Rifampicin-resistant tuberculosis in Botswana: barriers and risk factors influencing patient outcomes, case detection, and linkage to effective care and treatment

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Abstract

Rifampicin-resistant TB in Botswana: barriers and risk factors influencing patient outcomes, case detection, and linkage to effective care and treatment

Background: Botswana reports high treatment success for rifampicin-resistant tuberculosis (RR-TB), but many challenges remain. Case detection is lower than expected and varies by year, and mortality rates are high. Research aims included identifying: factors associated with mortality, access to culture and drug susceptibility testing (DST) for patients at risk of RR-TB, access to first- and second-line DST among RR-TB patients, time to RR-TB treatment, and patient and provider experiences with RR-TB management.

Methods: Retrospective data (multiple cohorts across 2006-2014) were extracted from Botswana national registers and information systems, with additional data collected by standardized, qualitative interviews (2017). Data analyses (Cox proportional hazards regression, survival and hazards curves, logistic regression) were conducted to describe significant associations. A systematic review and meta-analysis was conducted. Thematic analysis was performed for qualitative research.

Results: There was low access (42%) to culture testing among patients at risk of RR-TB (previously-treated TB patients); particularly associated with rural residence and having previous successful TB treatment, compared to previous treatment failure. While confirmation of first-line drug resistance was available for 85% of patients initiating RR-TB treatment, access to second-line DST was poor (24%), impacted by limited in-country laboratory capacity.

Genotypic DST by Xpert MTB/RIF at peripheral laboratories was associated with faster time to treatment from diagnosis compared to phenotypic DST at the centralized national lab, 5 versus 22 days (median, $p<0.001$), consistent with systematic review findings of time to RR-TB treatment.

Risk factors for mortality during treatment included unconfirmed RR-TB (aHR 2.9), Pre/XDR-TB (aHR 2.5), HIV positivity without ART (aHR 3.6) and receiving treatment at two (of five) specific facilities (aHR 2.6 and 2.3).

Qualitative interviews confirmed inconsistent adherence to national policies and identified additional challenges including frequent medication and reagent stock-outs, misperceptions about disease transmission from both providers and patients, and inadequate national level support for the RR-TB program.

Conclusion: Several clinical and demographic factors negatively influencing case detection and RR-TB mortality in Botswana were identified. General health system dysfunction and poor political commitment to the RR-TB program also contributed. Recommendations include increased focus on: early diagnosis through universal DST, consistent access to effective drugs, and overall adherence to policies.

Conference Proceedings

2015 The Union World Conference on Lung Health, Cape Town International Convention Center, Cape Town, South Africa.

Poster: Evaluation of the use of Xpert®MTB/RIF to Diagnose and Treat MDR-TB under Routine Program Conditions in Botswana

2016 The Union World Conference on Lung Health, Arena and Convention Center, Liverpool, United Kingdom.

Oral Presentation: Evaluation of Access to DST for Previously Treated Patients in Botswana

2018 The Union World Conference on Lung Health, The World Forum, The Hague, The Netherlands.

Poster: Increased mortality during rifampicin-resistant TB treatment associated with inadequate laboratory testing

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Many thanks to my UCT supervisor, Helen Cox, who provided patient and thoughtful guidance and support throughout the PhD process, from development of the research proposal and data collection tools to many reviews of the thesis drafts. Her experience, knowledge and passion about TB and the people affected by TB were very influential in my approach to this research.

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I would like to thank my colleagues at the Botswana Ministry of Health and Wellness and especially Dr. Botshello Kgwaadira who was the program manager of the Botswana National TB Program during the time of my research. He was very involved in and excited about this research and was always very interested in hearing about results. I'm very thankful for his support and trust in accessing health facilities, patients and data.

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writing this thesis. I'm thankful for the example they are in my life, their unconditional love, their interest in my research and the bottomless cup of coffee that kept appearing on the desk where I worked.

This thesis is dedicated to my parents, Jim and Carol Boyd.

Table of Contents

List of tables and figures

List of abbreviations

AFB	Acid-fast bacilli
aHR	Adjusted harzard ratio
aOR	Adjusted odds ratio
ART	Antiretroviral therapy
BNTP	Botswana National Tuberculosis Program
CHE	Current health expenditure
CI	Confidence intervals
CMS	Central Medical Stores
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest X-ray
DHMT	District Health Management Teams
DOT	Directly observed therapy
DRS	Drug resistance surveys
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
EPTB	Extrapulmonary tuberculosis
ETR	Electronic TB registry
GDP	Gross domestic product
HR	Hazard ratio
IQR	Interquartile range
IUATLD	International Union Against Tuberculosis and Lung Disease
LIS	Laboratory Information System
LJ	Lowenstein-Jensen solid media
LPAs	Line probe assays
MDR-TB	Multidrug-resistant tuberculosis
MeSH	Medical subject headings
MGIT	Mycobacteria growth indicator tube

MoHW	Ministry of Health and Wellness
MSF	Médecins Sans Frontières
NTM	Non-tuberculosis mycobacteria
NTRL	National Tuberculosis Referral Laboratory
OR	Odds ratio
PCR	Polymerase chain reaction
PPA	Patient-pathway analysis
Pre-XDR TB	Pre-extensively drug-resistant tuberculosis
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
PTB	Pulmonary tuberculosis
RMR-TB	Rifampicin mono-resistant tuberculosis
RR-TB	Rifampicin-resistant tuberculosis
RR-TB	Rifampicin-resistant tuberculosis
TB	Tuberculosis
TTT	Time to treatment
U.S. CDC	U.S. Centers for Disease Control
WHO	World Health Organization
WMD	Weighted mean differences
XDR-TB	Extensively drug-resistant tuberculosis
Xpert MTB/RIF	Xpert
XPRES	Xpert Package Rollout Evaluation Study

Chapter 1: Introduction

1.1 Chapter overview

Chapter one describes the rationale and context for the development and conduct of this doctoral research project, key definitions, and the hypotheses, aims and objectives of this research.

1.2 Rationale and context

The concept of this thesis was developed after living and working in Botswana for three years. I initially moved to Botswana in 2010 in a position as a public health advisor in the TB Research Division of the U.S. Centers for Disease Control and Prevention (U.S. CDC), based in the capital city of Gaborone. In this position, I worked very closely with the Ministry of Health and Wellness (MoHW) planning and conducting tuberculosis (TB) operational research projects and clinical trials. In my collaborations with the MoHW and the Botswana National TB Program (BNTP), I developed a strong interest in learning more about the management of rifampicin-resistant tuberculosis (RR-TB) in Botswana, and my colleagues at the BNTP expressed interest in having more research conducted to increase awareness and understanding of the successes and challenges of the RR-TB management program. The concept and research questions for this thesis were developed in consultation with colleagues at the BNTP and aimed to address issues and questions of the most interest to the program. Throughout the next four years in Botswana, I continued to work at the U.S. CDC office in Gaborone while also working on data collection and analysis for this doctoral research project in close collaboration with BNTP colleagues. During the final year of thesis writing, I had moved back to the U.S. but remained in close contact with BNTP colleagues. The primary supervisor for this doctoral work was Associate Professor Helen Cox (University of Cape Town). Technical support was provided by medical officers at the BNTP and the U.S. CDC Office in Botswana.

1.3 Key definitions

Key definitions are explained throughout the thesis as the concepts are introduced. It is important early on to define the terms related to the categorization of drug-resistant tuberculosis. Multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampicin, the two most potent drugs used for treating TB[1]. Extensively drug-resistant TB (XDR-TB) is defined as resistance to at least isoniazid and rifampicin plus resistance to any fluoroquinolone and at least one of three injectable second-line drugs[1]. Pre-XDR TB is defined as MDR-TB with resistance to a fluoroquinolone or an injectable second-line drug, but not both[2]. Rifampicin-resistant TB (RR-TB) is defined as resistance to at least rifampicin[1]. Rifampicin mono-resistant TB (RMR-TB) is defined as resistance to rifampicin and susceptibility to isoniazid[1]. The term RR-TB encompasses MDR-TB, XDR-TB and RMR-TB[1].

