COLLEGE OF MEDICINE AND HEALTH SCIENCES

Factors associated with mortality among Drug Resistant Tuberculosis patients in Rwanda:

A Retrospective study

A research report submitted in partial fulfilment of the requirements for the award of a Master of Science in Field Epidemiology and Laboratory Management in the School of Public Health

By

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August 2019

Declaration

I, BYIRINGIRO Rusisiro, do hereby declare that this dissertation submitted for the degree of Masters of Science in Field Epidemiology and Laboratory Management in the University of Rwanda/ College of Medicine and Health Sciences is my original work and has not previously been submitted elsewhere. Also, I do declare that a complete list of reference is provided including all the sources of information quoted or cited.

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Acknowledgements

I would like to first acknowledge my supervisor who sacrificed her time to bring this study to successful completion.

My sincere gratitude goes to UR-SPH Lectures, for their skills and knowledge they transmitted to us for building our capacity,

I deeply appreciate the Government of Rwanda for the support that enabled me to undertake this Master's program.

To the authorities of the Rwanda Biomedical Center for the access to the DR TB database provided and my warm thanks go to my classmates, FELTP 4th Cohort residents at School of Public Health for their support and encouragement.

I express my deep gratitude to my wife Jeanne RIZIKI and my children: Jelyssa, Brave and Nissia who, despite my overloaded schedule, supported and encouraged me all along my academic studies.

May my mother, brother, sisters and friends find here my sincere appreciation.

Above all, glory be to Almighty God.

Abstract

Introduction: Drug Resistant Tuberculosis (DR-TB) is a global public health threat that affects thousands of people every year. The World Health Organization as per the Global tuberculosis report 2018, reported that around 10 million fell ill in 2017, due to tuberculosis disease and among them 558,000 people had drug resistant tuberculosis. This health status is associated with an increasing risk of mortality, much greater while compared to the mortality in sensitive tuberculosis patients. We aimed to assess mortality and risk factors in order to contribute to the reduction of deaths among drug resistant tuberculosis patients in Rwanda.

Methods: Our study was a retrospective cohort design and we performed a data analysis using Rwanda National Tuberculosis's drug resistance tuberculosis excel database that includes patients from July 2014 to December 2017. Socio-demographics and clinical follow up information were collected using an established register at DR-TB centers then recorded electronically in excel database at National Tuberculosis Program. We analyzed using Stata 13 software; bivariate and multiple logistic regression were used to identify potential risk factors. P-values < 0.05 were considered as statistically significant.

Results: Overall 279 DR-TB patients were enrolled in drug resistant tuberculosis (DR-TB) centers from July 2014 to December 2017 and the male to female ratio being 2.3 (194/85). The mortality rate in DR-TB patients found was 11.1% (31/279). Multivariate analysis showed that people ≥55 years old are 9 times more likely to die from DR-TB (AOR=9.7; 95%CI [1.19-20.59]), compared to people ≤54 years old with DR-TB. Patients with DR-TB whose time to sputum conversion occur after month two, are around 13 times at risk of death (AOR=13.1; 95% CI [2.9-29.1]), compared to DR-TB patients that sputum converted before month 2.

Conclusion: Our study showed that male with DR-TB were double to female and age ≥55 years old, time to sputum conversion occurring after month 2 being risk factors of death in DR-TB patients. Special consideration is needed in management of the elderly patients with DR-TB and those with sputum that do not convert within the first two months of treatment. These interventions might reduce mortality among drug resistance tuberculosis patients in Rwanda.

Keyword: Drug resistant tuberculosis, mortality, associated factors, Rwanda

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List of Acronyms

aOR: Adjusted Odds Ratio

AFB: Acid-Fast Bacilli

ART: Antiretroviral Treatment

DH: District Hospital

DOTs: Directly Observed Treatment, short course

DST: Drug Susceptibility Test

DR-TB: Drug resistance tuberculosis

HIV: Human Immunodefisciency Virus

L J: Löwenstein – Jensen

LPA: Line Probe Assay

LTBI: Latent tuberculosis infection

DR-TB: Multidrug resistance tuberculosis

MDR/RR-TB: Multidrug resistance/Rifampicin Resistance tuberculosis

MOH: Ministry of Health

MT: Mycobacterium Tuberculosis

MTB/RIF: Mycobacterium tuberculosis/ Rifampicin

OR: Odds Ratio

RR: Rifampicin Resistance

SS+: Sputum Smear positive

TB: Tuberculosis

US: United States of America

XDR-TB: Ultra Drug Resistant Tuberculosis

WHO: World Health Organization

I.INTRODUCTION

The introduction chapter presents findings relating to key concepts definitions on Drug Resistant Tuberculosis (DR-TB), for better comprehension. Secondly, the recent epidemiological situation of DR-TB worldwide, in Sub Saharan and regional countries as well Rwanda, is presented for having an overview on the DR-TB burden across the world and justifying the reason of this study. Thirdly, the objectives of this study are proposed for better understanding what we want to achieve and reach at the end of this research.

1.1. Definition of key concepts

Drug resistance: " is the reduction in effectiveness of a medication such as an antimicrobial or an antineoplastic in treating a disease or condition" (Alfarouk *et al.*, 2015).

Primary resistance for tuberculosis drugs: "Patients with TB resistant to one or more anti-tuberculosis drugs, but who have never been previously treated for TB, are said to have "primary resistance" (or "initial resistance") due to transmission of a drug-resistant strain. Primary drug resistance is a theoretical concept, as history of prior anti-tuberculosis treatment is often difficult to accurately ascertain. Resistance among new cases (defined as cases with no or < one month history of treatment) has been selected as a proxy to estimate primary resistance" (WHO, 2009).

Acquired resistance for tuberculosis drugs: "Patients diagnosed with TB who start anti-tuberculosis treatment and subsequently acquire resistance to one or more of the drugs used during the treatment, are said to have developed "acquired resistance". In the past, resistance among previously treated cases (defined as cases with ≥ one month history of treatment) was used as a proxy for acquired resistance; however, this patient category is now known to also be comprised of patients who have been re-infected with a resistant strain, and patients who were primarily infected with a resistant strain and subsequently failed therapy or relapsed" (WHO, 2009).

Mono-resistance for tuberculosis drugs: resistance to one first-line anti-TB drug only (WHO, 2008a; World Health Organization, 2014).

Rifampicin resistance (RR): "resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin,

in the form of mono-resistance, poly-resistance, Multidrug Resistance or Extensive drug resistance" (WHO, 2008a; WHO, 2014).

Poly-resistance: "resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin" (WHO, 2008a;WHO, 2014).

Multi-drug-resistant tuberculosis (DR-TB): "a form of tuberculosis (TB) infection caused by bacteria that are resistant to treatment with at least two of the most powerful first-line anti-TB medications (drugs), isoniazid and rifampin" (WHO, 2008a; WHO, 2014).

Extensive drug resistance (XDR): "resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance" (WHO, 2008a; WHO, 2014).

1.2. Background

Drug Resistant Tuberculosis (DR-TB) is a global public health threat that affects thousands of people every year. The World Health Organization as per the Global tuberculosis report 2018, worldwide in 2017, around 10 million fell ill due to tuberculosis disease. Among the 10 million of tuberculosis cases, it was estimated that 558,000 people had drug resistant tuberculosis. It's assumed that 82% of people with drug resistant tuberculosis, had multi-drug resistant tuberculosis. The latest tuberculosis surveillance data on drug resistance collected and analyzed, shows that 3.5% of new tuberculosis cases and 18% of tuberculosis cases previously treated, have multidrug resistant tuberculosis or rifampicin resistant (MDR/ RR-TB) (WHO, 2018a). The misuse of isoniazid and rifampicin over the past three decades has led to the emergence and spread of DR-TB and extensively drug resistant tuberculosis (XDR-TB) to global scale (Migliori *et al.*, 2010). The burden of multidrug resistant tuberculosis largely affects three countries across the world: India, China and the Russian federation; which together account for nearly half of the world's drug resistance tuberculosis cases (WHO, 2018a).

