Clinical Outcomes of Patients with *Rifampicin Resistant other than Multi-Drug Resistant Tuberculosis* in Botswana; A 2006-2014 retrospective cohort analysis

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CANDIDATE'S DECLARATION

"The work contained in this dissertation was completed by the author at the University of Botswana between 2017 AND 2019. It is original work except where due reference is made and neither has been nor will be submitted for the award of any other University". Any part of this dissertation does not relate to any work previously done in connection with another qualification or award. The work of others used in any form in this dissertation were cited and indicated in the list of reference section.

Signed:  Date: 07-06-2019

Dr Lesego Kuate

DEDICATION

I would like to dedicate this work firstly to my loving and supportive husband who has been my rock throughout my academic life. My heart is filled with gratitude to God for blessing me with a loving and supportive mother who has been my cheerleader ever since I was born and my siblings for being there for me in every season of my life. I send love to my angel Abbie.

ABSTRACT

Background

Rifampicin resistant tuberculosis (RR-TB) cases were historically managed using different drug-regimen depending on the resistance patterns. *RR-TB other than MDR-TB* were treated using modified regimen (first-line regimen plus fluoroquinolone +/-amikacin). World Health Organization (WHO) recommended that all cases of RR-TB should be treated using standardized Multi-drug-resistance TB (MDR-TB) regimen since rifampicin resistance (RR) is always accompanied by isoniazid resistance (INH). However recent evidence has shown otherwise and WHO stated that country-specific data should be examined to determine the relationship between rifampicin and isoniazid resistance. The recommendation to treat all cases of RR-TB as MDR-TB cases might not be relevant in our setting since the former practice have not been evaluated.

Aim

To evaluate the clinical treatment strategies amongst patients with *rifampicin resistance other than MDR* and their impact on treatment outcomes from 2006-2014

Objectives

- To determine the prevalence of RR-TB with concomitant INH resistance among RR-TB cases
- To determine the clinical outcomes of *RR-TB other than MDR-TB* patients based on different treatment regimens
- To determine the risk factors for unfavorable outcomes of patients with *RR-TB other than MDR-TB*

Methodology

A retrospective cohort study was carried out involving the review of data of all RR-TB cases as per microbiologic confirmation from 2006 to 2014. Patients with resistance to second-line drugs and children (<15years old) were excluded. A proportion of RR-TB with concomitant INH resistance was calculated. Treatment outcomes were categorized as favorable and unfavorable. The former if patients were cured or completed treatment and unfavorable if they had treatment failure, loss to follow-up or death. Multivariate logistic regression model was used to determine predictors of unfavorable outcomes.

Results

One thousand one hundred and thirty six (1 136) cases of RR-TB were recorded from 2006 to 2014. The proportion of cases of RR with concomitant INH resistance varied by years, ranging from 61% to 90% across the years, the average being 79%. Out of two hundred and sixteen *RR-TB other than MDR-TB* patients, 79.6% (172/216) had the treatment outcome records and were included in the analysis. Of those, 66.3% (114/172) patients were initiated on first-line regimen, 20.3% (35/172) on modified regimen and 13.4% (23/172) on standardized MDR-TB regimen. The mean length of treatment was 222 (+/- 93) days) for first line regimen, 447 (+/- 177) for modified regimen and 568 (+/- 219) for MDR-TB regimen. There was no statistically significant difference in unfavorable outcomes across the three treatment groups; first-line regimen, MDR-TB and modified regimen with 27% (31/114), 22% (5/23) and 17% (6/35), respectively, Pearson chi square, 1.6, *P = 0.456.* However, 8% (9/114) treatment failure and 10% (11/114) relapse were found only among those treated with the first-line regimen. The study did not find any statistically significant predictors for unfavorable outcomes.

Conclusions

Rifampicin resistance may be a reliable proxy for MDR-TB in a significant number of cases in Botswana due to a high proportion of RR-TB with concomitant INH resistance. Though the overall treatment outcome was similar among the three regimens used, because of the potential risk of treatment failure and relapse, modified regimen and MDR-TB regimen appear to be treatment of choice in our setting.

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I would like to give a special thanks to my supervisor Dr Molefi and my co-supervisors Drs Tefera and Modongo for imparting their knowledge and skills to me and constant guidance in order to make this research a reality from its conception stage. I am also grateful to the research assistants, BNTP monitoring and evaluation staff and to the NTRL staff for assisting me with data collection.

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ABBREVIATIONS

ART- Anti-retroviral drug

DST- Drug resistant and susceptibility testing

ETR - Electronic TB Register

HIV- Human immunodeficiency virus

INH- Isoniazid

MDR- Multidrug resistant tuberculosis

M&E- Monitoring and evaluation

RMR – Rifampicin mono-resistant

RR- Rifampicin resistance

RR-TB – Rifampicin resistant Tuberculosis

TB- Tuberculosis

WHO – World health organization

OPERATIONAL DEFINITIONS

i. Resistance definition

Rifampicin resistance- *A patient with TB that is resistant to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs*

Rifampicin resistant TB other than MDR-TB (RR-TB other than MDR-TB)- *Rifampicin resistance without concomitant isoniazid (INH) resistance. It can either be mono-resistant (RMR) or poly-resistant TB*

ii. Pre-treatment classification of patients

New - *TB patient who has never received anti-TB treatment or has received anti-TB treatment for less than one month*
Relapse- *TB patient who previously received treatment and was declared "cured" or "treatment completed" AND has once again developed bacteriologically positive TB*

iii. Treatment regimen Definition

First line regimen- All group 1 drugs which are first line oral anti-TB drugs (Rifampicin, isoniazid, pyrazinamide, ethambutol with/without streptomycin)

Modified regimen- A combination of group 1 drugs (excluding Rifampicin) and group 3 drugs which are fluoroquinolones eg levofloxacin with or without group 2 drugs which are injectables (eg amikacin or kanamycin)

MDR TB regimen- A combination of the following drugs; group 2 drugs (eg amikacin or kanamycin), group 3 drugs which are fluoroquinolones eg levofloxacin , group 4 drugs which are Oral bacteriostatic second line drugs anti-TB drugs (eg ethionamide, cycloserine, p-aminosalicylic acid (PAS))

iv. Definition of treatment Outcomes

<u>For patients on First line and Modified TB regimen</u>

For the patients initiated on first line regimen, the definition of treatment outcomes for drug susceptible TB will be used as per The Botswana TB manual which was adapted from the WHO guidelines.

Cured- A patient who was initially sputum smear- positive at the beginning of treatment but who was sputum smear or culture negative in the last month of treatment and on at least one previous occasion
Treatment Completed- A patient who completed treatment but does not have a negative smear or culture results in the month of treatment and on at least one previous occasion.
Treatment Success- The sum of patients cured and those who have completed treatment.

Treatment Failure -A patient whose sputum smear or culture positive at 5 months or later during treatment or later found to have a multidrug-resistant strain at any stage of treatment, whether they are smear-negative or smear–positive.
Died-A patient who died from any cause during treatment.
Lost to follow up-A patient who interrupts treatment for two consecutive months or more.
Not evaluated- A patient whose treatment outcome is not known.

For patients on MDR TB regimen

For patients initiated on MDR-TB regimen, treatment outcomes as per the 2009 National guidelines for the management of Drug resistant TB which was adapted from the WHO guidelines was used.

Cured –A patient who has clinically improved and has taken treatment at least 18 months post culture conversion and has been consistently culture negative from samples collected at least 30 days apart (with at least 5 consecutive results) for the last 12 months of treatment.

Treatment completed - A patient who has clinically improved and has taken ATT for at least 18 months post culture conversion but does not meet the definition for cure because of insufficient bacteriological results (i.e. fewer than five cultures performed in the final 12 months of treatment)

Treatment failure- A patient with two or more positive results among the five cultures in the final 12 months of treatment or treatment stopped because of poor response or adverse effect

Died - A patient who died for any reason during the course of treatment.

Lost to follow up (previously termed Default)- A patient whose treatment was interrupted for two or more consecutive months for any reason

Successfully treated – The sum of cured and treatment completed

Composite outcomes

Favourable outcome= Either cured or completed treatment

Unfavourable outcome= Any of the following: death, Lost to follow up or treatment failure

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1. BACKGROUND

Globally tuberculosis remains a major global health issue, being the second leading cause of death from infectious disease after HIV(1). It is estimated that at least 10 million people developed tuberculosis (TB) in 2017 with 1.3 million dying from the disease (1). TB can either be drug sensitive or drug resistant (mono-resistant, poly resistant, multidrug resistant and extremely drug resistant). Rifampicin resistant TB (RR-TB) is the type that is resistant to rifampicin with or without resistance to other anti-TB drugs while Multidrug resistant tuberculosis (MDR-TB) is defined as tuberculosis caused by *Mycobacterium tuberculosis* (MTB) resistant to at least both rifampicin and isoniazid (INH) (2). *RR-TB other than MDR-TB* is rifampicin resistance without INH and can either be rifampicin mono-resistant (RMR) or rifampicin poly-resistant TB.