1.4 Hypotheses, aims and objectives

1.4.1 Overall research hypothesis

In Botswana, there are identifiable barriers and risk factors influencing RR tuberculosis case detection, linkage to effective care and treatment and patient outcomes.

1.4.2 Specific hypotheses, aims and objectives

Chapter 2 includes background information and a literature review, while chapter 3 describes methods.

Subsequent chapters will investigate the following specific hypotheses, aims and objectives.

Assessment of RR-TB case detection in Botswana (chapter 4)

Hypothesis 1: Case detection of RR-TB is suboptimal in Botswana

Aim: Conduct an assessment of access to TB culture and first-line drug susceptibility testing (DST) according to global and national guidelines

Objectives:

To determine the proportion of previously treated TB patients, registered in 2013-2014, with samples submitted for culture and first-line DST within 1 month of first-line TB treatment initiation

To identify risk factors associated with not having a sample submitted for culture and first-line DST for previously treated TB patients

Hypothesis 2: There are gaps in confirmed diagnosis of patients initiating second-line treatment in Botswana

Aim: Conduct an assessment of first and second-line DST for patients initiating second-line treatment

Objective:

To determine the proportion of patients registered for RR-TB treatment from 2006 to 2014 with first-line and second DST results available.

Risk factors and time to mortality among RR-TB patients initiating second-line treatment in Botswana (chapter 5)

Hypothesis 1: Mortality among patients initiating RR-TB treatment is associated with identifiable risk factors, some of which are modifiable

Hypothesis 2: Time to mortality is affected by specific risk factors.

Aim: To identify and determine risk factors for mortality among RR-TB patients in Botswana

Objectives:

To describe the proportion of cases initiating treatment who have died and risk factors for mortality

To describe time to mortality and factors associated with early and late mortality

To describe the frequency of co-morbidities and side effects and their impact on mortality

Time to treatment for rifampicin-resistant tuberculosis: a systematic review and meta-analysis (published Nov 2017, chapter 6)

Hypothesis 1: Time to treatment is influenced by diagnostic methods and model of care provided in various setting.

Aim: To conduct a systematic review and meta-analysis assessing time to treatment for RR-TB and variability by diagnostic testing methods and treatment delivery approach.

Objectives:

To assess treatment delay in terms of DST methods, access to ambulatory treatment compared to hospital based treatment, and the proportion of patients who initiate treatment.

Utilization of Xpert MTB/RIF (Xpert) and the impact on time to second-line treatment (chapter 7)

Hypothesis 1: Xpert improves time to treatment as compared to DST conducted at the centralized laboratory.

Hypothesis 2: There are gaps in confirmatory testing for patients initially tested by Xpert.

Aim: To assess patient management and linkage to care for patients with RR detected or RR indeterminate results by Xpert in 2013 to 2014.

When policy and practice do not align: a qualitative study of patient and provider experiences with RR-TB diagnosis and treatment in Botswana (chapter 8)

Hypothesis 1: There are gaps in the diagnosis and treatment process in Botswana that can be identified by patients, providers and government staff.

Aim: To identify and describe common themes through analysis of individual interviews with patients, health care providers, and national level government staff.

Chapter 2: Background and literature review

2.1 Chapter overview

Chapter 2 describes the country of Botswana and the context of TB and RR-TB, globally and in Botswana. More specific policy and background information is summarized at the beginning of each analysis chapter throughout the thesis. This section will include a high-level literature review of topics relevant to the development of the research plan for this thesis. Each chapter throughout the thesis will also include a detailed discussion section, describing literature in the context of the findings of this current research.

2.2 Botswana – general statistics and description of health system

2.2.1 Botswana general statistics

Botswana is a landlocked country in sub-Saharan Africa sharing boundaries with the Republic Of South Africa, Namibia, Zambia and Zimbabwe[3] (Figure 2.1). Botswana gained independence from Great Britain in 1966 and has remained politically stable since then[4]. The people of Botswana are referred to as Motswana (singular) or Batswana (plural). Ethnic groups include Tswana (67%), Kalanga (15%) San (1%), Ndebele (2%), Herero (1%), Afrikaner (1%) and other (13%)[3]. Botswana's economy is driven primarily by mineral extraction (principally diamonds) as well as tourism, and the country has a reputation of being one of the most stable economies in Africa[4]. Table 2.1 describes general statistics about Botswana.

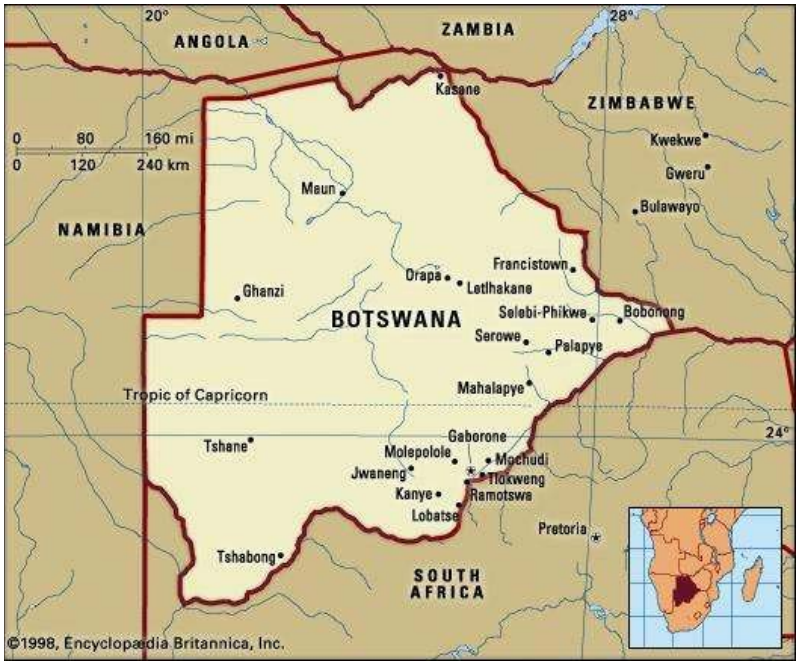


Figure 2.1. Location and map of Botswana[3]

Description	Measurement
Land area[5]	582,000 square kilometers
Population (2011)[6]	2,024,904
Rural population (2017)[7]	42% of total population
GDP (2017)[4]	$17.41 billion U.S. dollars
GDP per capita (2017)[4]	$7,595.60 U.S. dollars
Current Health Expenditure (2015)[8]	6% of GDP
Life expectancy (2016)[7]	66
Literacy rate (2014)[9]	88%
Unemployment rate (2013)[9]	18% (male); 22% (female)
Estimated HIV incidence per 100,000 (2016)[7]	444
Estimated ART coverage (2016)[7]	83%
Estimated TB incidence per 100,000 (2016)[7]	356

Table 2.1. General statistics, Botswana

2.2.2 Botswana health system

The Botswana health system is composed of public facilities, private facilities and traditional medicine, with 98% of the facilities in the public sector[10]. Nearly all Batswana seek health care in the public sector[11]. Health services in the public sector are decentralized to the district level; services are delivered through a network of health facilities. All health facilities are managed by District Health Management Teams (DHMTs)[12]. Botswana has 24 health districts as shown in Figure 2.2.

Table 2.2 describes the number public health facilities in the country. In addition to the health facilities listed in Table 2.2, there are 900 mobile health posts operating in Botswana. Most of the population (95% of the total population, 89% of the rural population) lives within 8 km of a health facility[12]. Patients move from lower facilities to hospitals through a referral system. Primary health care facilities are mainly staffed by nurses and midwives, and doctors visit health posts through a routine schedule as well as clinics which do not have their own doctors on staff. In addition to doctors, nurses and midwives, all hospitals have pharmacy, laboratory and radiology personnel. Referral hospitals have specialized care services. All health facilities have ambulance services for referrals and emergency calls[12].