Sub-Saharan Africa countries are estimated having high burden of tuberculosis, however drug resistance surveillance is not well conducted or applied (Lukoye *et al.*, 2015). Effective continuous tuberculosis drug resistance system applies a routine tuberculosis drug susceptibility testing to all patients with high risk of developing TB drug resistance such as previously treated TB cases,

people contacts of DR-TB patients (Zignol *et al.*, 2012). According to the 2018 WHO tuberculosis report/TB country profile report, estimated drug resistance tuberculosis for some sub-Saharan countries, Egypt has the highest estimation of MDR/RR-TB rate: 14% in new TB diagnosed and 30% in previously treated TB cases. Drug resistance tuberculosis in for sub-Saharan countries, is ranged from 0.4% to 14% in new tuberculosis patients and from 4.4% to 35% in previously treated tuberculosis patients (WHO, 2018a). However, DR-TB even a growing concern, it is largely under-reported, compromising control efforts (WHO, 2014).

As highlighted above, worldwide it's estimated that 558,000 people had drug resistance tuberculosis in 2017, but globally in the same year, only 160,884 cases of drug resistance tuberculosis were detected and notified. Among them only 139,114 were enrolled on treatment with a second line regimen of anti-tuberculosis drugs. WHO estimated that only 28.8% of drug resistance tuberculosis cases were diagnosed and only 25% of cases received access to DR-TB treatment (WHO, 2018a). This burden of DR-TB disease, is associated with an increasing risk of mortality during anti tuberculosis drugs, much greater while compared to the mortality in sensitive tuberculosis patients (Chung-Delgado *et al.*, 2015).

In 2017, the Rwanda TB incidence rate was 57 per 100.000 population while DR-TB being 1.2 per 100.000 population. This classify Rwanda as a low incidence of TB country, the cut off within low and high TB incidence being 100 per 100.000 population (WHO, 2018a). As per the Rwanda Health Management and Information System, 5.820 TB patients were notified and have started anti tuberculosis drugs in 2018. Treatment outcomes for tuberculosis patients are defined after the course of treatment and they are the following: cured, treatment completed, treatment failure, died, loss to follow up and not evaluated. Considering 5.699 TB patients that were notified during the fiscal year 2016-2017, treatment success rate is 85.9%(4.896/5.699). Those who failed on treatment plus others who were lost to follow up, considered as potential people for developing DR-TB were 3.9%(223/5.699) (Rwanda Ministry of Health, 2018).

The Rwanda Tuberculosis Program conducted in 2005, the first TB drugs resistance survey, to determine the prevalence of Mycobacterium Tuberculosis drug resistance, among new and previously treated TB cases. The survey revealed DR-TB prevalence rates of 3.9% and 9.4% respectively among new TB cases and previously treated TB cases (Umubyeyi *et al.*, 2007). The second nationwide survey of drug resistance tuberculosis prevalence in Rwanda was conducted in

2015, where findings have shown the prevalence of DR-TB being 1.5% in tuberculosis new cases and 10.4% in previously tuberculosis cases (Rwanda Ministry of Health, 2015b).

As per the Rwanda Health Information System, the National Tuberculosis Program had detected and notified 94 drug resistance tuberculosis patients in 2018 (Rwanda Ministry of Health: HMIS). Two DR-TB centers nationwide are established since 2005; in Kibagabaga and Kabutare District Hospitals. Once a DR-TB patient is detected in any hospital, the National TB Program is informed so an ambulance is sent for transferring the patient to one of the DR-TB centers, for hospitalization during the intensive phase of treatment. The second line regimen for MDR/RR-TB patients adapted in Rwanda as shorter regimen, combines Kanamycine, Moxifloxacine, Prothionamide, Clofazimine, Isoniazide, Pyrazinamide and Ethambutol (Rwanda Ministry of Health, 2015a).

Rwanda District Hospitals perform drug susceptibility testing through GeneXpert machine, that discovers either susceptibility or resistance to Rifampicin. Thus, any patient suffering from tuberculosis found with Rifampicin Resistance (RR), is referred to one of these two DR-TB treatment centers for 2nd line tuberculosis treatment. In addition, reliable DR-TB diagnosis capacity is available in 3 references laboratories: National Reference Laboratory, Kigali and Butare University Teaching Hospitals. The LPA testing (line probe assay) which is genotype MTB-DR plus test, diagnoses rapidly the presence of mutation conferring resistance to rifampicin and isoniazid in AFB smear positive sputum specimen. The LPA testing as recommended by the National TB Program, and it is performed for TB patient diagnosed with resistance on Rifampicin by GeneXpert (Rwanda Ministry of Health, 2015a).

1.3. Problem statement

Worldwide, there is evidence that drug resistance tuberculosis is increasing (Chung-Delgado *et al.*, 2015), and this collaborates with recent studies suggesting a rising of DR-TB prevalence in Sub Saharan Africa countries (Gandhi *et al.*, 2012). The treatment of DR-TB disease is complex and more difficult to treat: longer treatment duration (that require 18 to 24 months for previously treated tuberculosis patients), drugs more expensive, more toxic with increased treatment failure and mortality. The prolonged period of DR-TB treatment may result in patient non adherence, adverse treatment outcomes such as lost to follow up, failure and death (Gandhi *et al.*, 2012; WHO, 2016; Mibei *et al.*, 2016). Multi drug resistance tuberculosis is associated with an increasing risk

of mortality during anti tuberculosis drugs. A study conducted in Peru has revealed DR-TB mortality varying between 20% to 55%, that was much greater while compared to the mortality in sensitive tuberculosis patients ranged between 4.5% to 17% (Chung-Delgado *et al.*, 2015) and treatment outcomes in DR-TB patients are worse than in patients with drug susceptible tuberculosis (Gayoso *et al.*, 2018).

Considering recent studies from Africa countries, mortality due to MDR/RR-TB are various. For instance, a study conducted in Lesotho in 2012 on the outcomes of multi drug resistance tuberculosis patients initiated on treatment, mortality was estimated at 34% for MDR/RR-TB patients who initiated second line of anti-tuberculosis drugs (Satti *et al.*, 2012). In Nigeria, a study conducted in 2014 on the outcomes of hospitalized MDR/RR-TB patients from a nationwide cohort, this reveled 15% of death that were due to MDR/RR-TB (Oladimeji *et al.*, 2014). Respectively, in south Africa, Ethiopia and Kenya, mortality due to multi drug resistance tuberculosis were 20%, 13% and 9% (Mibei *et al.*, 2016)(Alene *et al.*, 2017). The impact of comorbidities conditions on unsuccessful MDR/RR-TB treatment outcomes such as human immunodeficiency virus (HIV) infection, diabetes mellitus, chronic kidney disease and alcohol misuse are all considered as factors of worse treatment outcomes (Samuels *et al.*, 2018).

1.4. Study justification

Improving DR-TB treatment outcomes is among key five priorities actions that are recommended by the World Health Organization for addressing the DR-TB global public health challenge (Alene *et al.*, 2017).