Rifampicin resistance (RR) without INH resistance has been reported to be rare. The samples from different continents in the world showed 95% of rifampicin-resistance with concomitant INH resistance (3). This high association of rifampicin with INH made rifampicin to be seen as a reliable proxy for MDR-TB, meaning that the detection of RR would be a strong indicator of MDR-TB (4). However, an analysis assessing whether resistance to rifampicin was a good surrogate marker for MDR-TB was performed and found that it was not a good surrogate marker in new TB cases. The use of rifampicin as a surrogate marker was found to be appropriate in previously treated cases where the prevalence of MDR-TB was above 40% with low *RR-TB other than MDR-TB* resistance (5). Traore etal concluded that the reliability of rapid rifampicin resistance detection test as a surrogate marker of MDR-TB depends on the sensitivity and specificity of the test and the prevalence of rifampicin mono resistance (RMR) in the study population(3).

Of note, in South Africa, studies have shown a rise in proportion of RMR cases amongst RR-TB cases, one in Kwa-Zulu Natal ranging from 7.3% to 10% in three years and another in Western Cape ranging from 8% in 2004 to 34% in 2008 (6, 7). Another study in Burundi also showed a rising number of rifampicin resistance with no concomitant INH resistance, the proportion of *RR-TB other than MDR-TB* amongst RR-TB cases was 25% (8). In these countries with reports of high RMR, using Rifampicin as a reliable proxy for MDR-TB is rather questionable since the previously mentioned analysis concluded that RR was a good proxy in areas of high MDR TB and low *RR-TB other than MDR-TB* resistance (5). The four surveys in Botswana carried out in 1995-1996, 1999, 2002 and from 2007-2008 showed a fluctuating proportion of RMR amongst all RR-TB cases. (9)

In 2010, WHO (World Health Organization) endorsed the Xpert MTB/RIF assay, a cartridge-based fully automated molecular diagnostic assay that uses real time PCR to identify *M. tuberculosis* complex DNA and the mutations associated with rifampicin resistance directly from

sputum specimens, in less than two hours. The evidence from the field and laboratory validations confirmed that this assay was highly sensitive(98%) with specificity of 98% in detecting *Mycobacterium tuberculosis* and Rifampicin resistance, which had been concluded to be a reliable proxy for MDR TB (10) . Following the WHO endorsement of Xpert MTB/RIF, Botswana adopted this rapid molecular diagnostic test and enrolled it in few places through partner support (11). The introduction of this rapid test required countries to be guided on how to treat RR-TB patients who have been detected within that short period of time. As a result, the WHO committee met in 2012 to provide advice on treatment of RR-TB patients and it was recommended that that all RR-TB patients must be treated using a full MDR-TB regimen (12) . There were no observational or trial studies that were available to the panel when the recommendation was made, only expert opinion using guiding principles. MDR-TB treatment, unlike the previous recommendation of drug regimen, is taken for a minimum of 18 months and has many undesirable side effects which include hearing loss and psychosis (2).

The recommendation, preceding that of 2012, by WHO on treatment of *RR-TB other than MDR*-TB (RMR and rifampicin poly-resistant TB) was to use modified regimen (all susceptible first line drugs with the addition of fluoroquinolones) for 12-18months, (13). The rationale for treatment duration of more than a year in modified regimen is that rifampicin has strong sterilizing effects and is the most potent anti-tuberculosis drug of the first line regimen (14). In the absence of rifampicin in the regimen, a shorter course therapy is associated with treatment failure relapse and further acquired resistance. A longer duration of treatment with the addition of an injectable agent was added in cases of extensive disease. If a rapid test of rifampicin resistance was used, a drug resistant and susceptibility testing (DST) was done to confirm whether it was MDR-TB or not, then treatment would be changed accordingly. There were no studies done for this recommendation as well, expert opinion was sought to come to that decision. MDR-TB regimen was used in confirmed MDR-TB cases or in cases with high suspicion of more acquired resistance. Botswana used to follow that recommendation until the new treatment recommendation was communicated by WHO in 2013 (15).

Despite the introduction of the new treatment guidelines of RR-TB guidelines, the WHO advises that country-specific data should be obtained on the frequency of concomitant INH resistance when rifampicin resistance is present (2). WHO is looking into exploring the feasibility of estimating the burden of all *rifampicin resistant other than MDR TB* cases since not much literature is available on that (10).

2. STATEMENT OF THE PROBLEM

MDR-TB treatment is taken for a minimum of 18 months and has many undesirable side effects which include hearing loss and psychosis (2). WHO has recommended that all cases of Rifampicin resistant TB (mono-resistance, poly-resistance, MDR-TB) must be treated as MDR-TB since Rifampicin resistance is often accompanied by INH resistance, however, also cautioned that country-specific data should be examined to determine the relationship between Rifampicin and INH. There is a gap in those data as Botswana has not yet conducted a formal assessment to determine (i) if indeed rifampicin resistance is always accompanied by INH in our setting (ii) if not, what is the percentage concomitance. Until outcomes have been assessed whether favorable or not, depending on different TB drug regimen used in the past, the recommendation to treat all cases of RR-TB (including *RR-TB other than MDR-TB* patients) as MDR-TB cases might not be necessary to implement. If the previously recommended regimen is comparable to the current recommended regimen, patients would be prevented from undergoing the MDR-TB treatment which is taken over a longer time and has many undesirable side effects.

The study could assist to determine the best way to proceed with the management of *RR-TB other than MDR-TB* cases in Botswana.

3. AIM AND OBJECTIVES

Aim

To evaluate clinical treatment strategies amongst patients with *rifampicin resistance other than MDR* and their impact on treatment outcomes, from 2006-2014

Objectives

- To determine the prevalence of RR-TB with concomitant INH resistance among RR-TB cases
- To determine the clinical outcomes of *RR-TB other than MDR-TB* patients based on different treatment regimens
- To determine the risk factors for unfavorable outcomes of patients with *RR-TB other than MDR-TB*

4. LITERATURE REVIEW

4.1. Prevalence of RR other than MDR-TB /RR-TB with concomitant INH resistance amongst all RR-TB patients

4.1.1. International

Globally RR-TB with INH concomitance resistance is higher in areas with high MDR prevalence as displayed by the lowest being 57% in low MDR TB setting and around 90% in high MDR TB settings (16) . The findings of the WHO world DRS report from 1992- 2002 showed RR with INH concomitance of close to 75% in America, Europe and Western pacific region among new patients. The proportion was however higher in previously treated patients only in Europe and western pacific and lower in America (53.8%). This in turn means the prevalence of *RR-TB other than MDR-TB* amongst RR-TB cases in these regions ranged between 6% and 46% (5).

A study in Iran showed RR-TB with INH concomitance resistance of less than 50% and concluded that a significant occurrence of RR-TB without INH had been verified (17). However, another study with a very low sample size in the same country showed a percentage of 89% of RR-TB with INH resistance (18). Another country that showed different results is Pakistan where a lower sample size study showed a slightly higher concomitance rate (19, 20). In UK, two studies showed a concomitance rate of just above 80% (21, 22), a finding similar to studies done in Mongolia and Bangladesh(23, 24). Other studies done in different countries like Peru and China found concomitance rate of just above 70% (25, 26) while hospital in Vietnam reported 98% (27) .

The studies quoted above show that that there is variability in RR-TB with INH concomitance in different countries.

4.1.2. Regional

The world DRS survey of 1999-2002 revealed the RR with INH resistance of 77.8% in new patients and an increase by 6% in previously treated patients in Africa (5). Although this was Africa statistics, only four countries were represented (Botswana included) and majority of patients were from South Africa. Southern Africa has the highest proportion of tuberculosis patients who are co-infected with HIV (28). A review of drug resistant TB in three high HIV burdened countries saw a lower concomitance rate of difference of 68% (29)

At least three studies done in Nigeria showed a concomitance of rate of 60% and 70% (30-32). Their findings were the same as the ones found in their neighboring country; Benin and in Malawi (33, 34). Generally, the concomitance rate varied from country to country and different regions of the African countries. The concomitance rate of just above 70% was found in studies

done in Burundi and Zimbabwe (8, 35). At least two studies done in South Africa displayed the highest concomitance rate of above 90% (7, 36).

The lowest concomitance rate of less than 50% was found in Zambia and Kenya (37), it is worth noting that these studies had low sample size and only covered certain parts of the countries. Interestingly these countries with the highest and the lowest concomitance rate (Zambia and South Africa) share a border with Botswana

4.1.3. Local- Botswana

According to the Botswana drug resistance surveys (DRS) done in 1995-1996, 1999, 2002 and 2007-2008, the cumulative proportion of RR-TB with INH resistance was 56.9 % for new patients and 66.7% for retreatment patients (9) . The proportion RR-TB with concomitant INH resistance in 2007-2008 was close to 70% in new TB patients and 50% in re-treatment patients which is quite different from the studies cited above which reported a higher concomitance rate in previously treated patients. An analysis of Botswana Gene Xpert data for tests done from October 2012 to December 2014 however showed a slightly higher proportion of RR with INH concomitance of 77.8% (38). It worth noting that this rate of RR-TB with INH concomitant resistance is still low compared to the ones that have been reported as more than 90% which led to the treatment guidelines to treat all RR-TB cases as MDR TB. From the gene Xpert data analysis findings communicated above, it means the proportion of *RR-TB other than MDR-TB* amongst all RR-TB cases was 22%, while it was 43.1 % for new patients and 33.3% for retreatment patients from the DRS (cumulative results) (9, 38). This is the population that is likely to benefit from less toxic modified regimen if the initial regimen of *RR-TB other than MDR-TB* treatment guidelines was followed.