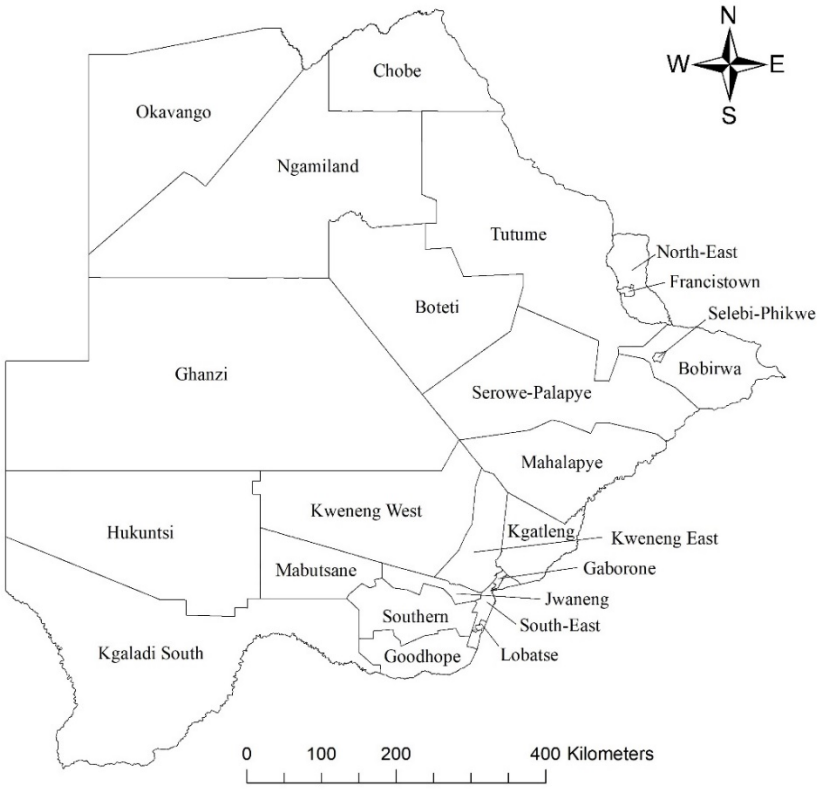


Figure 2.2. Health districts of Botswana

Health Facility Type	Number
Referral Hospitals	3
General Hospitals	15
Primary Hospital	17
Clinics	289 (181 w/out bed)
Health Posts	350 (13 w/out nurse)
Total public health facilities	674

Table 2.2. Public health facilities in Botswana (2012)[12]

2.3 TB and RR-TB globally and in Botswana

2.3.1 TB Epidemiology

Tuberculosis (TB) is a major global health problem. In 2017, the World Health Organization (WHO) estimated that 10 million people developed TB, and 1.6 million died from the disease, including 300,000 deaths among HIV-positive people[13]. The majority of individuals with TB worldwide in 2017 were in the South-East Asian (44%), African (25%) and Western Pacific (18%) regions[13]. Estimated TB incidence rates at the country level differ substantially, with 204 cases per 100,000 population in India, around 300 or more cases per 100,000 population in South Africa, Pakistan and Nigeria, and fewer than 25 per 100,000 population in parts of the Americas, Japan, Australia, New Zealand and several countries in Western Europe[13]. An estimated 9% of the 10 million people who developed TB globally in 2017 were HIV-positive[13]. Over half of these cases were in the African Region. For 2017, the WHO estimated TB incidence in Africa was 237 per 100,000 population and, specifically in Botswana, was 300 per 100,000 population[13]. The Botswana Ministry of Health and Wellness (MoHW) reported that 59% of all notified individuals with TB were HIV positive in Botswana in 2014[14]. As of 2017, an estimated total of 380,000 adults and children in Botswana were living with HIV; the estimated HIV prevalence among adults was 23%[15].

Prior to 1990, Botswana had shown success in controlling TB. Annual risk of infection surveys conducted in Botswana showed a decline from 5.8% in 1956 to 0.1% in 1989[16]. TB notification rates declined from 506 per 100,000 in 1975 to 199 per 100,000 by 1989[16]. However, in 1990 notification rates began to increase and peaked at 623 per 100,000 in 2002[3]. Based on studies of TB and HIV co-infection, it has become clear that the increase in TB was a result of the increasing prevalence of HIV in Botswana, as shown in Figure 2.3, and that the recent decline may be the result of high antiretroviral therapy (ART) coverage in Botswana[16].

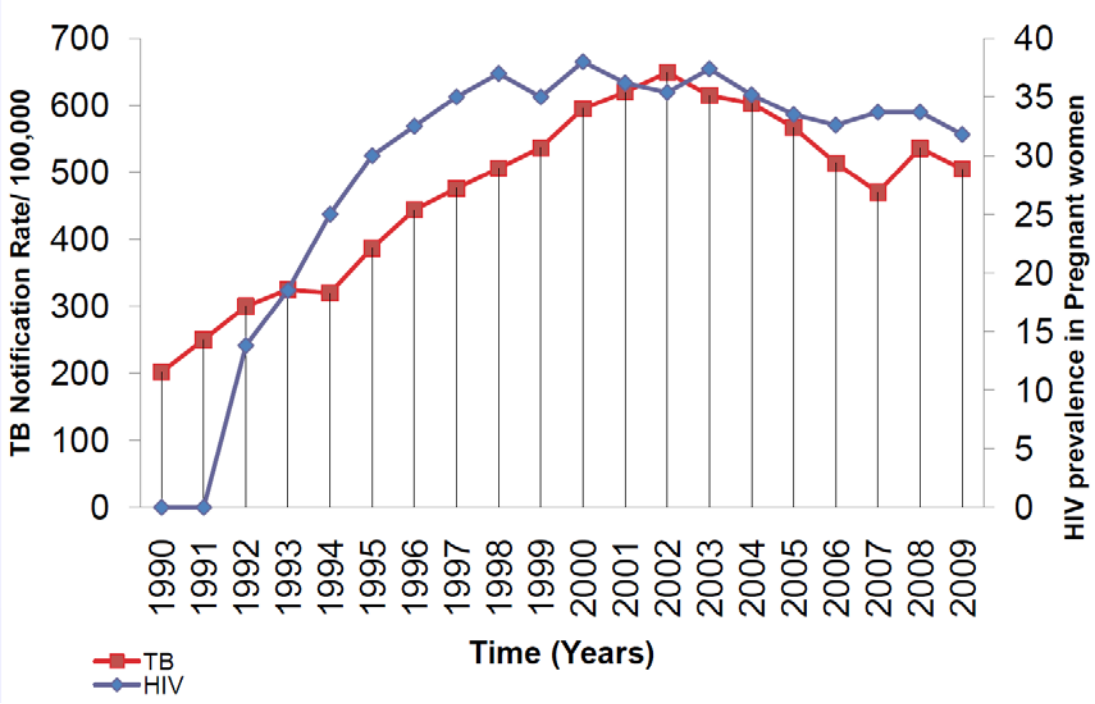


Figure 2.3 TB Notification Rate and HIV Prevalence among Adult Pregnant Women in Botswana, 1990 – 2009[16].
Sources: BNTP Annual Reports and ANC Sentinel Surveillance Reports

2.3.2 RR-TB epidemiology

RR-TB has emerged as a global epidemic with approximately 558,000 cases and 230,000 deaths estimated to occur in 2017[13]. RR-TB data from drug resistance surveys (DRS) and continuous surveillance among notified TB cases suggest that, globally, 3.6% of newly diagnosed TB patients and 18% of those previously treated for TB had RR-TB in 2012[13]. A total of 160,684 patients with RR-TB were notified globally in 2017[13], and 139,114 were reported to be started on second-line treatment. This represents only 25% of the 558,000 estimated cases globally in 2017[13]. In Botswana, 41% (87) of the estimated 210 RR-TB cases were detected and started on treatment in 2017[13].

