention and deep investigation in the specific regions are recommended to mitigate the current burden.

However, the main findings of our study included determining potential predictors, which were significantly associated with fatalities among TB patients on first-line treatment. These comprise the following: being underweight (BMI <18.5), being HIV-positive and not starting ART, having TB clinically diagnosed, and not being followed in the community by CHWs. Additionally, referral hospitals and district hospitals were qualified as determinants of the dependent variable. On the other hand, we found that being in prison was negatively associated with the outcome of interest, mortality, as a protective factor. The variables of age, gender, anatomical site of disease as extra-pulmonary, diabetes mellitus, and currently on Cotrimoxazole showed a positive association, but they did not show potential significance in our adjusted model, while in the other studies, there were found statistically significant. Control of sputum smears at the end of month two (C2), and HIV status were restricted in the model due to the presence of collinearity.

The high death rate is the main TB treatment outcome that hinders many national TB programs' performance to treatment success rate (TSR) below the set target, which is greater than 90%. This death rate of 8.7% remained unacceptably high compared to 6.5% targeted over FY 2020/2021 in the current TB National Strategy Plan 2019-2024, and prior studies conducted in which lower death rates were reported. In this regard, 6.7% of the death rate was found in a systematic review study conducted in Europe (29) and 5% in a study carried out in Ethiopia (30).

As far as the death rate is concerned, our findings corroborated consistently with the results reported in the National TB Program (NTP), which reported 8.8% for FY 2018/2019(31) and 8.2% for FY 2019/2020 (14) of all susceptible TB patients. This study found high death rates in patients clinically diagnosed (17.1%) and HIV-positive (16.9%) cohorts, which were nearly closer respectively to the percentages of 16% and 15% (32). The disparity in death rates in different settings may be attributed to the variance in the number of participants recruited in these various studies. Notably, the death rate in this present study was lower compared to other previous studies, for example, Nigeria (9.9%) (27), Malaysia 10.2% (33), and Zimbabwe with 22% (34).

A body mass index (BMI) less than 18.5 kg/m2 as a metric for poor nutritional status in TB patients during early therapy has been identified in different studies as a determinant for poor treatment outcomes. The majority of people with active tuberculosis are catabolic and lose weight. Low BMI, on the other hand, is significant in malnourished persons and may contribute to lowered immunity (35). This study reported a significant association between BMI < 18.5 at the initiation of treatment and mortality, the outcome of interest (aOR=1.78, 95% CI: 1.39-2.28). The finding highlights the importance of good nutritional status in improving the survival of individuals suffering from tuberculosis. This result is consistent with previous studies, which have demonstrated the impact of malnutrition on TB treatment outcomes. For example, a study by Zachariah et al. found that malnutrition was related to a greater risk of mortality among patients with tuberculosis (21).

Based on the findings of the current study, it was observed that clinical diagnosis of tuberculosis is associated with a higher risk of mortality among TB patients who received first-line therapy compared to those with bacteriologically confirmed TB (aOR=1.72, 95% CI: 1.27-2.34). The case fatality in clinically diagnosed tuberculosis patients was 17.1%, which is greater than the National objective of 6.5% by the end of 2021 and nearly three times higher than the mortality seen in the TB bacteriologically confirmed cohort (6.4%). These findings underscore the importance of timely and accurate tuberculosis (TB) diagnosis, especially in settings where there is a scarcity of medical professionals. A deeper understanding of the factors that impact the quality of medical services can aid in the identification of improved solutions for medical quality assurance (36). Clinicians should consider the potential impact of clinical diagnosis on patient outcomes and prioritize efforts to improve diagnostic accuracy and reduce mortality rates in TB patients.

Our result supports consistently other previous studies conducted in the sense that patients not on current ART were 9.22 times more likely to have the risk of dying (aOR=9.22, 95% CI: 6.39-

13.29), as compared to those who started ART. For instance, the studies conducted in Cameroon (aOR=2.45, 95% CI: 1.18-5.08) (37) and India (aOR=2.80, 95% CI: 1.15-6.81) (38) demonstrated that the risk of dying was greater for those not on ART.