The prevalence of RR with INH concomitance varies in the world, from country to country and from district to district within some countries. There are areas where the proportion is actually less than 50%, something that is rarely reported. Only a few countries reported concomitance rate of more than 90%, which includes South Africa. Majority of countries however reported prevalence of between 60 and 70% and the proportion reported in the studies did not differ according to sample sizes. Perhaps that is the reason why WHO recommends that each country must obtain its own data on the frequency of rifampicin with concomitant INH resistance.

4.2. Treatment outcomes of *RR-TB other than MDR-TB* per regimen

4.2.1. Patients enrolled on first line regimen

Very few randomized clinical trials have been performed to determine the best treatment for mono- or poly-resistant TB (39). A meta-analysis of the randomized controlled trials of treatment regimens for *RR-TB other than MDR-TB* had low yield of three studies with low sample sizes(two with two patients and one with five patients) (40). One of those studies carried out in Hong Kong reported outcomes of two patients who were initiated on first line drugs except for ethambutol (daily dosing vs thrice dosing) (41). Interestingly they both had negative cultures at the end of treatment however one with daily dosing had TB relapse. A multi-center study showed 100% cure rate of 5 patients who were initiated on first line drugs (except for streptomycin) across two 8-month arms (daily vs thrice weekly intensive phase) and 6-month arm (42). A similar drug regimen of two patients across different arms in India also showed 100 cure rates as well (43).

There are few observational studies looking at outcomes of patients with *RR-TB other than MDR-TB* initiated on first line regimen. A study in Saudi Arabia of 18 patients enrolled on first line regimen showed the highest cure rate of 100%, however 2 patients later relapsed (44). Two studies done in Philippines and in Korea showed cure rates of 78% while a study done in Peru showed a cure rate of 76% with 6% of patients having TB relapse (26, 45, 46). Relapse amongst patients were not reported in the last two studies (Philippines and Korea). These studies did not analyze treatment outcomes by previous treatment status, however a study done in 6 countries did that and showed a significantly lower treatment success rate among previously treated patients (47).All the observational studies cited above were assessing patients on shorter regimen (six months for new patients and 8 months for retreatment patients), however a study done in Japan assessed patients on drugs for a longer period, the cure rate was 74% (48). The conclusion was that if first line drugs are used, *RR-TB other than MDR-TB* can be cured by using four effective drugs for more than two months and at least 3 effective drugs for the total duration of 12-24 months.

Although these studies had low sample sizes, the outcomes are better than the global outcomes of all rifampicin resistant cases which is currently at showed a 52% (28)

4.2.2. Patients enrolled on modified regimen

A study in France examined patients who were enrolled on modified regimen (susceptible first line TB drugs with and without fluoroquinolone and injectable). Twenty percent of patients had treatment duration of less than 9 months while it was between 9 and 12 months for 44% of them. The remaining 37% were treated for more than 12 months (13-24months). Of the 25 cases that were analyzed, 64% had positive outcomes while the rest either died (for different

reasons not specified), relapsed (12%) and lost to follow up (12%). TB relapse occurred amongst those with treatment duration of less than 12 months (49). In another study, one of the three patients on modified regimen was cured, one died and the other one was lost to follow up (26) .

4.2.3. Patient enrolled on MDR TB regimen

Out of 818 patients with *RR-TB other than MDR-TB* patients with outcomes in South Africa, who were initiated on standardized MDR-TB regimen for 24 months, 45.2% had treatment success. the rest were unsuccessful treatment outcome (36). Majority of patients with unsuccessful treatment were due to loss to follow up followed by death. A study done in a community in South Africa however showed a slightly higher treatment success of 58% (50). Relapse rates were not reported in these studies.

There are very few studies that evaluated outcomes of *RR-TB other than MDR-TB* on patients enrolled on modified TB regimen and MDR-TB regimen. Despite that, comparing all the three regimen patients on first line regimen had higher proportion of treatment success followed by TB relapse.

4.3. Factors affecting Treatment outcomes of *RR-TB other than MDR-TB cases*

4.3.1. Favourable and unfavourable treatment outcomes

Few studies looked at the factors affecting treatment outcomes only in *RR-TB Other than MDR-TB*. With such limitation, studies discussed below were done in group of patients with other drug-resistant TB and drug sensitive TB (DS TB) which included *RR-TB other than MDR-TB*.

Several demographic factors have been seen to be associated with treatment outcomes. Males have been associated with unfavourable treatment outcomes in several studies (36, 51-53). However other studies did not find any association between treatment outcomes and gender (54). Another demographic factor associated with unfavourable treatment outcomes particularly death is advanced age (36, 52, 54).

Patients with previous TB treatment are also associated with unfavourable treatment outcomes (51, 52, 54, 55). Only one study did not show this association to be statistically significant (49). Other factors that have been seen as predictors for unfavourable outcomes are radiologic extent of the disease and initial positive smear disease (52, 54-56). In addition to that, low pre-treatment weight has also been identified as predictors of death (54)

From the above literature review, factors associated with successful or favourable treatment outcomes are females, age less than 60 years, new TB case, disease that is not extensive and BMI within normal limits.

4.3.2. HIV Status

TB and HIV are often referred to as the twin epidemics. TB is the commonest causes of illness and death among people living with HIV of all ages (57). HIV has been seen as a predictor of mortality both in area of high and low HIV prevalence rate (50, 53, 56). This could be due to the rapid progression of TB disease in the immune-compromised individuals. However, a study in France showed different results; no statistically significant difference in treatment outcomes was observed according to HIV status (49). An Irish study concluded that the quality of life amongst the HIV infected is impaired by the presence of co-morbidities (58). The studies previously mentioned did not consider the anti-retroviral therapy (ART) status of those infected. A study done in South Africa showed that HIV-infected patients on (ART) were as likely to be successfully treated as HIV-negative patients, however those who were infected and not on ART or had unknown HIIV status had high mortality risk (36). The WHO is therefore calling for all TB patients to be initiated on ART since between 2000 and 2015, among HIV-positive people, TB treatment **s**upported by ART averted an additional 9.6 million deaths (28).

5. METHODOLOGY

5.1. Study design

This is a retrospective cohort study, involving the review of data of RR-TB cases from the Botswana Electronic TB register, OpenMRS and National Tuberculosis Resistance laboratory (NTRL) from 2006 to 2014. This is the appropriate design since it examines an exposure (treatment regimen) and outcome (treatment outcome) of *RR-TB other than MDR-TB* cases using previously collected data.

5.2. Study site and study population

5.2.1. TB Data flow within Botswana

This study was carried out in Botswana. Tuberculosis control is headed by Botswana National Tuberculosis program (BNTP) which maintains national TB case registration database. The TB services are provided via different types of health facilities from health post to referral hospitals housed in different districts. TB data is collected from facilities on a monthly basis to BNTP Monitoring and evaluation (M&E) team which is kept in the electronic system called Electronic TB register (ETR) and Open Medical Record System (OpenMRS). There are six TB drug-resistance clinics in the country where drug resistant cases and complicated TB patients are referred to for consultation and follow up. These sites are in Gaborone, Francistown, Serowe, Ghanzi, Mahalapye and Maun.

TB culture and drug resistance testing in Botswana is carried out at National Tuberculosis Resistance laboratory (NTRL). The NTRL maintains national microbiologic register (culture and full DST) for all patients who have had TB drug resistance testing done. This database migrated from paper register to electronic register in 2009. Samples are couriered by road from remote health facilities across the country to NTRL by referring facility transport, for resistance testing. Distant and rural facilities usually send the samples weekly to NTRL in batches. The turnaround time for DST is 8 weeks and results are collected from NTRL and get delivered back to their requesting facilities by their transport officers. The NTRL personnel only informs the MDR-TB clinicians from the six MDR-TB clinics by means of telephone and by email if any of the samples test positive for MDR-TB and XDR-TB. Challenges faced which impact on timely delivery of results to facilities include transport issues such as shortage of vehicles in districts.

The Xpert® MTB/RIF (Xpert) was incorporated in the revised national TB guidelines in 2011 for diagnosis of TB among people living with HIV and those at risk of MDR-TB. Through partner support, thirteen devices were installed in peripheral laboratories and clinic sites in phased approach from 2012 to 2013. Samples of patients who tested RR-TB positive through geneXpert were sent to NTRL for DST to determine if it was RR-TB with concomitant INH resistance or not. Patients were then initiated on the appropriate treatment upon receiving the DST results.

However, from 2015 all cases who tested positive for RR-TB through GeneXpert were initiated on MDR-TB regimen regardless of the subsequent full DST results. In 2017 TB guidelines were revised and updated to include GeneXpert as the standard test for diagnosis in all presumed TB cases, hence more devices were procured through partner support to cover more health facilities in the country. DST was made mandatory for all bacteriologically confirmed cases. Prior to then, culture and DST was for retreatment cases, drug-resistant TB suspects and those at risk for DR-TB.