Botswana has conducted periodic, national anti-TB DRS in 1995-1996, 1999, 2002 and 2007-2008. A new survey is planned for 2019. In the 2007-2008 DRS in Botswana, resistance to isoniazid, rifampicin, ethambutol and streptomycin continued to rise among new TB patients compared to previous surveys[17, 18]. The proportion of new patients with any isoniazid or rifampicin resistance increased 1.7-fold since 2002, and MDR-TB increased 3.1-fold since 2002[17, 18]. The percentage of new, previously untreated patients with MDR-TB increased from 0.8% in the 2002 DRS to 2.5% in the 2007-2008 DRS, a statistically significant increase[18]. Although the percentage of previously treated patients with MDR-TB decreased from 10.4% in 2002 to 6.6% in 2007-2008, this change was not statistically significant (P=0.29)[18]. In the 2007-2008 DRS, any resistance to rifampicin was reported for 3.6% of new TB patients and 13% of previously treated TB patients[17, 18] in line with the current estimates from the

WHO for Botswana[13]. Drug-resistant TB appears to be increasing in Botswana. The trends of MDR-TB, over the four national drug resistance surveys suggest this, particularly the proportion among new patients who have not previously received TB treatment[17, 18] (Figure 2.4).

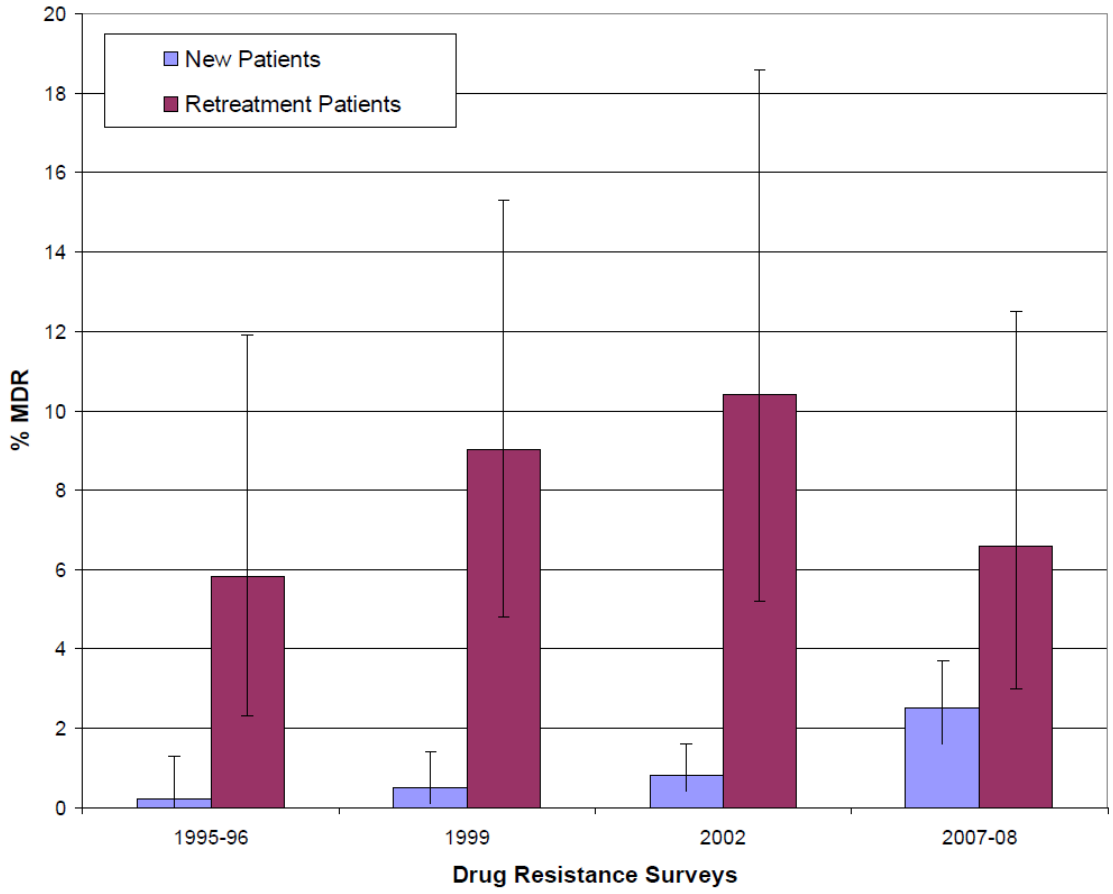


Figure 2.4. Results from drug resistance surveys, Botswana[18]

2.3.3 TB and RR-TB diagnosis

Summary of available diagnostics for TB

Diagnosis of TB has historically relied on smear microscopy and culture testing, but advances in TB diagnosis have led to more options in recent years[19]. The technique of detecting acid-fast bacilli (AFB) using smear microscopy is a TB diagnostic tool developed over 100 years ago[13], and while it is simple, quick and inexpensive[20], the sensitivity of smear microscopy ranges from 20-60%[21]. Xpert MTB/RIF (Xpert) is the only point of care, rapid molecular test for TB currently recommended by the WHO; rapid line probe assay tests (HAIN) are laboratory based tests and are also recommended by WHO[13]. Culture testing for TB (using solid or liquid media) is still considered the reference standard for the diagnosis of TB and RR-TB; culture based methods require more developed laboratory capacity, and can take as much as 12 weeks for results to be available[13].

Drug susceptibility testing

Testing for drug resistance is also recommended for patients diagnosed with TB; the WHO recommends universal drug susceptibility testing (DST) for all patients with signs and symptoms of TB[13]. While culture based DST, where bacteria are cultured in the presence of the drug to test for resistance, is the reference standard for DST, there are several other methods available as well. Xpert is a genotypic test which simultaneously tests for TB and for specific mutations known to confer resistance to rifampicin, the most effective first-line TB drug[13]. Rapid line probe assays (LPAs) are also genotypic tests available for both first and second-line DST. First-line LPAs were first recommended by the WHO in 2008 and test for resistance to isoniazid and rifampicin, and second-line LPAs were recommended by the WHO in 2016 and test for resistance to fluoroquinolones and injectable anti-TB drugs[13].

Xpert MTB/RIF

Xpert is a relatively new and improved diagnostic test that has been shown to have an impact on RR-TB diagnosis and linkage to care[22, 23]. The rapid molecular test simultaneously detects presence of *M. tuberculosis* and rifampicin drug resistance (RR) in sputum samples with high sensitivity and specificity[24], and results are available within 2 hours. In 2010, the WHO endorsed the use of Xpert as the initial diagnostic test for persons with presumed RR-TB or HIV-associated TB[25]. By 2017, 9449 testing machines and 34.4 million test cartridges had been procured by 130 of the 145 countries eligible for concessional prices[13].

After the initial endorsement of Xpert in 2010, the WHO policies regarding Xpert use were updated in 2013, taking into account the available body of evidence[26]. More than 85 peer-reviewed, published papers reporting on Xpert use were reviewed and summarized as part of this update. Xpert, when used as an initial diagnostic test, achieved overall pooled sensitivity and specificity of 88% and 99% respectively[26]. Among smear- and culture-positive TB, the pooled sensitivity was 98%, compared to 68% for smear-negative, culture-positive TB[26]. For people living with HIV, the pooled sensitivity was 79%, compared to 86% for people without HIV infection[26]. For detecting rifampicin resistance, Xpert achieved a pooled sensitivity of 95% and pooled specificity of 98%[26]. Xpert was initially recommended (in 2010) for the diagnosis of pulmonary TB in adults; the 2013 policy update expanded this recommendation to include use in children and to diagnose specific forms of extrapulmonary TB[26].