Different studies have been conducted worldwide in developed and developing countries, on predictors of mortality in DR-TB patients. They well contributed in the understanding of key drivers of deaths imputed to multidrug resistant tuberculosis threat.

The risks factors pointed out in literature were age over 60 years, XDR resistance, previous use of second-line drugs, higher number of resistant drugs on sensitivity test. The potential risk factors cited are; diabetes as increasing risk of death and treatment failure and immunosuppression with nine-fold greater risk of death (Gayoso *et al.*, 2018). Others risk factors of mortality in DR-TB we may mention are: HIV infection, malignancy, alcohol and malnutrition. Risk of death for a TB

patient increases with number of risk factors presents in the same patient (Kashongwe, M.I. *et al.*, 2017).

However, any study on risk factors associated with DR-TB that has been conducted in Rwanda. Even we may find such studies from others countries, there is a need to assess if the same factors might be responsible for the mortality among drug resistant patients in Rwanda, hence this constituting the research gap.

This study should contribute by informing the National Tuberculosis program, on potential risk factors of drug resistant tuberculosis patients in Rwanda, then effort might be focused more on specific causes for avoiding unnecessary deaths.

1.5. Objectives

Main objective

To assess mortality and risk factors in order to contribute to the reduction of deaths among drug resistance tuberculosis patients in Rwanda.

Specific objectives

1. To determine the proportion of death among drug resistant tuberculosis patients in Rwanda,
2. To describe clinical characteristics among drug resistant tuberculosis patients in Rwanda,
3. To identify risk factors associated with mortality among drug resistant tuberculosis patients in Rwanda

Research questions

- What is the proportion of death among drug resistant tuberculosis patients in Rwanda?
- What are the clinical characteristics of drug resistant tuberculosis patients in Rwanda?
- What are the risk factors associated with mortality in drug resistant?

II. LITERATURE REVIEW

The literature review chapter presents findings relating to drug resistance tuberculosis. First, general knowledge on tuberculosis; physiopathology and diagnosis will be described. Secondly, a through literature review of the published articles will be conducted to determine possible factors related to mortality in DR-TB. For instance, age, gender, malnutrition, HIV coinfection, form of tuberculosis resistance etc…

Two key databases were used to conduct the search to determine possible factors associated: PubMed and Hinari. The following list of key words was used to identify relevant studies: drug resistance, tuberculosis, mortality. The search was complemented by a review of the reference lists of identified articles and through searches of other health-related science websites.

2.1. General on Tuberculosis disease

‘’Tuberculosis is an infectious disease, spread almost exclusively by cough aerosol, caused by the Mycobacterium tuberculosis complex. It’s characterized pathologically by necrotizing granulomatous inflammation usually in the lung (~85% of cases), although almost any extrapulmonary site can be involved’’ (Dheda, K et al. 2016). Mycobacterium tuberculosis is a small, aerobic, nonmotile bacillus, discovered by Robert Kock in 1882 (Talip *et al.*, 2013). It may infect any organs of the human (extra-pulmonary tuberculosis), but most often infects the lungs (known as pulmonary tuberculosis) (Mandell, Bennett and Dolin, 2010). It’s spread through the air while patient with tuberculosis disease (active tuberculosis) cough, spit, speak or sneeze (WHO, 2015; CDC, 2016). General symptoms and signs of the active tuberculosis (TB disease), include a persistent fever, night sweats, chills, loss of appetite, weight loss and fatigue (Mandell, Bennett and Dolin, 2010). It’s estimated that presently one-quarter of the world’s population is thought to be infected by mycobacterium tuberculosis (WHO, 2018c). There is a form called “latent tuberculosis infection (LTBI)”; while individuals infected by mycobacterium tuberculosis without any signs or symptoms, being asymptomatic. With 10% lifetime chance, the latent tuberculosis infection will progress to the active tuberculosis or tuberculosis disease. In persons living with HIV infection, the risk of developing tuberculosis disease increases nearly to 10% a year (WHO, 2018b).

Others conditions such as suppression of cellular immunity by tumor necrosis factor-α inhibitors, organ transplantation, end-stage renal disease, etc…increase the risk of post primary tuberculosis development (Jeong YJ et al, 2017).

2.1.1. Pulmonary tuberculosis

Pulmonary tuberculosis is the infection by mycobacterium tuberculosis inside the lung parenchyma (WHO, 2008a). After infection via aerosol, and breathing of a few droplets having mycobacterium tuberculosis, the pathogenesis occurs in two stages. The first stage is an asymptomatic phase that may take many years in the host, called latent tuberculosis (Sharma and Sarkar, 2018). Mycobacterium tuberculosis inside the lung, cause a hypersensitivity immune reaction which harms the lung tissue while killing the foreign microorganism. Caseating granuloma and cavitation are consequences of hypersensitivity that develops in concert with the protective host immune response. The macrophages are the primary cells infected by mycobacterium tuberculosis. Tubercle bacilli drain to the regional lymph node which also often undergo caseous necrosis. Parenchymal lung lesion plus nodal involvement forwards to the ghon's complex (Sharma and Sarkar, 2018). The clinical manifestation includes general signs with chronic respiratory signs combining cough and expectoration (Pefura-Yone *et al.*, 2014). Additional clinical manifestation of pulmonary tuberculosis may include haemoptysis, breathlessness, weight loss, anorexia, fever, malaise, wasting, and cachexia (Campbell and Bah-Sow, 2006). The clinical diagnosis of pulmonary tuberculosis is suspected in patients with relevant clinical manifestations: cough >2 to 3 weeks' duration, lymphadenopathy, fevers, night sweats, weight loss and relevant epidemiologic factors; history of prior TB infection or disease, known or possible TB exposure, and/or past or present residence in or travel to an area where TB is endemic). The confirmatory diagnosis is made by isolation of *M. tuberculosis* from a bodily secretion (eg, culture of sputum, bronchoalveolar lavage, or pleural fluid) or tissue: pleural biopsy or lung biopsy (John Bernardo et al, 2019)**.** Others validated methods for active Tuberculosis detection that can be used are: nucleic acid amplification tests using GeneXpert MTB/RIF machine and cultures (Madhukar Pai. et al, 2016).

2.1.2. Extra-pulmonary tuberculosis

Extra-pulmonary tuberculosis is a form of tuberculosis where organs others than the lungs are involved. These organs are for instance the pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges (WHO, 2008a).

WHO classification criteria defines extra-pulmonary TB as an infection by mycobacterium tuberculosis which affects tissues and organs outside the pulmonary parenchyma and represents 14% of all TB cases (Ramirez Lapausa, Menendez Saldana and Noguerado Asensio, 2015; WHO, 2018a). Extrapulmonary tuberculosis arises from the hematogenous and lymphatic diffusion of mycobacterium tuberculosis bacilli beyond the lungs after the primary infection. This form of tuberculosis that involves organs others than the lungs, arises more frequently in immunosuppressed persons and young children. In those people living with HIV, it occurs in more than 50% of cases (Public Health Agency of Canada, 2005).

2.2. Drug resistance tuberculosis

As we mentioned previously, drug resistance is the reduction in effectiveness of a medication such as an antimicrobial or an antineoplastic in treating a disease or condition (Alfarouk *et al.*, 2015). Specifically, we are working on drug resistance tuberculosis that may have different types/forms either mono resistance tuberculosis, multi-drug resistance tuberculosis or extensively drug resistance tuberculosis. Drug-resistant tuberculosis (DR-TB) is an infection by mycobacterium tuberculosis that are resistant to anti-tuberculosis medications (drugs). The common type or form is the multi-drug resistance tuberculosis (DR-TB): a form of tuberculosis infection caused by bacteria that are resistant to at least two of the most powerful first line anti tuberculosis drugs. These two potent drugs are isoniazid and rifampicin (WHO, 2008a).