5.2.2. Inclusion Criteria

The following criteria was used for inclusion into this study.

- All files of RR-TB patients as per microbiologic confirmation in the TB register at NTRL from 2006 to 2014 and
- Were of patients aged 15 years and above and
- Were initiated on TB regimen and had treatment outcomes records

5.2.3. Exclusion criteria

- Non-RR TB cases
- Patients resistant to 2nd line TB drugs
- Patients less than 15 years of age
- No records of both TB regimen initiation and treatment outcomes

5.2.4. Source population

All RR-TB cases as per microbiologic confirmation in the TB register were identified, out of these, a subset of them (RR-TB other than MDR-TB) were included in the study to determine their treatment regimen and treatment outcomes. The rationale for the study period (2006 to 2014) is that guidelines for the programmatic management of drug-resistant tuberculosis were published in 2006 by WHO and that is when the country adopted the guidelines (13). The last cohort who would have treatment outcomes and post treatment surveillance for at least two years post MDR-TB treatment by 2018 are those who would have been initiated on MDR-TB regimen in 2014. In addition to that, in Botswana modified regimen was phased out beginning of 2015, so all RR-TB patients including the *RR-TB other than MDR-TB* were initiated on MDR-TB regimen from that period.

5.3. Data collection

A data extraction tool was developed and used to collect relevant information of the patients (demographics, clinical details, laboratory data and clinical outcomes). Data of all patients with RR-TB was extracted from NTRL and was disaggregated into MDR-TB and RR-TB other than MDR-TB. The records collected for *RR-TB other than MDR TB* were matched with those that are in the ETR (Electronic TB Register) and OpenMRS to ensure consistency. Patients' demographics and treatment regimens, and treatment outcomes were derived from both ETR and Open MRS. HIV status were derived from the ETR, Open MRS and NTRL records, however ART status were derived from OpenMRS and ETR only because it was captured in those two systems. Data collected were stored and prepared for analysis on password protected Excel sheets.

6. DATA ANALYSIS

Data analysis was carried out using Stata® version 14 (Stata corp, Texas). A subset of *RR-TB other than MDR*-TB cases was derived as a complement of the proportion of RR-TB with concomitant INH resistance (MDR-TB) out of all RR-TB patients. Baseline characteristics of patients in this subset are displayed in table (2). Normality for quantitative data such as age was checked using the Shapiro-Wilk test (59) - in this case all test p-values were less than 0.05 thus medians and interquartile ranges were used as summary measures. Categorical variables such as gender, percentages were used.

Categorical variables included gender, HIV status, previous TB history, AFB smear, resistance pattern and TB foci. Gender categories were male and female, history of previous TB as 'yes' or 'no' while resistance pattern was stratified into mono and poly resistant. HIV status were captured as either positive, negative or unknown while ART status was captured as the following; on ART, Not on ART, unknown and defaulted. Sputum smear at baseline was categorized as positive, negative and unknown. TB foci was categorized as pulmonary, extra-pulmonary and both. Age was captured as numeric variable and categorized in two groups; by median age (35years) and by another category that is used to report TB notification by WHO and BNTP.

Patients were grouped according to the treatment regimen that they were initiated on (first line, modified and MDR-TB regimen). Treatment outcomes of *RR-TB other than MDR-TB* patients were classified as favorable (cured and treatment completion) or unfavorable (treatment failure, death, *Lost to follow up*). Any occurrence of bacteriologically positive TB amongst cases after being declared either cured or treatment completed were classified as relapse at per WHO definition. Proportions of clinical outcomes of *RR-TB other than MDR-TB* patients in three different treatment groups were calculated.

Associations between the dependent variable (unfavorable outcome) and independent variables (age, gender, HIV and, ART status, previous TB history, baseline sputum smear result, resistance pattern and TB foci) were assessed by means of a binary logistic regression model, where the dependent variable was formatted as unfavorable outcomes (exposed group) vs favorable outcome (unexposed group), and generating odds ratios (OR) through bivariate logistic regression modelling. A relaxed p-value of <0.25 was employed for the selection of predictors at bivariate level for building the multivariable model in this association between unfavorable outcome and select independent factors for the bivariate binary logistic regression model. This relaxed p-value of <0.25 criterion was selected so as to avoid excluding important variables which might be statistically significant in multivariable regression (60, 61). The independent factors significant at bivariate level, were then recruited into the multivariable binary logistic regression. Unless stated otherwise, throughout the write-up, the statistical significance was set at $p<0.05$ and precision of point estimates at 95% Confidence interval.

7. ETHICAL CONSIDERATIONS

- Ethical approval to conduct the study was sought from the University Of Botswana Institutional Review Board (Ref: UBR/RES/IRB/BIO/GRAD/034) and the Research unit at the Ministry of Health and Wellness. (Reference no: HPDME:13/18/1)
- The study involved usage of secondary data so no interviews of patients were held hence waiver of consent was granted
- Strict confidentiality of all patients was ensured, by assigning each file a unique identifier for the purposes of maintaining anonymity throughout the subsequent study processes (data management to dissemination).

Electronic data derived from the data abstraction forms was kept in a password protected computer with backup. Furthermore, the data file within the computer was encrypted with a password. The data abstraction forms were kept in a locked room where there was access only to those authorized by the investigators

8. RESULTS

8.1. Prevalence of RR-TB with concomitant INH resistance among RR-TB patients

The total number of rifampicin resistant cases registered at the NTRL as per microbiologic confirmation from 2006 to 2014 was 1136 (*table 1*). The proportion of RR with concomitant INH resistance amongst RR-TB cases varied by years. It was lowest in 2009 at 98 cases, amounting to 62%. The lowest proportion of RR with concomitant INH resistance was recorded in 2006 at 62 %(95 CI 53%-69%). The highest proportion was recorded in 2010 at 90% (CI 85% -95%). The average prevalence of RR-TB with concomitant INH resistance from 2006 to 2014 was 79% (CI 76%-81%) while it was 21% (CI 19% -24%) for *RR-TB other than MDR-TB*.

Table 1 – *Prevalence of Rifampicin resistance with concomitant INH resistance from 2006 to 2014*

YEAR	Total RR-TB cases	Proportion of RR-TB with concomitant INH resistance, 95% Confidence Interval
2006	49	71%, (0.567 - 0.834)
2007	156	88%, (0.824 – 0.930)
2008	236	86%, (0.805 – 0.898)
2009	159	62%, (0.536 – 0.692)
2010	155	90%, (0.845 – 0.945)
2011	69	84%, (0.733 – 0.918)
2012	88	80%, (0.696 – 0.874)
2013	129	71%, (0.619 – 0.782)
2014	95	67%, (0.570 – 0.766)
TOTAL	1136	79%, (0.764 – 0.812)

8.2. Characteristics of RR-TB Other than MDR-TB patients

Two hundred and sixteen (216) cases of *RR-TB other than MDR-TB* cases who are more than 15 years old were registered between 2006 and 2014. Of these only 172 cases were included in the analysis as they met the inclusion criteria (figure 1).

The total number of *RR-TB other than MDR- TB* reported each year during the study period varied between 8 and 46 cases. The highest proportion of cases; 27% (46/172) were registered in 2009 followed by 2013 at 16% (28/172). The least number of cases (8/172) were registered in 2011. Majority of cases 23% (39/172)) were registered at Gaborone district followed by Kweneng-East at 14% (25/172).

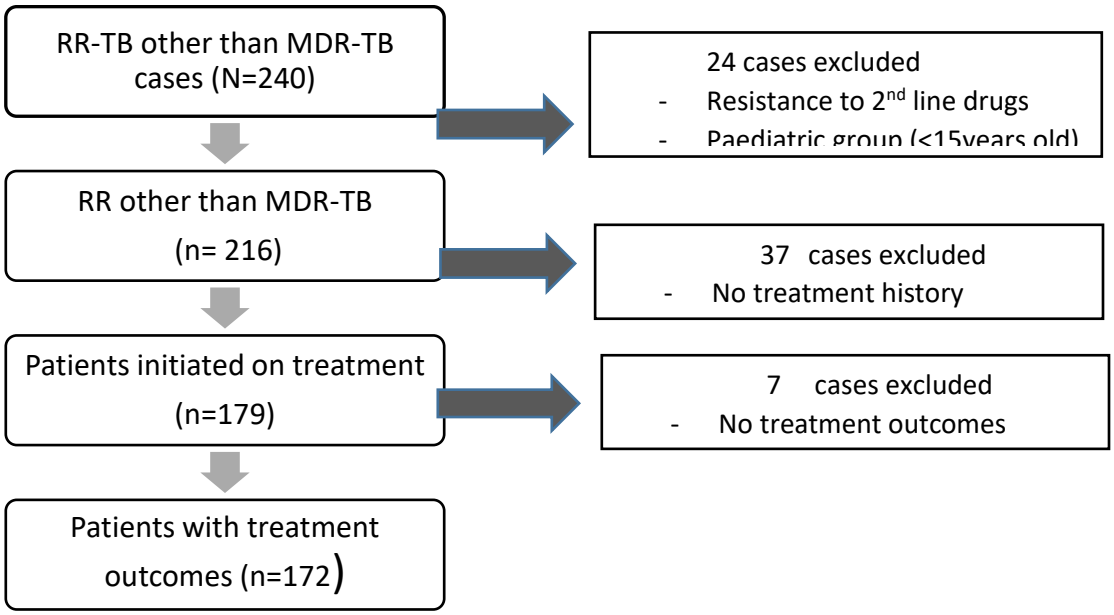

Figure 1. ***Patients included in the analysis of baseline characteristics and reported outcomes***.