Given the WHO recommendation for universal DST, defined as rapid DST for at least rifampicin[27], Xpert can be utilized by programs to achieve universal DST. In regards to confirmatory DST, the WHO recommends that patients at high risk of MDR-TB with a diagnosis of RR-TB by Xpert should immediately have follow-up DST for at least isoniazid, fluoroquinolones and second-line injectables[28]. For patients at low risk of MDR-TB with a

diagnosis of RR-TB by Xpert, the WHO recommends a second Xpert test; in the event the second test is also positive for RR, the WHO recommends follow-up DST to confirm rifampicin resistance as well as susceptibility testing for isoniazid, fluoroquinolones and second-line injectables[13].

Since the introduction of this rapid TB diagnostic, research has been published to describe the implementation of Xpert. Research has indicated that it is feasible to use Xpert in resource-limited settings. A study reporting on Xpert use in decentralized testing locations in South Africa, Peru, Indian, Azerbaijan, Uganda and the Philippines, reported that Xpert could be effectively utilized in these settings with accurate and early diagnosis[29]. Theron, et al reported that Xpert can be accurately utilized by nurses in clinic settings in South Africa and resulted in more patients with a same day diagnosis and treatment[30]. A study in Botswana also indicated that Xpert implementation was feasible at both point of care sites and at district level laboratories[31]. As well as being feasible to implement, research also confirms that Xpert provides accurate diagnosis. A systematic review of 27 studies reported that Xpert, used as an initial diagnostic test, is sensitive (89%) and specific (99%) among both HIV positive and negative patients[32]. The same systematic review reports high sensitivity (95%) and specificity (98%) for the detection of rifampicin resistance[32].

Several studies have reported on challenges with Xpert implementation. Inconsistent access to both cartridges and required maintenance have been reported by several studies[33-35]. Xpert has been adopted quickly in many settings, however national guidelines and testing algorithms are not always updated and disseminated as quickly to align with new testing recommendations[35, 36]. The requirement for consistent power supply has been reported as a barrier for Xpert implementation[36], and in Botswana, one in five error results by Xpert were attributed to power supply[31].

Despite the challenges observed during Xpert implementation, the benefits of Xpert for RR-TB diagnosis and linkage to care have been well documented. Whereas results from culture based DST are available after weeks or months[29], Xpert testing results are available the same day. Therefore, many studies have reported on shortened time to initiation of treatment as a result of Xpert implementation[37-41]. Research also indicates that Xpert can increase RR-TB case detection[42-44] and lead to less empiric treatment[45]. A systematic review has been published recently indicating that Xpert may have a population-level impact by decreasing mortality, particularly among people living with HIV[22].

Diagnosis of TB and RR-TB in Botswana

In Botswana, all health facilities in each health district have the capacity to collect and transport sputum or other specimens (i.e. gastric aspirate, bronchial alveolar lavage, etc.) for TB testing; all hospitals and some clinics have the capacity to conduct lumbar punctures to collect cerebrospinal fluid. Specimens from patients presumed to

have TB are submitted from health facilities to peripheral laboratories for smear microscopy. Peripheral laboratories (36 in total) with the ability to conduct smear microscopy are available throughout the country. For patients in whom it is indicated (to be described more fully in relevant chapters), specimens are submitted to the National Tuberculosis Reference Laboratory (NTRL), through the peripheral laboratories, for mycobacterial culture and DST.

The NTRL is the only laboratory facility in Botswana with the capacity to conduct TB culture and phenotypic DST, and is located in Gaborone. The NTRL has been conducting culture testing since approximately 2000, and first-line solid media DST was introduced in the early 2000s (exact date unknown). During the time of this research, the majority of culture and DST was performed using Mycobacteria growth indicator tube (MGIT) or Lowenstein Jensen (LJ) solid media. The NTRL has suffered several closures in recent years. In 2011, the laboratory closed for renovations and once these were completed in 2012, capacity remained limited due to lack of reagents. The NTRL was fully opened by 2013 but was closed again from the end of 2014 through 2016. The closure in December 2014 resulted from a laboratory evaluation, which discovered a malfunction with the airflow system, creating positive pressure in the laboratory. This required a significant renovation, and the laboratory re-opened in 2016. There was an additional TB research laboratory, which was owned and managed by US CDC until 2017, used for research study-related testing. This research laboratory was a separate containerized TB laboratory co-located with the NTRL, and was not routinely used for testing non-study participants. In 2017, this research laboratory was transferred to the NTRL and continues to be used for research as well as a backup laboratory as needed.

Xpert was first introduced in Botswana in 2012 through an operational research study, the Xpert Package Rollout Evaluation Study (XPRES), conducted by the U.S. CDC in Botswana in collaboration with the Botswana Ministry of Health and Wellness. The study aimed to compare the sensitivity of microscopy-based and Xpert-based pulmonary TB diagnostic algorithms in diagnosing sputum culture-positive TB and to evaluate the impact of Xpert and intensified case finding on all-cause, 6-month, adult antiretroviral therapy (ART) mortality[46]. During this time, thirteen Xpert devices were placed throughout the country in district laboratories or in TB/HIV clinics (point of care), further described in Chapter 7. The study enrolled and followed up all HIV positive persons initiating ART with symptoms of TB seeking treatment at 22 participating TB/HIV clinics from 2012 to 2014[46]. The devices were also used by the government of Botswana for routine testing of patients with presumed TB at the participating clinics.

After the XPRES study ended and follow-up was complete (2015), the Xpert devices were donated to the MoHW. The MoHW subsequently installed additional devices as well, bringing the total Xpert devices in use to 34 by 2015. Xpert was not fully incorporated into the National TB Program in Botswana until 2016, when the

diagnostic algorithm including Xpert (Appendix A) was finalized and distributed. While Xpert was used prior to 2016, it was not intended to replace routine practices in the country, described in the first paragraph. Any patient who would have had a sample sent to the NTRL for testing should still have had a sample sent to the NTRL, regardless of Xpert result. Additionally, the government specifically released guidance to all facilities utilizing Xpert, instructing that any patient with an Xpert test indicating RR-TB should have confirmatory DST conducted at the NTRL and should be initiated on second-line treatment while waiting on results of confirmatory culture and DST. Guidance also indicated that any test with an RR indeterminate result by Xpert should have a repeat Xpert test and follow-up testing at the NTRL if warranted based on the second test or other recommendations for routine testing. This guidance was sent to health facilities as a savings gram (official government communication) from the Botswana National TB Program (BNTP) in 2012 when XPRES started introducing Xpert devices.

Throughout this thesis, reference is made to confirmatory testing and confirmatory DST, which includes confirmation of empirical diagnosis as well as confirmation of rifampicin resistance diagnosed by Xpert, along with inclusion of additional testing (e.g. isoniazid resistance). Given the low level of RR-TB among TB patients in Botswana, it is important and recommended to conduct confirmatory testing for all empiric and Xpert diagnosed RR-TB patients.

2.3.4 TB and RR-TB treatment

Effective medications for the treatment of tuberculosis were first developed in the 1940s[13]. Currently, the recommended regimen for drug-susceptible TB is a six month regimen of four first-line drugs: rifampicin, isoniazid, ethambutol and pyrazinamide[13]. The treatment for RR-TB is longer and requires more toxic medications[13]. Patients with RR-TB are treated with a combination of second-line drugs, usually for 18 months or more[13]. A shorter, 12 month, regimen was conditionally recommended by the WHO in 2016, recommended only under specific conditions (no previous second-line treatment, no resistance to fluoroquinolones or second-line injectable drugs)[47].

In Botswana, based on the most recent national guidance (2011 TB Program Manual and 2009 National Guidelines for Management of DR-TB), all RR-TB patients are placed on a standardized RR-TB regimen composed of amikacin, levofloxacin, ethionamide, cycloserine, pyrazinamide and P-aminosalicylic acid (PAS) (Figure 2.5)[16, 48]. Prior to 2009, the standardized second-line regimen consisted of fewer TB drugs: amikacin, ethionamide, pyrazinamide, and ciprofloxacin[49]. An adjustment of treatment is considered based on DST results or if adverse events are documented warranting a change. The recommendations that remain in place suggest the duration of second-line treatment in Botswana is 18 months after culture conversion[48]. More detailed information about RR-TB treatment in Botswana is provided in Chapter 5.