"The mycobacterium tuberculosis has natural defenses against some drugs, and may acquire drug resistance through mutations. The mycobacterium tuberculosis does not have the ability to transfer genes for resistance between organisms through plasmids. Some mechanisms of drug resistance include"(Sandhu and Akhter, 2018). These mechanisms are the following:

- **Cell wall:** "The cell wall of M. tuberculosis (TB) contains complex lipid molecules which act as a barrier to stop drugs from entering the cell",

- **Drug modifying & inactivating enzymes**: "The TB genome codes for enzymes (proteins) that inactivate drug molecules. These enzymes usually phosphorylate, acetylate, or adenylate drug compounds".
- **Drug efflux systems:** "The TB cell contains molecular systems that actively pump drug molecules out of the cell".
- **Mutations:** "Spontaneous mutations in the TB genome can alter proteins which are the target of drugs, making the bacteria drug resistant" (Louw, G.E. *et al.*, 2009).

"In some TB bacteria, the acquisition of mutations can be explained by other mutations in the DNA recombination, recognition and repair machinery" (Hanekom *et al.*, 2011). "Mutations in these genes allow the bacteria to have a higher overall mutation rate and to accumulate mutations that cause drug resistance more quickly" (Ford *et al.*, 2013).

Following spontaneous chromosomal mutation, the drug-resistant mutants can be selected by poor physician prescription, poor patient adherence and poor supply or quality of drugs. Other factors such as difference of metabolism and nutrition are possible. Therefore, drug-resistant TB is mainly a man-made phenomenon. The earliest published instance of drug-resistance in Mycobacterium tuberculosis was associated with the use of streptomycin shortly after its discovery. Then combined resistance of streptomycin with other drugs such as isoniazid, pyrazinamide, ethambutol and rifampicin emerged in bacillary strains. Worldwide, the emergence of multidrug-resistant and extensively drug resistant has increasingly threatened the global control of TB. DR-TB generally indicates disease with bacillary resistance to at least Rifampicin and Isoniazid. XDR-TB is usually defined as DR-TB with additional bacillary resistance to fluoroquinolone(s) and one or more of the second-line injectable. To worsen the drug-resistance scenarios, bacillary strains designated as totally drug-resistant have been recently reported (Migliori *et al.*, 2012).

2.3. Risk factors of mortality in DR-TB patients

Regarding the death outcome, the risks factors pointed out in literature were age over 60 years, XDR resistance, previous use of second-line drugs, higher number of resistant drugs on sensitivity test. Diabetes is associated with increased risk of death and treatment failure. Immunocompromised patients had nine times greater risk of death (Gayoso *et al.*, 2018). Others risk factors of mortality in DR-TB are: HIV infection, diabetes mellitus, malignancy, alcohol and

malnutrition. Risk of death for a TB patient increases with number of risk factors presents in the same patient (Kashongwe *et al.*, 2017).

Age

The spread of tuberculosis is a global emergency and this infectious disease affect all vulnerable people, including the elderly population (age ≥65 years). Tuberculosis in aging persons remains a clinical and epidemiological issue. Older people are potentially at risk for tuberculosis especially for those never exposed to mycobacterium tuberculosis, those with latent and dormant primary infection it may be reactivated. Atypical clinical manifestations of tuberculosis in older persons can result in delay in diagnosis and initiation of treatment; so unfortunately higher rates of morbidity and mortality from this treatable infection can occur. Therapy for tuberculosis in aging individuals is challenging because of the increased incidence of adverse drug reactions (Rajagopalan, 2002).

The elderly people in developed countries, represents a large reservoir of tuberculosis infection across all ethnic and sex subsets. Clinical manifestations of tuberculosis in older adults can be uncommon and may be mixed up with age-related illnesses. Disseminated or miliary tuberculosis, tuberculous meningitis, and skeletal and genitourinary tuberculosis increase in frequency with advancing age. Miliary, or disseminated, tuberculosis arises with greater occurrence among aging patients; many cases are detected only at autopsy (Yoshikawa, 1992; Davies PD, 1997). Developed countries, including the United States, have reported an estimated of 380 million persons infected with mycobacterium tuberculosis; and around 80% of infected persons in Europe are above 50 years of age. Similar increases in the incidence of tuberculosis have been demonstrated in association with advancing age in other regions of the world, such as Southeast Asia (Davies PD, 1997).

Evidences from different studies revealed that age above 60 years old, is reported as a significant risk factor for mortality in drug resistance tuberculosis patients. As increasing in age, this is associated with an increase of general physical deterioration as well increase of comorbidities (Schnippel *et al.*, 2015; Chingonzoh *et al.*, 2018).

Sex

Globally, tuberculosis cases are reported in male than in female. In many developing countries, the ratio of male to female cases of tuberculosis is approximately 2:1. What concludes that notification rates of tuberculosis are higher in men than in women (WHO, 2004). Same findings related to the sex ratio male/female in low-income countries and countries with high prevalence, it's stated that due to various socioeconomic reasons like males being sole workers, higher chances of being employed in the unorganized sectors, smaller chances of awareness about diseases, probability of default is high and leading to male more affected by tuberculosis disease than female (Rao, 2009).

Differences in gender regarding tuberculosis epidemiology may arise either as a consequence of differences in biological functioning, differences in exposure as a consequence of differences in the societal roles of men and women. Often, these differences are hard to distinguish (Holmes, C.B et al, 1998).

HIV infection

The coinfection HIV and drug-resistant tuberculosis (DR-TB) has been reported as significant since the spread of DR-TB among immuno-suppressed patients was observed. HIV infection is a potential risk factor for all forms of tuberculosis: drug-susceptible and drug-resistant tuberculosis (Wells *et al.*, 2007). HIV-positive people are subject and vulnerable to suffer from drug-resistant tuberculosis. This situation of coinfection was observed by the rapid and deadly increase of extensively drug-resistant tuberculosis among HIV positive people in South Africa and elsewhere (Gandhi *et al.*, 2006). For people with latent infection by Mycobacterium tuberculosis, HIV infection is the strongest risk factor leading to tuberculosis disease; either drug-susceptible or drug-resistant tuberculosis (Reid *et al.*, 2006). HIV infection, Multi Drug Resistance Tuberculosis and Extensive drug resistance tuberculosis are compromising the Tuberculosis control program worldwide. Drug resistant tuberculosis, more threatens tuberculosis control because of high treatment failure and death rates, and difficulties in detection and treatment (WHO, 2008b; Ormerod, 2005). The leading cause of mortality among HIV infected patients in the developing countries is tuberculosis. People living with HIV are at a higher risk to suffer from multi drug

resistance and extensive drug resistance tuberculosis associated with increased death, and greatly reduced life time (Corbett *et al.*, 2003).

Different studies have shown a high mortality in patients with coinfection of HIV and multidrug resistance tuberculosis. In Peru more than 50% of DR-TB patients with HIV infection died within two months of diagnosis and in United Kingdom it has been estimated that DR-TB patients who are HIV infected have nine times risk of death than HIV non infected people. In South Africa (KwaZulu-Natal), in an outbreak of XDR-TB, 98%(52/53) of co-infected patients (HIV and extensive drug resistance tuberculosis) have died (Gandhi *et al.*, 2006). Evidence from a study conducted in Tanzania in 2017, on predictors for mortality among DR-TB tuberculosis patients found that HIV infection was significant risk factor for mortality among DR-TB patients (Mollel and Chilongola, 2017).