Approximately two thirds of the cases (62%) were males (*table 2*). The cases' age ranged from 16 to 98, with a median age of 35. Sixty-four percent of cases (110/172) had been previously treated for TB. HIV status was documented in 96% (165/172) of cases, and 77% (127/165) of them were HIV positive while the rest were HIV negative. Eighty-two percent (105/127) of the HIV infected were on ART, while 9% were not on ART. One patient had defaulted from ART and a total of 11/127 (8%) had undocumented ART history.

Pulmonary TB was the commonest among all cases at 90% followed by 9% who had both pulmonary and extra-pulmonary TB. Only two patients (1%) had extra-pulmonary TB which was TB adenitis and pleural TB. Majority of the cases (91%) were smear positive and mono resistance (RMR) was the commonest resistance pattern at 70%, the remaining cases were

poly-resistant cases. The commonest poly-resistance pattern was resistance to rifampicin and streptomycin at 85 % followed by resistance to rifampicin, ethambutol and streptomycin at 8%.

Table 2- ***Characteristics baseline descriptive characteristics of RIF-resistant TB patients registered at NTRL from January 1, 2006 to December 30, 2014***

Characteristic	**Count (n=172)**	**Proportion (%),95% Confidence Interval**
Gender		
Male	107	62 (0.545 – 0.695)
Year of registration		
2006	13	8 (0.041 – 0.126)
2007	12	7 (0.037 – 0.119)
2008	23	13 (0.087 – 0.194)
2009	46	27 (0.203 – 0.340)
2010	9	5 (0.024 – 0.097)
2011	8	5 (0.020 - 0.090)
2012	11	6 (0.032 – 0.111)
2013	28	16 (0.110 – 0.223)
2014	22	13 (0.082 – 0.187)
Previous TB history		
No	62	36 (0.289 - 0.437)
Age		
15-24	17	10 (0.059 – 0.154)
25-34	64	37 (0.300 – 0.449)
35-44	53	31(0.240 – 0.383)
45-54	26	15(0.101 – 0.214)
55-64	7	4 (0.017 – 0.082)
≥65	5	3 (0.100 - 0.067)
Age		
≤35	91	53 (0.452 – 0.605)
HIV Status		
HIV negative	38	22 (0.161 – 0.290)
HIV positive	127	74 (0.666 – 0.802)
HIV status unknown	7	4 (0.017 – 0.082)

ART history		
On ART	105	83(0.750 – 0.888)
Not on ART	10	8 (0.038 – 0.140)
Unknown/not documented	11	9 (0.044 – 0.150)
Defaulted	1	1 (0.0002- 0.043)
TB foci		
Pulmonary	155	90 (0.846 – 0.941)
Extra pulmonary	2	1 (0.001 0.041)
Both	15	9 (0.050 – 0.140)
Sputum smear at baseline		
AFB negative	15	9 (0.050 – 0.140)
AFB positive	156	91 (0.853 – 0.946)
Unknown	1	1 (0.001 – 0.032)
Resistance		
Mono	120	70 (0.623 – 0.765)

ART= Anti-retroviral therapy; AFB= Acid- Fast Bacilli; TB= Tuberculosis

8.3. Treatment regimens and outcomes of RR-TB other than MDR-TB patients

Hundred and fourteen patients (66.3%) were initiated on first line regimen. Thirty-five patients (20.3%) were initiated on Modified regimen while 25 patients (13.4%) were initiated on MDR-TB regimen. The median length of treatment was 214 (IQR 182 – 262) for those treated by first line regimen, 397 (IQR 363-519) for Modified regimen and 548(IQR 548-664) for MDR-TB regimen (Figure 2).

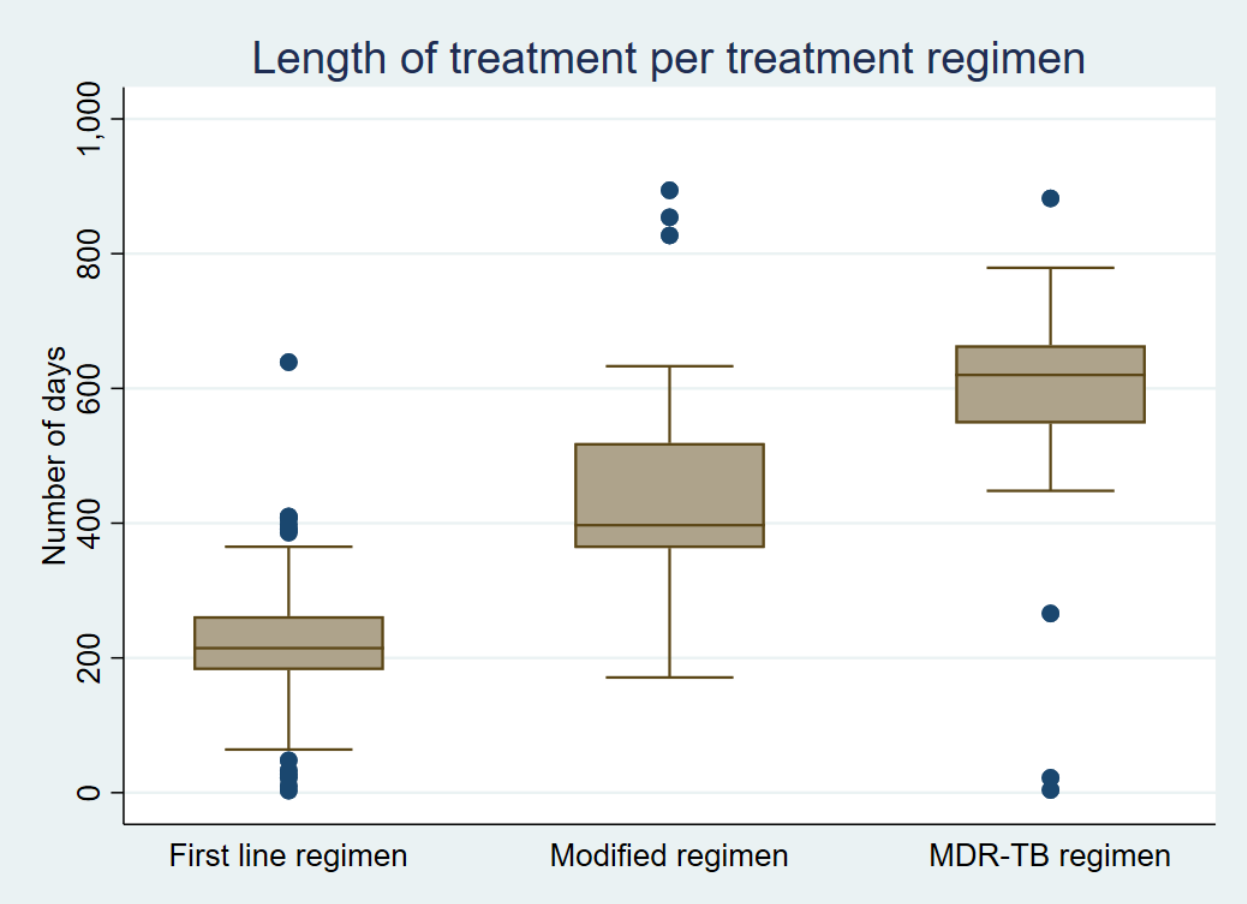

Figure 2. ***Length of treatment of RR-TB other than MDR-TB cases per different regimen (January 1, 2006 to December 31st, 2014)***

Table 3. ***Clinical characteristics of patients according to treatment regimen groups***

Characteristics	First line (n=114)	Modified (n= 35)	MDR-TB (n= 23)
Gender			
Male	68 (60%)	22 (63%)	17 (74%)
Previous TB history			
No	50 (44%)	8 (23%)	4 (17%)
Age			
15-24	12 (10%)	3 (8%)	2 (9%)
25-34	46 (40%)	10 (29%)	8 (34%)
35-44	32 (28%)	14 (40%)	7 (30%)
45-54	20 (18%)	4 (11%)	2 (9%)
55-64	3 (3%)	2 (6%)	2 (9%)
≥65	1 (1%)	2 (6%)	2 (9%)
Age2			
≤35	65 (57%)	15 (43%)	11 (48%)
HIV Status			
HIV negative	24 (21%)	9 (26%)	5 (22%)
HIV positive	83 (73%)	26 (74%)	18 (78%)
HIV status unknown	7(6%)	0	0
ART history			
On ART	65 (78.3%)	23 (88%)	17 (94%)
Not on ART	7 (8.4%)	2 (8%)	1 (6%)
Unknown/not documented	11 (13.3%)	0	0
Defaulted	0	1 (4%)	0
TB foci			
Pulmonary	101 (88%)	33 (94%)	21 (91%)
Extra pulmonary	2 (2%)	0	0
Both	11 (10%)	2 (6%)	2 (9%)
Sputum smear at baseline			
AFB positive	103 (90%)	31 (89%)	22 (96%)
AFB negative	10 (9%)	4 (11%)	1 (4%)
Unknown	1 (1%)	0	0
Resistance			
Mono-resistance	82 (72%)	25 (71%)	13 (57%)

ART= Anti-retroviral therapy; AFB= Acid- Fast Bacilli; TB= Tuberculosis

Out of the 114 cases that were initiated on first line regimen, a total of 83 cases (73%) had favorable outcomes (table 4). Death was the most frequent outcome under unfavourable outcomes at 12%, followed by treatment failure and lost to follow up at 8% and 7% respectively (see table 4). Eleven patients (13%) who had favourable outcomes had TB relapse on post-treatment surveillance. Two of those cases developed MDR-TB a year after completing treatment. A higher proportion of patients who relapsed (82%) had TB relapse within two years post treatment completion, only two cases had TB relapse after three and four years respectively.