Treatment Phase	Recommended dose (mg/day)		
	<50kg	50 – 70kg	>70kg
Intensive Phase*			
Pyrazinamide	1000	2000	2500
Amikacin	750	1000	1000
Levofloxacin	750	750	1000
Ethionamide	500	750	750
Cycloserine	500	750	750
P-aminosalicylic acid (PAS) #	8000	8000	8000
Continuation Phase**			
Pyrazinamide	1000	2000	2500
Levofloxacin	750	750	1000
Ethionamide	500	750	750
Cycloserine	500	750	750
P-aminosalicylic acid (PAS)	8000	8000	8000

#For weight < 33 kg, give 150 mg/kg/day
*The intensive phase is for a minimum of 4 months post-culture conversion and not less than 6 months total
**The continuation phase is for a minimum of 18 months post-culture conversion

Figure 2.5. Standardized MDR-TB treatment regimen in Botswana[16]

2.3.5 Barriers to TB and RR-TB diagnosis and accessing treatment

Barriers to accessing effective TB and RR-TB diagnosis and treatment are likely to be present at many levels. Barriers to TB diagnosis at the healthcare system level can include lack of awareness about program testing guidelines and protocols among providers, limited supplies, unreliable transport and no specimen tracking methods[50]. At the patient level, socioeconomic barriers are often barriers to seeking care and treatment[51]. Additionally at the patient level, age, distance to care and treatment centers and male gender have been associated with treatment delays[52]. Specific groups, such as individuals with substance use disorders and subsistence farmers have experienced delays in diagnosis and treatment[53]. The WHO reports that one of the barriers countries face for access to treatment for RR-TB is reliance on centralized, hospital-based models of care, and recommends the use of outpatient models of care; this will be discussed further in section 2.3.8.

Many TB programs are developed from the top down and focus on where health system capacities currently exist, rather than where patients actually present for care[54]. As part of the End TB Strategy, the WHO includes patient centered-care as a core principle, focusing on ensuring universal access to TB services with increased attention to vulnerable and hard to reach populations. Hansen, et al described the patient-pathway analysis (PPA) approach which was developed for programs to better understand the association between patient care seeking behaviors and availability of TB services[54]. The PPA can be used at national and subnational levels and includes the following indicators, by health facility level and sector, to assist in understanding the patient-pathway: 1) initial care seeking (the proportion of patients who initiate care); 2) diagnostic coverage (the proportion of health facilities with diagnostic services); 3) diagnostic access (the proportion of patients who

initiate care in a facility with TB diagnostic services); 4); treatment coverage (the proportion of health facilities that have TB drugs or that can provide treatment supervision); 5) treatment access (the proportion of patients who initiate care in a facility that has TB drugs available); 6) notification location (the location of case notification for cases notified to the WHO); 7) treatment outcome (treatment outcomes among cases notified to the WHO)[54]. A report of five countries which implemented the PPA indicate that it is a useful tool for programs to understand where they may find TB patients who are currently being missed[55]. Among the five countries (Kenya, Ethiopia, Philippines, Indonesia and Pakistan), 76% of patients initially sought care in a TB care facility which did not have capacity for TB diagnosis. Other findings included insufficient referral processes, facilities with strong diagnostic capacity but low proportions of patients initiating care (particularly centralized hospitals) and limited engagement of the private sector[55]. Treatment availability appeared to be more aligned with patient care-seeking[55]. All five countries reported differences in the patient-pathways within the country, indicating that subnational assessments are important to fully understand where patients are seeking TB care in different regions[55].

To further understand how to best address barriers to diagnosis and treatment, research has examined what makes certain programs successful. A program analysis of three successful RR-TB programs reported on six areas that were common among each program[56]. First, each program conducted baseline and repeat qualitative assessments to identify areas needed for program improvement. Second, each program identified and emphasized relationships with key collaborators, such as those involved in policy making, laboratory services and drug procurements. Third, programs identified where patients initially seek TB care. Fourth, all programs worked to minimize costs to the patients. Fifth, each program identified vulnerable populations at increased risk of RR-TB and/or increased risk of poor treatment outcomes, and interventions were developed (i.e. universal screening among mine workers, support for patients with substance abuse issues). Lastly, all programs received significant technical assistance from an external partner (Partners In Health), in their early development, and all receive funding from both government and Global Fund[56].

2.3.6 Delays and time to treatment

For the minority of RR-TB patients who are appropriately diagnosed and receive second-line treatment, delays to treatment initiation are often many months in some settings.[37, 57-61] Such delays are likely to increase mortality and loss to follow-up while waiting for treatment,[62, 63] in addition to potentially contributing to poorer treatment outcomes among those who do start treatment.[64] Long delays to treatment are also likely to contribute substantially to transmission, in both community and nosocomial settings.[65-67] Given that the majority of RR-TB patients in high burden settings are likely due to direct transmission,[68] scale up of diagnosis and rapid initiation of effective treatment are required to improve patient outcomes and reduce ongoing transmission.[69]

Chapter 6 provides a systematic review of literature reporting on factors influencing time to treatment for RR-TB patients.

Qualitative research has explored factors that contribute to delays in diagnosis and/or treatment. A study in Vietnam reported findings from focus groups and in-depth interviews with MDR-TB providers. Challenges to MDR-TB detection and linkage to treatment included inadequate screening capacity at district hospitals, inconsistent training and poor communication and implementation of policy changes; updates regarding policy changes were not always communicated at all levels of the health system[70]. Other research has indicated that inadequate sample transportation systems contribute to delay, as well as inefficient systems for tracking and referring patients to treatment[71].

A study in Cape Town, South Africa identified both enablers and barriers to early MDR-TB diagnosis and treatment[72]. Patients diagnosed by Xpert attributed their rapid linkage to treatment to the new technology[72]. Patients who had previous TB episodes and recognized the symptoms reported seeking health care early, while those who thought the symptoms had another cause, delayed seeking care[72]. Patient perceptions of poor services in the public sector contributed to delays[72]. Health system delays were present, including lack of testing at initial health contact, poor adherence to testing algorithms, unavailable results and delays in recalling patients when results are available[72].

2.3.7 Mortality and risk factors

In addition to reducing ongoing transmission of disease, a key goal of treatment is to reduce mortality. In the absence of treatment, the mortality rate from TB is very high. Tiemersma, et al described the natural history of tuberculosis and mortality among HIV negative individuals with untreated pulmonary tuberculosis[73]. This study reported on patients who were diagnosed before drug treatments became available (from research published between 1900 and 1966). Seventy percent of patients with untreated smear positive TB died within 10 years, and the 10-year case fatality rate among patients with smear-negative culture-positive TB was estimated to be 20%[73].

Given the greater risk of receiving ineffective treatment, compared to drug sensitive TB, the risk of mortality is higher among patients with RR-TB; a study in Peru reported that patients with RR-TB had significantly higher probability of death compared to drug sensitive TB patients[74]. Globally, mortality as a treatment outcome among RR-TB patients who initiated treatment in 2015 is reported as 15%; success (cured or completed treatment) among this same cohort is reported as 55%, and the remaining have outcomes of treatment failure (8%), lost to follow-up (14%) or no outcome information (7%)[13]. In comparison, Botswana has reported mortality as a treatment outcome for 17%, treatment success for 78%, lost to follow-up for 2% and treatment failure for 2% among the cohort included in this research (those initiating second-line treatment 2006-2014).