Drug-resistant tuberculosis is often associated to higher mortality rates in patients' immuno-suppressed (with HIV). Thus, a better integration of HIV and drug-resistant TB services is important, both in high HIV prevalence settings, but also in any setting where HIV co-infection is common among tuberculosis patients. Early diagnosis of drug-resistant TB and HIV, timely initiation of adequate second line anti-tuberculosis drugs and antiretroviral treatment (ART), an efficient patient support, and implementation of basic infection control measures are all essential components in the management of drug resistant TB in people living with HIV for good and effective outcomes (World Health Organization, 2014).

Alcohol use

The issue caused through alcohol consumption, its volume or the type of alcohol consumed, lead to adverse health outcomes, and constitute a key driver of poor TB treatment response (Rehm *et al.*, 2009). While comparing to patients who do not use alcohol, those who take alcohol, and especially patients who regularly consume alcohol, were found having delayed culture conversion and higher rates of treatment failure, relapse and death (Volkmann *et al.*, 2015). Regular and more use of alcohol impacts retention in care and treatment, and this is linked with missed Directly Observed Therapy (DOT) visits (Theron *et al.*, 2015). A study on multi drug resistant tuberculosis patients who consume alcohol during anti tuberculosis drugs, found out an average of 18 more missed doses in the intensive phase (Duraisamy *et al.*, 2014). Bad treatment adherence and loss to follow

up constitute ones of poor clinical outcomes in patients with active tuberculosis (Rehm *et al.*, 2009). Alcohol consumption disorders increase issues in multi drug resistance tuberculosis management and control. Alcohol use is linked to increased risk of multi drug resistance and extensively drug-resistant tuberculosis in many health settings and poor clinical outcomes among multi drug resistant tuberculosis patients (Massi *et al.*, 2011).

Alcohol use has been reported to increase the risk of certain complications during tuberculosis treatment, including hepatotoxicity, neuropathy, and psychosis (Grant AD. et al., 2010). The mechanisms by which alcohol consumption leads to poor clinical outcomes are both biological and social, including death from alcohol-related causes and default or failure due to non-adherence and adverse events (Amuha *et al.*, 2009). However, the root causes by which problem alcohol use affect tuberculosis treatment response, are poorly understood. This is due largely to difficulties in studying patients with alcohol-related consequences and a lack of detailed data on their TB treatment adherence (Theron *et al.*, 2015).

Tobacco smoking

In 2015, the Global Adult Tobacco Survey has reported that there were 879 million people using tobacco, including 721 million men and 158 million women among GATS countries. The Global Adult Tobacco Survey Atlas presents statistics from 22 countries, through Global Adult Tobacco Survey data that cover nearly 60 percent of the world's population (WHO, 2017).

It has been shown that there is substantial evidence to assume that tobacco smoking is associated with tuberculosis infection and active tuberculosis. Smokers have two times greater risk of tuberculosis infection and active tuberculosis (Lin, H.H. *et al.*, 2009). As per a systematic review study on the association between tobacco smoking and drug-resistant tuberculosis conducted in 2018, it was found substantial evidence that tobacco smoking is associated with an increased risk of drug resistance tuberculosis. Associations were also found in subgroup analyses: for multi drug resistant tuberculosis and for any drug resistant tuberculosis (Wang *et al.*, 2018). Cigarette smoking is not only strongly linked to an increased risk of tuberculosis, but also associated with the recurrence and severity of pulmonary tuberculosis (Wang *et al.*, 2018). Smoking; both current and former or passive and active, is assumed to increase the risk of contracting mycobacterium tuberculosis and of developing active tuberculosis, as well as the severity of disease and the risk

of death (Leung *et al.*, 2010). Evidence from a study conducted in Tanzania in 2017, on predictors for mortality among DR-TB tuberculosis patients found that smoking and HIV infection were significant risk factors for mortality among DR-TB patients (Mollel and Chilongola, 2017).

Adherence or compliance

As per the WHO guidelines, during tuberculosis treatment it's suggested and recommended that all patients receive directly observed therapy for the whole treatment course (WHO, 2012). The World Health Organization global targets for multidrug resistant tuberculosis treatment success and adherence are currently 75%, which is lesser than the 85% target for drug-sensitive TB. This low treatment success and adherence reveal both the increased rates of mortality and barriers to treatment adherence worldwide. A low therapeutic compliance or non-adherence to anti tuberculosis drugs increases tuberculosis prevalence and leads to emergence of new subtypes strains of mycobacterium tuberculosis resistant to regular treatment, prolonged infectiousness and worse clinical outcomes (WHO, 2011).

In addition, this involves an increase in morbidity and mortality; and in the costs of tuberculosis control programs (Palaci *et al.*, 2007). Patients suffering from tuberculosis who are not cured or non- adherent to their treatment present a major risk for individuals and community, but also pose a challenge to effective tuberculosis control (Dooley *et al.*, 2011).

Tuberculosis drug resistant patterns

The patterns of drug resistance were found as potential factors that impacts the clinical outcomes in drug resistant tuberculosis patients on anti-TB treatment (Lingshuang *et al.* (2018). Tuberculosis drug resistant patterns indicate the whole range of subtypes of mycobacterium tuberculosis resistant to anti-tuberculosis drug: mono-resistance, multidrug resistant and extensively drug resistant. Drug resistance tuberculosis substantially increases mortality (Anuwatnonthakate *et al.*, 2013). Talking specifically about one among different tuberculosis drug resistant patterns, it's suggested that patients with multi drug resistance tuberculosis, have lower cure rates and higher mortality rates than patients with drug-susceptible tuberculosis (Nathanson *et al.*, 2006). For mono-resistance tuberculosis patterns, a cohort study carried out in Thailand in 2013, showed that isoniazid mono-resistance was the most common pattern, when rifampicin mono-resistance had the highest impact on mortality (Anuwatnonthakate *et al.*, 2013).

Different studies have revealed that in health care systems with effective tuberculosis care services delivery and control programs, the success rate for drug-susceptible tuberculosis treated with first-line anti-TB medications is 95%. However, in DR-TB or rifampicin resistant the success rate is estimated between 60-70% and 30% for patients with extensively drug resistant tuberculosis (Blöndala, 2007). Evidence from two studies carried out in Denmark and US, showed that isoniazid resistance, did not affect treatment and clinical outcome of standard treatment (Bang *et al.*, 2010; Cattamanchi *et al.*, 2010).

Previous TB episodes

Recurrent episodes are defined as a new episode of TB in patients who have had TB in the past and for whom there was bacteriological confirmation of cure and/or documentation that treatment was completed. In this line such TB cases are called relapse TB cases or retreated TB cases (Glaziou Philip. et al. 2015).

Evidence from a study carried out in in Lima - Peru in 2014, revealed that larger number of previous TB episodes has been linked to higher risk of mortality (Chung-Delgado *et al.*, 2015).

In addition, findings from different studies on mortality among DR-TB tuberculosis patients found that history of previous tuberculosis was linked with DR-TB death (Roya Alavi-Naini, et al. 2013).

Side effects of DR-TB drugs

As per multiple studies, one of the most important factors leading to treatment failure is side effects of multi drug resistance tuberculosis (Yang *et al.*, 2017). Multi Drug resistance tuberculosis therapy takes long time (9 to 24 months) and the number of molecules/drugs is relatively higher than for drug susceptible tuberculosis, and thus many side effects are observed. These unacceptable adverse drug reactions, need quick recognition and interruption thus changing of regimen (Prasad, Verma and Jain, 2005).