Twenty-nine cases (83%) who were initiated on Modified regimen had favorable outcomes. None of the cases initiated on Modified regimen had TB relapse or treatment failure. Four cases (11%) were lost to follow up while 6% of them died.

Eighteen cases (78%) initiated on MDR-TB regimen had favorable outcomes. As it was observed under those initiated on Modified regimen, there were no treatment failure or TB relapse under those initiated on MDR-TB regimen. Death accounted for the highest proportion under unfavourable outcomes.

Patients initiated on first line regimen had a higher proportion of unfavorable outcomes (27%) followed by those on MDR-TB and modified regimen at 22% and 17%, respectively. There was no statistically difference in outcomes based on different treatment regimen (p = 0.456), however, all of those who had treatment failure (n=9) and relapse (n=11) were from the first line regimen group.

Table 4. ***Treatment outcomes of patients according to treatment regimen***

Treatment outcome	Treatment regimens			
	First line (n=114)	Modified (n=35)	MDR-TB (n= 23)	p-value
Favourable outcomes	83(73%)	29(83%)	18(78%)	
Cured	30 (26%)	8 (23%)	5 (22%)	0.897
Treatment completed	53 (47%)	21 (60%)	13 (57%)	0.312
Unfavourable outcomes	31 (27%)	6 (17%)	5 (22%)	
Failed	9 (8%)	0 (0%)	0 (0%)	0.098
Defaulted	8 (7%)	4 (11%)	1 (4%)	0.674
Deceased	14 (12%)	2(6%)	4 (17%)	0.343
Relapsed	11 (10%)	0 (0%)	0 (0%)	

8.4. Predictors of unfavourable outcomes for RR-TB other than MDR-TB patients

In bivariate analyses, there were no statistically significant predictors of unfavourable outcomes (table 5). Variables with P<0.25 (age >65, >35, unknown HIV status, previous history of TB and poly-resistant RR-TB) were recruited into the multivariable logistic regression. Backward hierarchical selection using stepwise approach was used to remove variables whose p-value was more than 0.05 significance. Unfortunately, none of the variables employed fulfilled that criteria, thus no multivariable model could be used to predict the outcome (table 6). There was no evidence of confounding nor significant interaction observed in this analysis

Table 5. Bivariate regression model for predictors of unfavourable outcomes

Characteristics	N	Unfavourable outcome n (%)	Odds ratio (95% CI)	Pvalue
Age				
15-24	17	5(29)	1	
25-34	64	12 (19)	0.553 (0.163-1.871)	0.342
35-44	53	13(25)	0.780 (0.231-2.632)	0.689
45-54	26	7(27)	0.884 (0.228-3.432)	0.859
55-64	7	2(29)	0.960 (0.137-6.704)	0.967
≥65	5	3(22)	3.60 (0.454-28.562)	***0.225**
Age 2				
≤35	91	17(19)	1	
>35	81	25(31)	1.943 (0.958 – 3.942)	***0.066**
Gender				
M	107	29(27)	1	
F	65	13(20)	0.672 (0.320-1.413)	0.295
HIV Status				
HIV negative	38	7(18)	1	
HIV positive	127	32(25)	1.492 (0.610 – 3.630	0.388
HIV status unknown	7	3(43)	3.321 (0.673 – 16.894)	***0.153**
ART history				
Not on ART	10	2(20)	1	
On ART	105	27(26)	1.384	0.609
Unknown/not documented	11	2(18)	0.889 (0.123 – 6.385)	0.916
Defaulted	1	1(100)	0	***0.08**
Previous TB history				
No	62	12(19)	1	
Yes	110	30(27)	1.563 (0.739 – 3.294)	***0.248**

Sputum smear at baseline				
AFB positive	156	38(24)	1	
AFB negative	15	4(27)	1.129 (0.359 – 3.581)	0.843
Unknown	1	0		0.571
Resistance				
Mono	120	25(21)	1	
Poly	52	17(33)	1.846 (0.898 – 3.789)	***0.099**
TB foci				
Pulmonary	155	39(25)	1	
Extra pulmonary	2	1(50)	2.974	0.423
Both	15	2(13)	0.458 (0-1.910)	0.307

ART= Anti-retroviral therapy; AFB= Acid- Fast Bacilli; TB= Tuberculosis

*** P<0.25, to be included in multivariate analysis**

Table 6. Multivariate regression model for predictors of unfavourable outcomes

Characteristics	Odds ratio (95% CI)	Pvalue
Age		
15-25	**1**	
≥65	0.903 (0.543-1.487)	0.690
Age 2		
≤35	**1**	
>35	1.899 (0.627-5.754)	0.257
HIV Status		
HIV negative	**1**	
HIV status unknown	1.181 (0.774-4.236)	0.171
ART history		
Not on ART	**1**	
Defaulted	1.212 (0.782-1.77)	0.388
Previous TB history		
No	**1**	
Yes	1.441 (0.648-3.206)	0.370
Resistance		
Mono	**1**	
Poly	1.648 (0.781-3.477)	0.190

9. DISCUSSION

9.1. Prevalence of RR-TB with INH concomitance amongst RR-TB cases

The proportion of RR with INH concomitance resistance in this study was found to be lower than the ones previously reported in studies that concluded that RR is always accompanied by INH resistance (3). The proportion in this study varied by years, however the average proportion over 9 years was 79%. Although a comprehensive assessment of proportion of RR-TB with INH concomitance has never been carried out in Botswana prior to this study, a two year analysis of Botswana Gene Xpert data for 54 patients over two years showed a similar concomitance rate (38) . However, previous four drug resistance surveys in the country have shown much lower cumulative proportion of RR-TB and INH concomitance (9).

The findings of this study are consistent with those found in Peru, California and DRS survey results for Africa (5, 26, 62). A review of drug resistant TB in three high HIV burdened countries like Botswana reported a lower concomitance rate than the one reported in this study (29). In the neighboring country; South Africa, the prevalence of *RR-TB other than MDR-TB* varies by provinces. Due to that, the predictive value of rifampicin as a surrogate marker of MDR-TB is diminished with wide variability amongst provinces (63)

Considering the findings of this study, it is quite evident that the RR-TB with concomitant INH resistance varies annually with average concomitance rate over almost a decade being close to 80% (IQR 62% to 90%). Although this rate is lower than the global rate of 95% which informed the recommendation, it is still a high percentage. In light of that, using rifampicin resistance as a reliable proxy for MDR-TB in Botswana may be considered. However in other regions, country-specific data may be used as much as possible to formulate policies affecting treatment of patients. This was done in Iran, where after reviewing country specific data, it was concluded that RR may no longer predict MDR-TB in a significant number of people (64).

9.2. Description of the RR-TB Other than MDR-TB cases

Incident rates of tuberculosis globally and locally have shown to be greater in males than females, with the ratio being 2:1 globally (1). In keeping with this trend, a higher proportion of the *RR-TB other than MDR-TB* patients in this study were males, a finding similar to other regional and international studies (6, 18, 26, 62). A five-year cohort study in France however reported a different trend where majority of the patients with *RR-TB other than MDR-TB* were females (49). The TB/HIV co-infection rate in this study was found to be higher than the national Botswana co-infection rate (65). Although HIV status varies by different regions in the world, *RR-TB other than MDR-TB* has previously been correlated with HIV positivity rates (66-68). The proportion of TB patients tested for HIV and initiated on ART was slightly above 80%, although this finding is commendable it was far from the national target of 100%.

A higher proportion of *RR-TB other than MDR-TB* patients in this study and most African countries seems to have had previous TB compared to developed countries (49, 62, 69). This

could be due to the high HIV burden in these TB endemic countries leading to high TB recurrence rates. In addition to that, resistance test is not routinely done in new TB patients regionally due to limited resources unless there is high suspicion of resistance. This practice causes delay in diagnosing and treating drug resistant TB cases. Key global priorities for TB care and control include improving early case-detection and the End TB Strategy calls for universal access to drug susceptibility testing (DST) globally (1).