Past studies show a range of risk factors for mortality after diagnosis of RR-TB, including clinical and social factors. A 13 year retrospective study in Beijing showed that chronic obstructive pulmonary disease and hypertension are both independent risk factors associated with death among patients on second-line treatment[75]. In Lithuania, a retrospective national cohort study (all MDR/XDR-TB patients 2002-2008) showed that older age, alcohol use, lower education levels, unemployment, cavitary disease, being smear positive at the time of diagnosis and HIV positivity were associated with poorer survival[76]. In a study in Latvia, 20% of patients were underweight (BMI < 18.5) and these patients were significantly more likely to have clinical evidence of advanced disease and had a greater risk of death[77]. A South African study has also shown that lower baseline weight is associated with a higher hazard of death[78]. It should be noted that low BMI and baseline weight are most likely to be indicators of advanced clinical disease.

High death rates among HIV-infected RR-TB patients have been well documented, especially in high HIV burden settings[78-80]. A systematic review assessing treatment outcomes among HIV-RR-TB co-infected patients reported a mortality rate during treatment of 38% in adults and 11% in children; compared to HIV negative RR-TB patients, mortality was higher particularly among adults[81]. Several studies have reported that HIV is independently associated with mortality. Studies have reported HIV as an independent risk factor for mortality among MDR-TB patients initiating treatment in South Africa in the early 2000s, prior to ART access[78, 80]. Even after the availability of ART, research continues to show HIV as an independent risk factor for mortality[82]. A study in Eastern Europe, among RR-TB patients registered for treatment in 2009, reported median survival after treatment initiation of 5.9 years in patients with RR-TB; in patients co-infected with HIV survival reduced to 1.9 years[83]. However, some studies highlight this increased risk of mortality during RR-TB treatment only among HIV positive persons not on ART[84]. In particular, patients with a low CD4 count have been shown to have a higher risk of mortality while on RR-TB treatment. A case-control study of MDR-TB patients in South Africa who died within two years of diagnosis showed that mortality was associated with a greater degree of immunosuppression (CD4 count ≤ 50 and 51-200 cells/mm^3) and drug resistance (resistance to all six drugs tested)[85]. In Nigeria, mortality has also been linked to low CD4-counts among HIV-positive patients[86]. A previous study in Botswana reported a two fold increase in mortality among HIV positive persons with baseline CD4<100, compared to HIV negative persons[87].

2.3.8 Models of care for RR-TB treatment

Historically, global recommendations for management of RR-TB included hospitalization for up to 8 months; however, the WHO has recommended ambulatory models of care since 2011[88], and systematic reviews suggest that hospitalization is not associated with better outcomes compared to ambulatory treatment[89, 90]. The 2017 Médecins Sans Frontières (MSF) Out of Step Report indicated that fewer countries now require hospitalization for DR-TB treatment initiation, and none of the nine countries from Sub-Saharan Africa surveyed for the Out of Step report required hospitalization for treatment[91]. It should be noted however that the report is based on current country policies, but how these policies are actually implemented in practice was not reported. The WHO also recommends models of care that include directly observed therapy (DOT) (second-line treatment given by DOT throughout the entire course of treatment) and active contact tracing[88].

RR-TB in Botswana is managed at specialized facilities with both inpatient and outpatient care. RR-TB care has been decentralized from two referral hospitals in 2009 to five facilities by 2010 (a sixth facility was added in 2017 but was not operating during the time period covered by this research). The five facilities, and the catchment areas which they serve, are shown in Figure 2.6. These five centers are managed by a team including physicians and nurses trained in RR-TB care. Based on the 2011 national TB guidelines, all presumptive and bacteriologically confirmed RR-TB patients are referred to one of five specialized government RR-TB treatment centers located around the country.

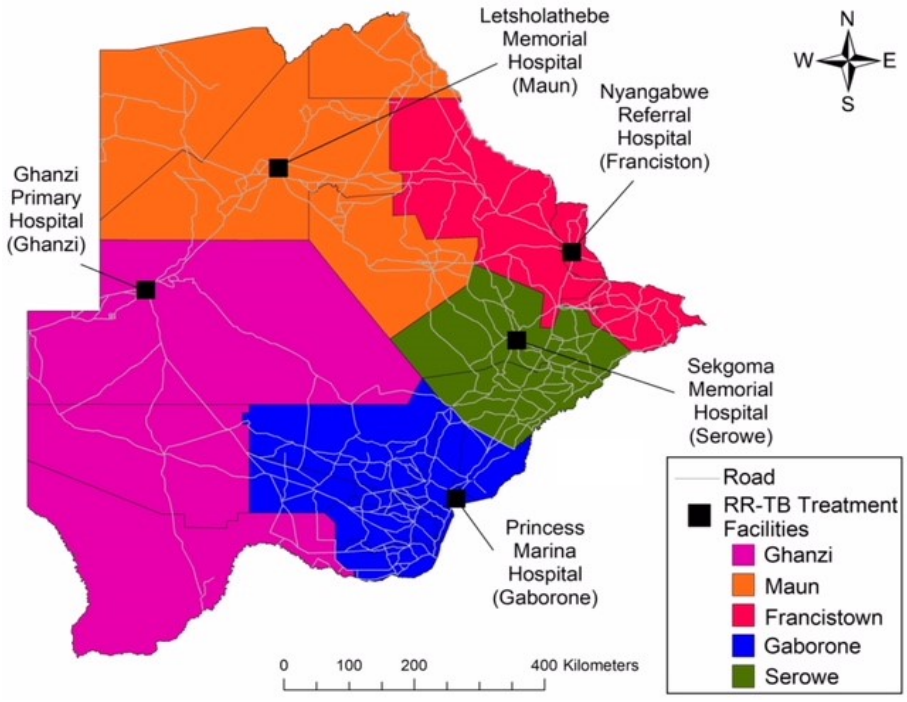


Figure 2.6. Catchment area of RR-TB treatment facilities in Botswana, as of 2010

According to the Botswana National 2011 TB Program Manual and the 2009 National Guidelines for Management of DR-TB, most RR-TB patients receive treatment as outpatients[16, 48]. Figure 2.7 from the 2011 TB Program Manual shows the flow of patients from primary clinics to an RR-TB treatment facility for treatment initiation (isolation in this figure refers to hospitalization). For ambulatory treatment, patients come with the TB coordinator or treatment adherence partner to one of the MDR-TB treatment centers and are reviewed on a monthly basis throughout treatment. Hospitalization during the intensive phase of treatment (until culture conversion or clinical stability) is recommended only for certain groups of people who the program considers to be at high-risk because of clinical characteristics, non-adherence, or are thought to be at high risk of infecting others. The program considers the following patients to be at high risk of clinical complications during treatment and therefore recommends they are hospitalized until clinically stable: confirmed and presumptive XDR-TB patients, clinically unstable patients, patients with severe adverse events, and patients with failure to culture convert after four months of treatment. Patients who have demonstrated poor adherence, based on reports from treatment monitors, are also recommended to be hospitalized for close monitoring to promote adherence to the treatment regimen. The program also recommends hospitalization for patients with no options for isolation in home (defined as a separate space in the home where the patient can be isolated from other members of the household), particularly those with children; the program considers these patients at high risk of infecting others[48]. The 2017 updated national guidelines for management of drug-resistant TB (still in draft, 2019) retained these recommendations[92].