Common adverse/side effects of multidrug resistance tuberculosis therapy that have to be regularly monitored are : rashes, gastrointestinal symptoms, psychiatric symptoms, jaundice, ototoxicity and peripheral neuropathy (Nathanson *et al.*, 2004). Psychiatric adverse effects are known and observed in the treatment of multi drug resistance tuberculosis and are associated to greater death rate and unfavorable prognosis (Tabarsi *et al.*, 2011).

Diabetes mellitus

Diabetes Mellitus usually goes with decreased immunity, and has consequences on multi drug resistance tuberculosis transmission, as it's the case with other immune-suppressive related disease like HIV (Mesfin *et al.*, 2014). Evidences from different studies showed a high prevalence of diabetes mellitus among multi drug resistant tuberculosis patients. The prevalence is estimated between 10 to 23%, and expressing this as a serious cause for concern (Aragon et al, 2003; Garcia, F., et al, 2007).

Globally, the growing prevalence of tuberculosis and diabetes mellitus comorbidity brough a new challenge to clinical management and health systems control strategy (Garcia, F., et al, 2007). It was noted that patients who suffer from diabetes mellitus complicated with tuberculosis, often their sputum culture conversion are delayed, an increased risk of death and recurrence of active tuberculosis is observed (Fengling *et al.,* 2013).

Malignancy

Malignancies or cancer and cancer treatment worsen the immune system. Cancer immunosuppression leads to tumor progression and metastasis develops by constitution of an immunosuppressive network (Kim, R. et al, 2006). Numerous malignancies show an expanding trend in immunocompromised individuals compared with the general population (Prakash, Gill and Farr, 2002). This immunodeficiency state leads to the manifestation of opportunistic infections such as tuberculosis disease. Evidences from a study carried out in Taiwan in 2014, showed that malignancy, liver cirrhosis, renal failure and miliary predicted mortality in all tuberculosis deaths (Nielsen *et al.*, 2014).

Bacteriological conversion

Sputum smears and culture conversion are often performed to assess microbiological evolution and eventually treatment response of anti TB drugs in pulmonary tuberculosis patients. The sputum sterilization confirmed by sputum and/or culture conversion, is a cardinal index of treatment success (Su *et al.*, 2011). Findings from the study carried out in Latvia in 2006, have shown that failure to achieve sputum and/or culture conversion in less than month 2 after initiation of anti TB treatment, leads to a worse treatment outcome: death, default and failure (Timothy, H.H. *et al.*,

2006). Sputum culture conversion has been confirmed by medical doctors to be helpful for ensuring the effectiveness of TB treatment. Furthermore, the sputum bacteriology conversion has been reported to be a good indicator of DR-TB treatment outcomes (Peng *et al.*, 2017).

2.4. Conceptual framework

As per findings through the literature review, looking for potential risk factors that could be associated with mortality among drug resistance tuberculosis patients, studies reported that patient related factors such as: behavior and attitudes being associated with treatment outcomes in patients with drug resistance tuberculosis. Socio demographic - economic characteristics and healthcare system as well may influence DR-TB treatment outcomes (De Vries *et al.*, 2017). Behavior and attitude as risk factors of death among patients with DR-TB such as: alcohol use, smoking and adherence or compliance to treatment, may be potential determinants of DR-TB mortality. In addition, socio demographic and economic for instance age, sex, education level may as well influence the DR-TB outcomes.

Clinical and patient related risk factors like HIV infection, diabetes mellitus, malignancy, malnutrition and alcohol were reported as increasing the risk of mortality in DR-TB patients. Also, the risk of death for a TB patient increases with number of risk factors presents in the same patient drug resistance tuberculosis (Kashongwe *et al.*, 2017). Others underlying and intermediate factors: types of resistance, greater number of previous tuberculosis episodes, side effects, chronic pulmonary heart disease, chronic respiratory insufficiency, drugs availability, clinical – laboratory investigation facilities and nutrition - financial support might influence DR-TB mortality. The figure 1 below, highlights underlying and intermediate factors that lead to death in DR-TB patients.

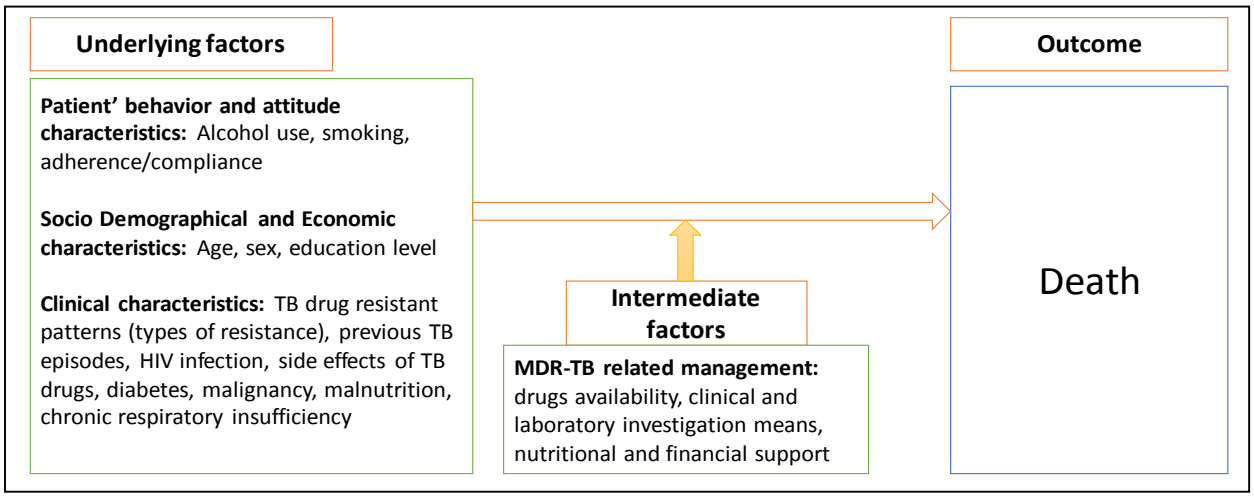

Figure 1. Conceptual Framework of DR-TB patient's mortality

III. METHODOLOGY

3.1. Study design

The current study is a retrospective cohort using secondary data of the Rwanda National Tuberculosis Program: DR-TB excel database.

The Rwanda National TB Program's DR-TB excel database is an excel sheet that was designed by the National Tuberculosis Program, a manual record performed electronically at National level. This database contains clinical information of patients diagnosed with drug resistance tuberculosis.

3.2. Study setting

The National Tuberculosis Program under Rwanda Biomedical Center/MOH, has two drug resistance tuberculosis centers, located in two district hospitals catchment area: Kabutare DH and Kibagabaga DH. Kabutare District Hospital is located in the Southern Province specifically in Huye District and Kibagabaga District Hospital is found in Kigali City - Gasabo District.

All RR(Rifampicin Resistance) and DR-TB patients diagnosed across the country; are referred either at Kabutare DR-TB center or Kibagabaga DR-TB center. After the first phase of DR-TB treatment that takes 4 months, patients are referred to the nearest health facility of their respective households, where they continue DOTs (Directly Observed Therapy). All clinical related information and treatment outcome are documented and sent back to their respective DR-TB centers and at the National Tuberculosis Program.

3.3. Study population

Our study population included all patients who were referred for rifampicin resistance and/or drug resistance tuberculosis management at Kabutare and Kibagabaga DR-TB centers, from July 2014 and December 2017. A total of 279 drug resistant tuberculosis patients referred and initiated on second line of anti-tuberculosis drugs during the period mentioned above, were included in our population cohort.