The prevalence of *RR-other than MDR-TB* cases was high amongst the age between 25 and 44. This could be due to the fact HIV prevalence in the country is highest within that age group (70). Other studies reported the same results as this study (7, 26) .

9.3. Management of RR-TB other than MDR-TB patients and their treatment outcomes

The highest proportion of patients were treated with first-line regimen which was contrary to the local and the international guidelines at the time. These patients were treated at their local health facilities instead of being referred to the nearest TB drug-resistance clinics. The treating clinicians may not have been aware of the results that showed resistance. This could be due to the fact that, unlike for confirmed MDR or XDR TB cases by NTRL, notification via telephone and email was not in place for mono or poly resistant cases. Transport issues such as shortage of vehicles could have caused delay in transporting samples and results between NTRL and health facilities especially those that were further away from NTRL. The long turnaround time of DST results could have also led to DST results not being followed up or results probably being lost on transit to the requesting facility.

First line regimen, which was not the recommended treatment of choice for patients with *RR-TB other than MDR-TB,* yielded a lower percentage of favourable outcomes compared to other regimens, although the difference was not statistically significant. All the patients who had TB relapse and treatment failure were from this specific treatment group. The results of treatment outcomes of patients initiated on first line regimen are consistent with findings in studies with varying study populations (26, 44, 71). The same studies reported the same percentage of the relapsed patients as this study which was at 11% (26, 44). Two cases in this study had TB relapse after more than two years post-treatment. It would be difficult to distinguish relapse from re-infection amongst these cases without epidemiological and spatial factors and genotype sequencing. Studies carried out in three countries reported true relapses (confirmed by molecular analysis) which occurred more than two years post treatment. The proportion of those true relapses amongst TB reoccurrence were 49%,27% and 7% in China, South Africa and Malawi respectively, showing that true relapses can occur two years and more post treatment (72-74). Similar to this study, two patients on first line regimen in South Korea became MDR-TB, displaying inadequate treatment of TB using first line regimen (71).

The highest proportion of patients who had favourable outcomes were from the Modified regimen group, this was however not statistically significant compared to other regimens. Homogenous findings, were reported in a one study where 91% of patients on modified regimen had favourable outcomes compared to the 85% in both first line regimen and MDR-TB treatment groups (71). Another study reported 100% cure rate of patients initiated on Modified regimen with no relapse on surveillance (75).

The proportion of favourable outcomes amongst patients initiated on MDR-TB regimen was close to 80%, a finding consistent with a study in South Korea (71). However, a study of 8433 patients in South Africa showed contrasting findings where only 45% of patients initiated on MDR-TB regimen had favourable outcomes (36). Majority of patients on MDR-TB regimen appear to have a higher lost to follow up rates compared to first line and modified regimens which contributes to unfavourable treatment outcomes (36, 71). This could be due to the longer treatment duration and many undesirable side effects.

Missing data has the potential to affect the statistical power of a study by reducing it leading to invalid conclusions. In this study, cases were excluded due to missing data on treatment history and treatment outcomes, however 80% (172/216) of the population who met the inclusion criteria (>15 years and no second-line drug resistance) were represented. Attrition is a potential source of bias in cohort studies. In this study 8% (13/172) were lost to follow up decreasing the number of cases with meaningful treatment outcomes. However, it was within the rule of thumb of less than 20% (76)meaning that it was unlikely to have effects of generalizability or potential for bias.

This study could not determine the exact efficacy of treatment regimen and optimal duration of therapy like a randomized trial would. Differences in the proportion of favourable treatment outcomes among the three regimen subgroups were not statistically significant. Albeit short of statistical significance, the proportion of favourable outcomes was lowest in the first-line group. TB recurrence and treatment failure was only observed in the same treatment group suggesting that it is not the treatment of choice for this group of patients as per previous local and international guidelines. The study suggests that favourable outcomes can be obtained with either Modified regimen or MDR-TB regimen. However, since MDR-TB regimen is associated with many adverse effects and is taken over a long period of time, Modified regimen could be considered for *RR-TB other than MDR-TB patients*. Modified regimen will minimize exposure to the toxic MDR-TB regimen of longer duration, while ensuring favourable treatment outcomes which is a priority in the management of TB. Short MDR-TB regimen however has shown promising results in selected patients in some countries, perhaps this could be an option for some of these patients.

9.4. Predictors of unfavorable outcomes

The study did not find any predictors of unfavorable outcomes. There were statistically significant associations between unfavourable outcomes and some patients' characteristics at bivariate binary logistic regression level, however, the same variables did not achieve statistical significance at multivariate binary logistic regression model. A study looking at *RR-TB other than MDR-TB* patients identified previous TB history and being HIV positive not on ART as predictors for unfavourable outcomes, however these findings were not statistically significant just like this study (49). Although advanced age (>55years) did not show statistically significant results in being a predictor of unfavourable outcome, it was found to be statistically significant in other studies which were looking at outcomes of different types of drug resistant TB. Poor adherence, radiologic extent of the TB disease, immune-suppression and underweight been reported to be risk factors for unfavourable outcomes in many MDR-TB studies (36, 77) . However, those variables were not captured as the data collected was restricted to the variables that were available owing to the retrospective type of study.

9.5. Limitations

This study has a number of limitations. Due its retrospective nature, some data of patients were missing which includes treatment outcomes and they were excluded from the analysis, this shows the reality in routine TB reporting which impacts on data quality. Some important variables that have been observed to have impact on treatment outcomes in some studies such as CD4 count, extent of TB diseases as per chest xray findings, patients' weight and treatment adherence were not available in the electronic data. The NTRL was non-operational between 2011 and 2012 which led to 40% decrease of TB notification as per report from the BNTP (65). Very few samples were reported to have been sent for resistance testing in South Africa during that period. A significant number of *RR-TB other than MDR-TB* patients could have been missed during that period however the proportion of RR-TB other than MDR-TB would not have changed. The seemingly small number of 172 patients was more than sufficient to explore predictors of unfavorable outcomes because there were at least ten individuals per variable hence making it possible to include the variables in the full model (60). In addition to that, 95% CI observed in all the variables evaluated at bivariate and multivariate level was narrow hence ruling-out sample size as an issue in this study

9.6. Strengths of this study

This is the first comprehensive study to evaluate management and treatment outcomes of RR-TB other than MDR-TB patients in the country. The heterogeneity of the management of *RR-TB other than MDR*-TB across the country was highlighted in this study. Majority of patients were initiated on first line regimen at their local health facilities instead of being referred to TB drug-resistance clinics for appropriate management. This seemingly lack of adherence to the

recommended guidelines in practice is likely due to resistance test results not reaching the referring sites leaving clinicians to initiate on first line regimen due to lack of awareness of the true resistance profile of the concerned patients. This highlights the importance of rapid test with a short turnaround time in RR-TB TB diagnostic test like GeneXpert to ensure adherence to the set treatment guidelines. The real rifampicin resistance profile of the country over 9 years was reported, which is important in determining the importance of using rifampicin resistance as proxy for MDR-TB ultimately selecting the best treatment for *RR-TB other than MDR-TB* patients.

10. CONCLUSIONS

Rifampicin resistance may be a reliable proxy for MDR-TB in a significant number of cases in Botswana even though the proportion of RR-TB with concomitant INH resistance is lower than global proportion. There is still a need for concerted efforts towards increasing DST coverage while ensuring rapid DST tests for both Rifampicin and INH to distinguish *RR-TB other than MDR-TB* from other RR-TB cases. A reliable and rapid referral system would also need to be in place for resistant cases to be referred immediately after results are released from the laboratory. Though the overall treatment outcome was similar among the three regimens used, because of the potential risk of treatment failure and relapse observed in the first line regimen group, modified regimen and MDR-TB regimen appear to be treatment of choice in our setting. Patients who test positive for RR-TB will benefit from being initiated on empiric MDR-TB regimen while awaiting full DST results.

11. RECOMMENDATIONS

Majority of patients were initiated on first line regimen against the guidelines. This shows a deficit in the TB care, perhaps the treating clinicians were not aware of the DST results of those patients. In addition to that, the DST results of these concerned patients were not entered into ETR. A functional referral system is an essential aspect of the appropriate management of drug-resistant TB patients, where clinics follow up on TB resistant tests results refer drug resistant patients to MDR-TB clinics. The Botswana NTRL currently has a system whereby all names of all TB patients who test positive for MDR-TB are forwarded to all DR-TB clinicians. This system could improve appropriate management of DR-TB patients if it could be extended to cover all types of drug resistant TB instead of concentrating on MDR-TB only. A committee could be formed and tasked with tracking all patients with DR-TB in the country so that they could be initiated on appropriate therapy to ensure adherence to treatment guidelines. The team could also ensure appropriate recording of patients' DST results in TB electronic systems. Patients who have risk factors for drug resistance with no full DST test/results available would benefit from empiric MDR-TB regimen while waiting for culture results. A comprehensive frequent

profiling of drug resistance in the country is recommended to inform DR-TB policy using country-specific data.