A study carried out in Thailand provided evidence that delaying the initiation of antiretroviral therapy (ART) during tuberculosis treatment increases the risk of death. Additionally, the study demonstrated a significant association between the use of antiretroviral medication and a reduced risk of death (HR:0.16, CI: 0.20-0.83) (39). A systematic review and meta-analysis by Hermans et al. demonstrated also that ART was associated with a 77% reduction in mortality among co-infected TB/HIV patients (40). ARV decreases the risk of TB by 67% (95% CI: 61-73), halves TB recurrence rates, reduces mortality risk by 64-95% in cohorts studies, and prolongs survival (41). According to F. Mugusi, S. Mehta, and their colleagues, the mortality rate among TB/HIV co-infected patients remains both during and after anti-TB treatment, particularly in cases where antiretroviral treatment is not administered (42). However, to reduce the risk of death in HIV-positive patients with tuberculosis, the most recent WHO guidelines 2021 recommended beginning antiretroviral as soon as feasible, within two weeks of starting TB therapy, regardless of CD4 level or WHO clinical status (19) (43).

For drug-sensitive TB, community-based therapy was found to be more than twice as cost-effective as clinic-based care for drug-sensitive tuberculosis (44). Our findings revealed that patients who did not receive DOTS from community health workers were much more likely to die than those who were followed by CHWs. According to a recent systematic review study, community-based directly observed treatment, short course (DOTS) programs exhibited higher rates of treatment completion and cure, along with reduced mortality, compared to clinic-based DOTS. Community health workers play a crucial role in these programs as they are well-placed to provide patient education, support adherence to treatment, and prevent disengagement throughout the course of lengthy treatment regimens (44).

The study also discovered that district hospitals and referral hospitals had considerably more fatalities among TB patients enrolled in first-line therapy than health centers. This may be attributed to the country's referral system, in which patients with poor prognoses at health centers considered as lower level are transferred to district and referral hospitals for more sophisticated therapy. Moreover, patients with advanced TB who require more intensive medical care are often admitted to hospitals, and this may contribute to higher inpatient mortality rates compared to those treated at lower-level health centers.

Limitations of the study

Our study has certain limitations since we depended on secondary data. Because we extracted data from routine TB surveillance, some variables such as socio-demographic (occupation, education, marital status), social-economic characteristics (income, social category), clinical factors (adherence, level of drug absorption, viral load suppression for HIV-positive patients), behavioral factors (knowledge and attitude, alcohol use, cigarette smoking), and geographical assessment were not available for further investigation. The study especially examines the population of TB patients receiving first-line treatment in Rwanda, acknowledging that the findings may have limited generalizability to other populations or settings. Factors such as disparities in healthcare access or other variables that could potentially affect TB mortality rates might differ between populations, thereby influencing the applicability of the study's results.

The parameters such as weight and height was used in this current study to calculate the BMI accurately tied on data quality audits validated by the National TB Program across the country in collaboration with district hospitals at occasion of data quality validation meetings. However, this study proposes performing a health-care facility-based prospective study to investigate the explanatory variables of early death during and after TB treatment among TB patients on first-line treatment.

CHAPTER SIX: CONCLUSION AND RECOMMENDATION

6.1. Conclusion

The study found that 8.7% of TB patients enrolled first-line treatment in Rwanda experienced mortality, surpassing the national target of 6.5% set for the end of 2022. It emphasizes the critical importance of prompt tuberculosis diagnosis and treatment, along with the need for comprehensive healthcare services and follow-up at district and referral hospitals. Special attention should be given to underweight patients, those clinically diagnosed, or those patients not receiving antiretroviral treatment. Additionally, the study sheds light on the potential benefits of prison healthcare systems in managing TB and the role of the community. These findings could inform public health policies and interventions aimed at decreasing mortality rates in TB patients in Rwanda and other similar settings.

6.2. Recommendations

6.2.1. Concerning the stakeholders, policy, and decision-makers:

- To determine strategic interventions to address the identified factors associated with mortality in support of the community participation approach.
- To narrow the analysis to the point that allows determining probable risk factors of death at all recording and reporting levels, and discover the one with the highest contribution to the present national mortality rates.
- To advocate for the provision of nutritional support in terms of food supplements and/or dietary counselling to TB patients with BMI less than 18.5 including TB/HIV co-infection patients.

6.2.2. Concerning the Referral and district hospitals:

- To enhance the treatment of tuberculosis patients who are followed up on at referral hospitals, provincial hospitals, and district hospitals, as well as to strengthen the linkage between health institutions and CHWs.
- To implementing patient-centered care, models and the provision of psychosocial support can significantly improve the overall experience and outcomes of TB patients.