3.3. Data collection

Data were extracted from the DR-TB excel database. The Rwanda National TB Program's DR-TB excel database, is a manual record performed electronically at National level. Clinical

information of patients diagnosed with drug resistance tuberculosis are captured. When a case of drug resistance tuberculosis is diagnosed, the patient is transferred to the DR-TB center; either at Kibagabaga or Kabutare Hospital. At the DR-TB center, socio demographic, clinical as well laboratory information are documented in pre-established registers. The DR-TB patient at the DR-TB center where he is initiated on treatment, the minimum time to be spent is 4 months for the first phase. Then he/she is referred back to the nearest health facility of his/her household, where he/she continues DOTs (Directly Observed Therapy) during the second phase of DR-TB treatment. Regular clinical follow up, laboratory tests are performed up to the end of treatment and clinical related information and treatment outcomes are documented and updated within the DR-TB excel database at the National Tuberculosis Program.

3.5. Data analysis

The DR-TB excel database contains a number of variables that include: socio-demographic characteristics (age, sex, residence, DR-TB center/Hospital). In addition, the database includes clinical variables: Date of DR-TB treatment initiation, site of TB disease, HIV status, previous TB episode, previous DR-TB episode, resistance to Rifampicin, types of resistance to tuberculosis drugs and treatment outcome (date ending DR-TB treatment, cured, died, treatment failed, lost to follow up).

Measurement of variables

- **Dependent variable**

Death: death occurring during the tuberculosis treatment period: a dichotomous variable: **Yes** (died) or **No** (alive).

- **Independent variables**

a) Age: Age of the participant, categorized in 4 age groups. Two specific age groups < 15 years old and > 55 years old as classified among high risk groups for contacting tuberculosis disease as per the national tuberculosis guidelines (Rwanda Ministry of Health, 2015a). Two others age groups; of young adults (15 – 34 years old) and adults (35 – 54 years old).

However, in bivariate and multivariate analysis we considered 4 age groups**:** ≤ 24 years old, 25-34 years old, 35-54 years old and ≥ 55 years old, given that the age group below 15 years old was not found with deaths imputed to DR-TB.

b) Sex: Sex of the participant, a dichotomous variable: female or male

c) DR-TB center/Hospital: DR-TB center during the first phase of treatment, a dichotomous variable: Kubagabaga Hospital or Kabutare Hospital

d) Site of DR-TB disease: a dichotomous variable: pulmonary site or extra pulmonary site

e) HIV status: a dichotomous variable: HIV positive or HIV negative

f) Previous TB episode: a dichotomous variable: New diagnosed with TB disease or Previous episode of susceptible TB

g) Previous DR-TB episode: a dichotomous variable: New diagnosed with MTB TB disease or Previous episode of MTB TB disease

h) Tuberculosis drug resistant patterns: categorized in three categories: mono resistance to TB drugs (rifampicin or isoniazid), multi drug resistance to TB drugs (resistance for both rifampicin or isoniazid) and ultra-resistance to TB drugs (resistance to any fluoroquinolone, and at least one of three second-line injectable drugs)

i) Sputum Bacillary Load: sputum smear was graded into 3 categories: sputum bacillary load grade 1+, sputum bacillary load grade 2+, sputum bacillary load grade 3+.

j) Time to sputum smear conversion in smear positive pulmonary (bacteriological conversion): categorized into two categories: time to sputum conversion below month 2 and time to sputum conversion above month 2

A descriptive analysis has been used to compute proportions. Bivariate analysis of socio demographic and clinical variables were performed to assess differences between "**died**" during DR-TB treatment and "**alive**" during DR-TB treatment. The chi-square test comparing frequencies, corresponding odds ratio, and 95% confidence interval were computed to assess if the bivariate association between independent and dependent variables was significant and the magnitude of the association. Then logistic regression was used to examine the contribution of each independent variable in predicting death that may occur during DR-TB treatment. Full model or multivariate model was applied using binary logistic regression to control confounding then those which were found significant at a p-value of **0.05** were reported in our results.

3.6. Ethical consideration

The proposal of this study was submitted to the ethical review committee of the University of Rwanda for review and approval / ethical clearance was obtained before being implemented.

We got permission for using DR-TB excel database from the National Tuberculosis Program and data security and usage were ensured for keeping confidentiality. The electronic data were stored in computer with password that can be accessed by the principal investigator and supervisor upon request and permission.

The findings should be used by the National Tuberculosis Program for developing specific interventions in order to reduce deaths among DR-TB patients in Rwanda.

3.6. Dissemination of results

Final results of this study will be presented at the University of Rwanda, College of Medicine and Health Sciences, School of Public Health, to the Ministry of Health and Rwanda Biomedical Center – National Tuberculosis Program to guide programmatic decision making. Publication in a reputable journal and presentation of results in conferences will be processed after submitting a copy of the reports/publications to the National Tuberculosis Program.

IV. RESULTS

4.1. Background characteristics of DR-TB patients in Rwanda

A total of 279 drug resistant tuberculosis patients were referred for treatment in DR-TB centers (Kibagabaga and Kabutare DHs) in Rwanda, from July 2014 to December 2017. The table below shows the high proportion of male (69.5%), and many DR-TB patients were referred at Kabutare District Hospital (64.4%).

Table 1. Demographic characteristics of DR-TB patients in Rwanda from July 2014 – December 2017

	Frequency	Percentage
	(n=279)	%
Sex		
Female	85	30.5
Male	194	69.5
Age		
0-14	7	2.5
15-34	104	37.3
35-54	114	40.9
55+	54	19.3
DR-TB center/Hospital		
Kibagabaga DH	99	35.5
Kabutare DH	180	64.5

The table 2 below, shows that for almost all DR-TB patients registered, the site of DR-TB was pulmonary (99.3%), and most of them being primary acquired DR-TB patients (97.8%).

Table 2. Clinical characteristics of DR-TB patients in Rwanda from July 2014 – December 2017

	Frequency (n=279)	**Percentage %**
Site of DR-TB		
Extra pulmonary	2	0.7
Pulmonary	277	99.3
HIV status		
Positive	127	45.5
Negative	152	54.5
Previous TB episode		
Relapse	101	36.2
New TB case	178	63.8
Having been on anti TB 2nd line		
Yes	6	2.2
No	273	97.8
DR-TB patterns		
Isoniazid	2	0.7
Rifampicin	192	68.8
Rifampicin - Isoniazid	85	30.5
Sputum Bacillary Load		
1+	212	76
2+	28	10
3+	39	14
Time to sputum smear conversion		
Before Month 2	166	59.5
Above Month 2	113	40.5

4.2. Factors associated with mortality in drug resistance tuberculosis

4.2. Bivariate and Multivariate analysis

Given findings from multivariate analysis, patients with drug resistance tuberculosis aged above 55 years were more likely to die, than those below 55 years old; AOR=11.4 and 95%CI [1.3-24.1]. Also, patients with time to sputum conversion above month 2, were more likely to die than those with time to sputum conversion before month 2; AOR=13.1 and 95% CI [2.9-29.1].