12. DISSEMINATION PLAN

An oral presentation will be made and presented to the BNTP and stakeholders. Written reports will also be submitted to the institutions. Manuscripts will be developed from this work and submitted to reputable suitable journals. Opportunities to present at local and international conferences will also be seized.

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14. APPENDIX

Table 5. – Prevalence of Rifampicin resistance with/out concomitant INH resistance from 2006 to 2014

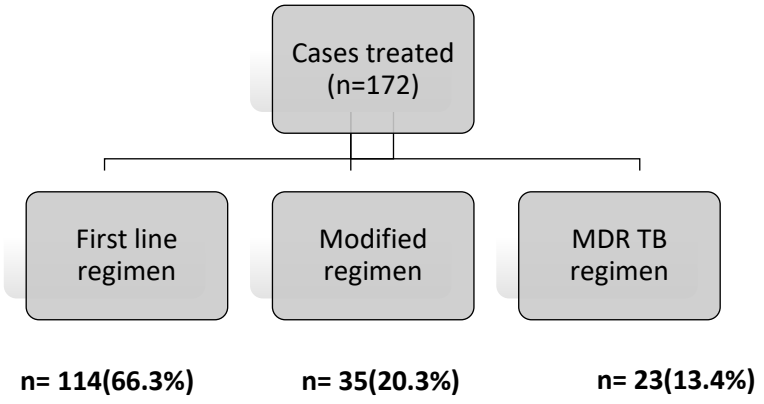
YEAR	Number of cases with resistance to Rifampicin	INH Susceptibility among cases with any Rifampicin resistance, N (%)	
		Susceptible to INH (RR-TB other than MDR-TB)	Resistant to INH (MDR-TB)
2006	49	14 (29%)	35 (71%)
2007	156	18 (12%)	138 (88%)
2008	236	34 (14%)	202 (86%)
2009	159	61 (38%)	98 (62%)
2010	155	15 (10%)	140 (90%)
2011	69	11 (16%)	58 (84%)
2012	88	18 (20%)	70 (80%)
2013	129	38 (29%)	91 (71%)
2014	95	31 (33%)	64 (67%)
TOTAL	1136	240 (21%)	896 (79%)

Table 6. Treatment outcomes of patients according to treatment regimen

Treatment outcome	Treatment regimens			
	First line (n=114)	Modified (n=35)	MDR-TB (n= 23)	p-value*
Favourable outcomes	83(73%)	29(83%)	18(78%)	0.456
Unfavourable outcomes	31 (27%)	6 (17%)	5 (22%)	

*Pearson chi-square= 1.6

Figure 3. Treatment of RR-TB other than MDR-TB per different regimen



Data extraction tool

Clinical Outcomes of Patients with Rifampicin Resistant other than Multi-Drug Resistant Tuberculosis in Botswana; A 2006-2014 retrospective cohort analysis

A. Patient Identification Information / Demographics
1. Sex: ☐ Male ☐ Female ☐ Unknown
2. Date of Birth: __ __ /__ __ /__ __ __ __ DD/MM/YYYY
3. Patient Unique Identifier_____
4. TB Registration Number: _____

B. Patient Locating Information	
5. District of Residence	_____
6. DOT Site / DHT Clinic	_____
7. MDR Facility ***(If applicable)***	☐ PMH (Gaborone) ☐ Sekgoma (Serowe) ☐ NRH (Francistown) ☐ Letsholathebe (Maun) ☐ Ghanzi Primary Hospital ☐ Other, name of facility _____

C. TB History ***(If past TB treatment was taken for more than 4 weeks)***	
Past TB Episodes:	
8. **Episode 1** ***(If none, skip to section D)***	__ __ __ ***YYYY*** AFB/Smear-positive: ☐ Yes ☐ No ☐ Unknown
14a. Category:	☐ New ☐ Retreatment after ***(circle one)***: Failure Default Relapse
14b. Outcome:	☐ Completed ☐ Cured ☐ Failure ☐ Default ☐ Unknown
9. **Episode 2**	__ __ __ __ ***YYYY*** AFB/Smear-positive: ☐ Yes ☐ No ☐ Unknown
15a.Category:	☐ New ☐ Retreatment after ***(circle one)***: Failure Default Relapse
15b. Outcome:	☐ Completed ☐ Cured ☐ Failure ☐ Default ☐ Unknown
10. **Episode 3**	__ __ __ __ ***YYYY*** AFB/Smear-positive: ☐ Yes ☐ No ☐ Unknown
16a. Category:	☐ New ☐ Retreatment after ***(circle one)***: Failure Default Relapse
16b. Outcome:	☐ Completed ☐ Cured ☐ Failure ☐ Default ☐ Unknown

D. TB/HIV Data	
11. HIV-positive	☐ Yes ☐ No ☐ Unknown ***If No, skip to Section E***
12. CD4	__ __ __ __
13. IPT History	☐ Yes ☐ No ☐ Unknown
14. On ART	☐ Yes ☐ No ☐ Unknown ***If Yes,*** Date: __ __/__ __/__ __ __ __
15. Defaulted ART	☐ Yes ☐ No ☐ Unknown ***If Yes,*** Date: __ __/__ __/__ __ __ __

E. Laboratory Data – For the current TB	
16. AFB/Smear at Start	☐Positive ☐ Negative ☐ Contaminated ☐ Unknown Date of AFB/Smear: __ __/__ __/__ __ __ __ DD/MM/YYYY
17. AFB/Smear at month 2	☐Positive ☐ Negative ☐ Contaminated ☐ Unknown Date of AFB/Smear: __ __/__ __/__ __ __ __ DD/MM/YYYY
18. AFB/Smear at end of treatment	☐Positive ☐ Negative ☐ Contaminated ☐ Unknown Date of AFB/Smear: __ __/__ __/__ __ __ __ DD/MM/YYYY
19. Culture at Start	☐Positive ☐ Negative ☐ Contaminated ☐ Unknown Date of Culture: __ __/__ __/__ __ __ __ DD/MM/YYYY
20. Culture at month 2	☐Positive ☐ Negative ☐ Contaminated ☐ Unknown Date of Culture: __ __/__ __/__ __ __ __ DD/MM/YYYY
21. Culture at the end of treatment	☐Positive ☐ Negative ☐ Contaminated ☐ Unknown Date of Culture: __ __/__ __/__ __ __ __ DD/MM/YYYY
22. Drug Sensitivity test	Date: __ __/__ __/__ __ __ __ DD/MM/YYYY Resistant- H ☐ R ☐ Z ☐ E ☐ S ☐

*H= Isoniazid R= Rifampicin Z= Pyrazinamide E= Ethambutol S= Streptomycin

F. TB Diagnosis and Care	
23. TB Registration Category	☐ **New** *(TB patient who has never received anti-TB treatment or has received anti-TB treatment for less than one month)* ☐ **Relapse** *(TB patient who previously received treatment and was declared "cured" or "treatment completed" AND has once again developed bacteriologically positive TB)* ☐ **Treatment After Default** *(TB patient who stopped treatment for any reason for at least 2 months, then returned to be treated again)* ☐ **Treatment After Failure of New Treatment** *(A patient on a New Treatment regimen whose sputum smear or culture is positive at 5 months or later)* ☐ **Treatment After Failure of Retreatment** *(A patient on a Retreatment regimen whose sputum smear or culture is positive at 5 months or later)*
24. TB Foci	Pulmonary ☐ Extra Pulmonary ☐
25. TB treatment	Start Date: __ __ /__ __ /__ __ __ __ DD/MM/YYYY End Date: __ __ /__ __ /__ __ __ __ DD/MM/YYYY H ☐ R ☐ Z ☐ E ☐ Am ☐ Lfx ☐ Cap ☐ ☐ Other Anti- TB drugs, specify: _____
26. MDR Treatment	H ☐ R ☐ Z ☐ E ☐ Am ☐ Lfx ☐ PAS ☐ Cs ☐ Eto ☐ Cap ☐ ☐ Other Anti-TB drugs, specify: _____
27. Compliant	☐ Yes ☐ No ***If No,*** Days of Treatment Missed: _____

*H= Isoniazid R= Rifampicin Z= Pyrazinamide E= Ethambutol Cap= Capreomycin
*Am= Amikacin Lfx= Levofloxacin Cs= Cycloserine Eto= Ethionamide
*PAS= Para-aminosalicylic acid

G. Treatment Outcome and Follow-Up Post Treatment - clarify that this is for the current (to differentiate with the past history of TB)

33. Treatment Outcome and Date: __ __ /__ __ /__ __ __ __ DD/MM/YYYY

- ☐ Died
- ☐ Defaulted
- ☐ Completed
- ☐ Failed
- ☐ Cured
- ☐ Other, specify:

_____

34. Follow-Up Outcome (at 1 year)

- ☐ Alive
- ☐ Lost to follow-up
- ☐ No relapse
- ☐ Died

35. Follow-Up Outcome (at 2 years) and Discharge Date: __ __ /__ __ /__ __ __ __ DD/MM/YYYY

- ☐ Alive
- ☐ Lost to follow-up
- ☐ No relapse
- ☐ Died

_____

Research Permits