6.2.3. Concerning the Health facility and community engagement:

- To reinforce the capacity building of healthcare providers across the country in different primary healthcare settings to improve earlier diagnosis and treatment for Tuberculosis and HIV.

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APPENDIX:

Appendix 1: Ethical Clearance and approval from CMHS Institutions Review Board (IRB)

UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 20th/02/2023
Ref: CMHS/IRB/**126**/2023

NSHIMIYIMANA Kizito
Field Epidemiology Training Program (FLTP)
School of Public Health, CMHS, UR

Dear NSHIMIYIMANA Kizito

RE: ETHICAL CLEARANCE

Reference is made to your application for ethical clearance for the study entitled ***"Factors Associated with Mortality in TB Patients on First-Line Treatment in Rwanda, From July 2019 To June 2022."***

Having reviewed your application and been satisfied with your protocol, your study is hereby granted ethical clearance. The ethical clearance is valid for one year starting from the date it is issued and shall be renewed on request. You will be required to submit the progress report and any major changes made in the proposal during the implementation stage. In addition, at the end, the IRB shall need to be given the final report of your study.

We wish you success in this important study.

Prof Stefan JANSEN
Ag Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:

- Principal, College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate studies, UR

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Appendix 1: Profile of TB death rate among study participants per District Hospital catchment areas

Sub District	Completed	Cured	Died	Total	Proportion (%)	Death rate
Gatonde	2	25	1	28	0.1%	3.6%
Gisenyi	308	450	37	795	2.9%	4.7%
Ruli	14	42	3	59	0.2%	5.1%
Kabgayi	50	429	26	505	2.1%	5.1%
Kaduha	22	33	3	58	0.2%	5.2%
Gakoma	26	148	10	184	0.8%	5.4%
Gahini	31	171	12	214	1.0%	5.6%
Ngarama	6	91	6	103	0.5%	5.8%
Kibilizi	24	169	12	205	1.0%	5.9%
Ruhengeri	105	319	28	452	2.2%	6.2%
Muhima	120	395	35	550	2.8%	6.4%
Nyamata	60	261	22	343	1.7%	6.4%
Shyira	82	87	12	181	1.0%	6.6%
Ruhango	18	189	15	222	1.2%	6.8%
Gihundwe	129	87	16	232	1.3%	6.9%
Kiziguro	31	195	17	243	1.3%	7.0%
Rutongo	31	158	15	204	1.2%	7.4%
Kirehe	106	216	26	348	2.1%	7.5%
Butaro	36	74	9	119	0.7%	7.6%
Mibilizi	59	114	15	188	1.2%	8.0%
Nyagatare	86	153	21	260	1.7%	8.1%
Kibagabaga	296	831	107	1234	8.5%	**8.7%**
Rwamagana	318	939	121	1378	9.6%	**8.8%**
Nyarugenge	528	548	108	1184	8.6%	**9.1%**
Gitwe	31	98	13	142	1.0%	**9.2%**
Kibuye	44	117	17	178	1.3%	**9.6%**
Masaka	442	722	123	1287	9.7%	**9.6%**
Murunda	52	79	14	145	1.1%	**9.7%**
Mugonero	23	42	7	72	0.6%	**9.7%**
Kigeme	87	111	23	221	1.8%	**10.4%**
Nyanza	102	232	40	374	3.2%	**10.7%**
Munini	23	51	9	83	0.7%	**10.8%**
Kabutare	200	554	92	846	7.3%	**10.9%**
Gatunda	20	56	10	86	0.8%	**11.6%**
Muhororo	27	56	11	94	0.9%	**11.7%**
Kibogora	32	85	16	133	1.3%	**12.0%**
Remera	61	234	43	338	3.4%	**12.7%**
Rwinkwavu	52	102	23	177	1.8%	**13.0%**
Nemba	24	35	9	68	0.7%	**13.2%**
Kibungo	58	263	49	370	3.9%	**13.2%**
Kinihira	6	33	6	45	0.5%	**13.3%**
Kirinda	18	48	11	77	0.9%	**14.3%**
Byumba	35	161	33	229	2.6%	**14.4%**
Bushenge	59	61	24	144	1.9%	**16.7%**
Kabaya	22	19	12	53	1.0%	**22.6%**
Total	**3906**	**9283**	**1262**	**14451**	**100.0%**	**8.7%**

Source: Rwanda e-TB Study's Participants Database, FY 2019-2022