Table 3. Biavariate and Multivariate analysis of factors associated with mortality in DR-TB

		Bivariate analysis			**Multivariate analysis**		
		Odds Ratio (OR)	**P value**	**95% CI**	**Adjusted OR**	**P value**	**95% CI**
Sex							
	Female	Ref					
	Male	1.29	0.5	0.5-3	1.1	0.808	0.4-2.7
Age							
	0-24	Ref					
	25-34	4.5	0.1	0.5-39.4	4.7	0.1	0.5-41.4
	35-54	4	0.1	0.5-32.5	4.4	0.1	0.5-37.8
	55+	**9.7**	**0.03**	**1.19-20.59**	**11.4**	**0.02**	**1.3-24.1**
DR-TB center/Hospital							
	Kibagabaga DH	Ref					
	Kabutare DH	1.36	0.42	0.6-2.9	1.02	0.9	0.4-2.3
HIV status							
	Negative	Ref					
	Positive	1.7	0.14	0.8-3.7	2.1	0.06	0.9-5.0
Previous TB episode							
	New TB case	Ref					
	Relapse	1.12	0.7	0.5-2.4	1.4	0.4	0.5.-3.4
Having been on anti TB 2nd line							
	No	Ref					
	Yes	1.62	0.6	0.1-14	1.1	0.8	0.08-9-2
DR-TB patterns							
	Rifampicin or Isoniazid	Ref					
	Rifampicin and Isoniazid	1.09	0.8	0.4-2.4	1.1	0.8	0.4-2.8
Time to sputum smear conversion							
	Before Month 2	Ref					
	Above Month 2	11.7	**0.001**	**2.74-50**	**13.1**	**0.001**	**2.9-29.1**

V. DISCUSSION

The objective of this study was to determine factors associated with mortality in drug resistance tuberculosis patients in Rwanda, from July 2014 up to December 2017, using the individual data within the patient' DR-TB excel database.

The results of this study revealed that the age above 55 years old was associated with mortality in drug resistance tuberculosis. Our findings correlate with others studies elsewhere (Kanwal, Akhtar and Ahmed, 2017; Chingonzoh *et al.*, 2018; Gayoso *et al.*, 2018). The tuberculosis disease affects all vulnerable populations including the elderly population (age ≥65 years). Older persons are potentially at risk for tuberculosis especially for those never exposed to mycobacterium tuberculosis. Older people with latent and dormant primary infection it may be reactivated. Atypical clinical manifestations of tuberculosis in older persons can result in delay in diagnosis and initiation of treatment; so unfortunately higher rates of morbidity and mortality from this treatable infection can occur. Therapy for tuberculosis in aging individuals is challenging because of the increased incidence of adverse drug reactions (Rajagopalan, 2002).

The elderly population in developed countries, represents a large reservoir of tuberculosis infection across all racial and sex subgroups. Clinical manifestations of tuberculosis in older adults can be uncommon and may be confused with age-related illnesses. Disseminated or miliary tuberculosis, tuberculous meningitis, and skeletal and genitourinary tuberculosis increase in frequency with advancing age. Miliary, or disseminated, tuberculosis occurs with greater frequency among aging patients; many cases are detected only at autopsy (Yoshikawa, 1992; Davies PD, 1997). Developed countries, including the United States, have reported an estimated of 380 million persons infected with M. tuberculosis; and around 80% of infected persons in Europe are above 50 years of age. Similar increases in the incidence of tuberculosis have been demonstrated in association with advancing age in other regions of the world, such as Southeast Asia (Davies PD, 1997).

Different factors contribute to the increased susceptibility during the old age to infectious diseases, factors that we may combine into immune dysfunction, especially T cell functional decline. In advanced age hematopoietic stem cells that give rise to the production of others blood cells, deviate from lymphoid linage to myeloid lineage. This is followed by production of monocytes,

macrophages, neutrophils, basophiles, …instead of producing more lymphoid cells that include T cells, B cells and natural killer cells, most efficient in immune response. The thymus gland shrinks after puberty and this is followed by the production of naïve T cells. In addition, T-cells receptor repertoire diversity decline as well the functional decline of B cells, have great impact on immune response in elderly age (Isobe, K. et al, 2017).

Furthermore, the advanced age is susceptible to comorbidities such as diabetes and malignancy which increase in prevalence as the age increases, and those comorbidities have been shown as potential risk factors contributing to DR-TB (Chingonzoh *et al.*, 2018). Comorbidities were not assessed as not captured in the routine DR-TB database excel sheet of the National TB program. Our study only assessed HIV co-infection on DR-TB mortality, independent factor that was found not associated with mortality. Others studies have determined that HIV co-infection constitutes a potential risk factor for mortality in DR-TB. HIV co-infected patients not receiving ART were more likely to die during DR-TB treatment (Chingonzoh *et al.*, 2018)(Schnippel *et al.*, 2015). As per the recent Rwanda National TB program annual report, the ART coverage among TB-HIV co-infected patients is above 98.4%, reason that might explain why HIV co-infection was not associated to DR-TB mortality in Rwanda country (Rwanda Ministry of Health, 2018).

In addition, the results of this study showed an association between time to sputum smear conversion and drug resistance tuberculosis mortality. It was found that DR-TB patients with time to sputum smear conversion after month 2, have higher mortality rates than those with sputum smear conversion occurring before month 2. Different studies have found similar findings: A study carried out in Latvia in 2006, have shown that failure to achieve sputum and/or culture conversion in less than month 2 after initiation of anti TB treatment, leads to a worse treatment outcome: death, default and failure (Leimane *et al.*, 2006). Also, the study conducted in China confirmed that DR-TB patients with persistent sputum positivity, their prognosis were inferior to those whose sputum bacteriology conversion was observed (Lingshuang *et al.*, 2018).

The sputum culture conversion has been confirmed by medical doctors to be helpful for ensuring the effectiveness of TB treatment, while sputum bacteriology conversion has been reported to be a good indicator of DR-TB treatment outcomes (Peng *et al.*, 2017). Also, the sputum sterilization confirmed by sputum and/or culture conversion, is a cardinal index of treatment success (Su *et al.*, 2011).

STRENGTH AND LIMITATION OF THE STUDY

The below are the strength of the study:

- As our study was retrospective cohort design, it helped to make causal inference and facilitated analyzing DR-TB patient clinical features during 2nd line TB drugs period.
- Good flow system in capturing DR-TB related data, between the TB National program, DR-TB centers and health facilities nearest to patients during the phase of continuation of second line anti TB treatment. This has helped getting DR-TB data for all patients that were detected with resistance during 3 years half.

However, there are several limitations on available data on DR-TB excel sheet database:

- DR-TB excel sheet database where all patients diagnosed and followed across the country does not capture all variables that might be needed for an exhaustive and comprehensive deep analysis.

V. CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the age ≥ 55 years old and time to sputum conversion after month 2 are significant risk factors for higher mortality rates among DR-TB patients in Rwanda. We recommend that elderly people diagnosed with DR-TB might be considered as a high risk group for specific and special close clinical follow up during the whole treatment phase of 2nd line of anti-tuberculosis drugs. The DR-TB treatment has two phases of treatment: the intensive phase spent at MDR-TB center then after the continuation phase while the patient return back at his/her nearest health facility for DR-TB treatment administration. While leaving the MDR-TB center for the continuation at health facility level, elderly people on DR-TB treatment might get clinical visits by the MDR-TB center medical team for clinical evaluation and effective management.

Based on the results from our study, a special consideration is required for patients with DR-TB disease displaying persistent sputum positivity above 2 months on treatment. An early drug susceptibility testing for 2nd line TB treatment might be performed for patients diagnosed; at the initiation of treatment even after, then adjust with sensitive and effective drugs based on drug susceptibility result.

Future studies

- There is a need to extend the DR-TB excel database, adding other variables related to DR-TB disease condition and clinical history information.

  This may help performing further research with exhaustive and comprehensive DR-TB data, in order to deeply explore others potential risk factors and contribute more in reducing the mortality due to DR-TB in Rwanda.

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