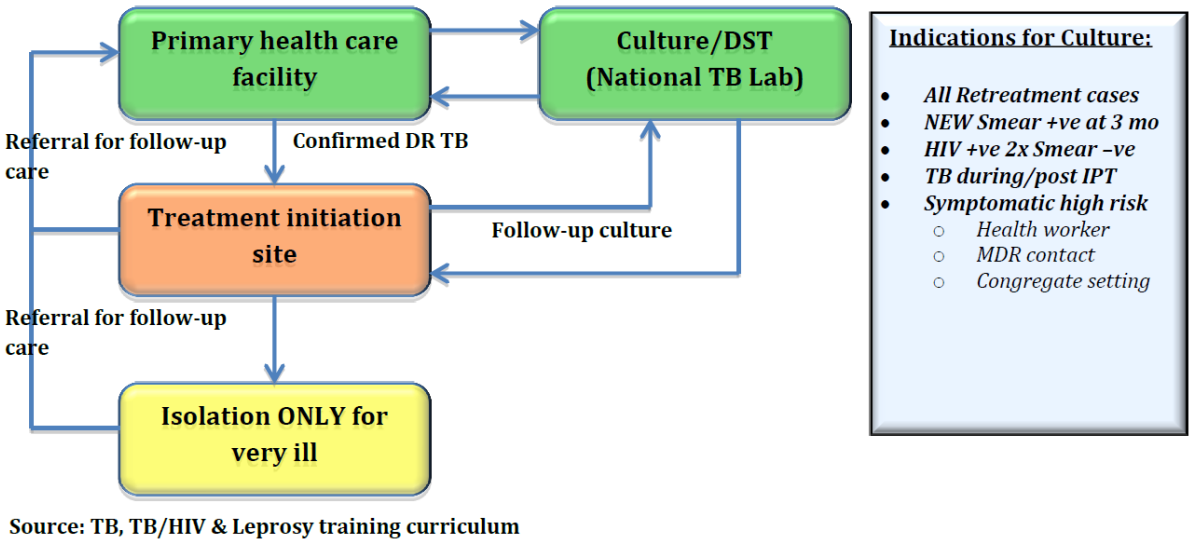


Figure 2.7. Schematic Flow of drug-resistant TB patients, Botswana[16]

National policies also address DOT and contact tracing. Guidelines suggest that RR-TB patients should receive DOT, provided by health facilities (hospitals, clinics, health posts) or by trained community volunteers.

Throughout the entire course of treatment, patient treatment cards are supposed to be signed every day by a DOT provider to record adherence[48]. Regarding contact tracing, national guidelines indicate that all close contacts of RR-TB patients, including household members, co-workers and schoolmates who have close contact with the source case, should be screened for signs and symptoms of TB[48].

2.3.9 Patient experiences with RR-TB treatment

Treatment for RR-TB is lengthy, up to two years for many patients, and is challenging for patients[93, 94]. Receiving daily injections, the high pill burden and the long duration of treatment have been reported as challenges for patients[94]. The toxic medication and harsh side effects are also very challenging for patients[94]; some report the side effects are unbearable[95].

Psychological challenges have been reported by patients, including depression, stigma and discrimination[96]. Patients have reported losing their sense of identity because they cannot work and are socially isolated[97]. Fear is a common feeling reported by RR-TB patients, fear of death or fear that it would be hard to find or pay for medication[97].

Patients also report economical hardships[96]. Economic hardships are often a result of losing a job due to the prolonged illness or not being allowed to work because of the perceived risk from their workplace[97]. Patients who work manual labor jobs or farm their own land have reported not being able to do so because of the effects of the medicine and losing income due to this[97]. Patients living in rural areas have reported economic hardships and selling their assets due to centralized care and having to travel to treatment sites[98].

Many studies indicate that patients prefer ambulatory care for RR-TB treatment[95, 99, 100]. Patients report they feel they are able to recover better at home, have better psychosocial support from family members and friends, and have time for other activities such as social interactions or having small jobs[100]. Patients also report being afraid of contracting other infections while at the hospital[100]. Patients have expressed frustration with delays in diagnosis and long pathways to care[72, 101], as previously described in Section 2.3.6.

2.3.10 Timeline of key events

Table 2.3 describes the timeline of key events related to TB and RR-TB in Botswana. Data for this timeline was collected through reviews of all annual reports and TB program manuals produced for the past 20 years, as well as through personal communication with members of the BNTP and NTRL.

YEAR(S)	
1910	TB is thought to be introduced in Botswana by miners returning from South Africa[102]
1956	Annual risk of TB infection in Botswana = 5.8%[16]
1970s	Documented resistance to isoniazid, streptomycin and thioacetazone in Botswana[103]
1975	National TB Program Established[16]
1986	Rifampin first used in Botswana[104]
1989	Annual risk of TB infection = 0.1%[16]
1990	TB cases began to rise again[16]
1995	Introduction of first fully oral regimen (2EHRZ/4HR)[16]
1995	Adopted DOTS Strategy[16]
1995	1st DRS conducted[16]
1995	9 patients with MDR-TB notified – first documented account[48]
1996	First guidelines for management of TB in lab setting produced[105]
1996	First national guidelines for management of MDR-TB developed but not finalized or distributed[105]
1999	2nd DRS conducted[16]
1999	Program review conducted. Identified priorities: 1) MDR-TB Guidelines: develop and disseminate; 2) Ongoing surveillance of DR-TB[105]
1999	Funding provided by CDC to construct the NTRL[106]
~2000	Culture testing began at the National Health Lab (limited basis)[106]
~2002	1st line solid media DST validated[106]
2002	3rd DRS conducted[16]
2006	Routine screening and treatment of RR-TB patients begun[104]
2006	NTRL opened[104]
2008	4th DRS conducted[16]
2008	3 XDR-TB cases confirmed[48]

2009	Guidelines for management of drug-resistant TB finalized and disseminated[48]
2010	Liquid culture (MGIT) validated at the NTRL[106]
2011-12	Interrupted/Limited laboratory (NTRL) services (renovations and limited reagent availability)[14]
2012	LPA validated[106]
2012	1st line liquid DST validated[106]
2012	Xpert implementation pilot study introduced – limited use
2014	2nd line liquid DST validated[106]
2014-2016	The NTRL closure – Evaluation discovered positive pressure; complete renovation needed[11]
2016	Xpert algorithm finalized and disseminated[11]
2016	2nd line solid DST validated[106]
2017	Draft Guidelines for MDR-TB Management developed[92]

Table 2.3. Timeline of key events related to TB and RR-TB in Botswana

Chapter 3: Data sources and methodology

3.1 Chapter overview

This chapter will describe the data sources used for this research, both existing national datasets and new data collected for this research. The chapter will further describe the methods used to develop the final databases used for this research, including verifying data in existing data sources, combining data from multiple data sources and adding new data collected. This chapter will also describe ethical review of the research. Specific analytical methods will be described in the relevant chapters.

3.2 Description of existing data sources

3.2.1 Existing data sources

I. Electronic TB Registry (ETR)

The ETR includes data on all patients initiating first-line TB treatment in Botswana. Traditionally, information about TB patients in Botswana has been reported to the national level through a routine paper-based TB recording and reporting system, based on the World Health Organization (WHO) guidelines[38]. In 1996 Botswana introduced a case-based electronic TB registry (ETR) designed in Epi Info. The Botswana National Tuberculosis Program (BNTP) transitioned the ETR to a Windows based version of the ETR called ETR.net in 2004. The ETR.net is a Microsoft.net–based computer software program, based on the WHO and the International Union Against TB and Lung Disease (IUATLD) recording and reporting formats. The ETR.net was developed and is managed by WAM Technology, a South African software development and support company. The ETR.net is a stand-alone system with Access back end and .net front end. The server for the system is located at the BNTP in Gaborone. From 2006 to present, the data in the ETR has been considered complete and reliable, according to the BNTP[11]. Data flow involves paper forms at the facility level that are transported to the district level. This should occur on a monthly basis but is not always the case. Also on a monthly basis, data entry staff or TB coordinators at the district level are to enter data into the database and forward to the national level.

Individual TB patient records are entered from a standard manual facility TB Register into a District-based (Local Service Area-/Sub-district-based) data entry program that provides interactive guidance and support. The program then generates different patient listings, with a management and supervision function (i.e. a list of patients lost to follow-up, etc.), and standard quarterly and annual reports on case finding, sputum conversion, and treatment outcome. In addition to the report tables, the program also provides graphs (time trends) and maps (geographic distribution) on important TB indicators. These reports are also used to provide feedback to the districts. The ETR includes data on patient identifying information, demographics and clinical information;

this includes name, national identity number, date of birth, age, HIV status, treatment dates, smear results, health care facility and home district. Patients are identified as new or previously treated for TB in the ETR.

II. RR-TB registry

While Botswana does have a web-based RR-TB registry (OpenMRS), it is not used consistently due to limited internet connectivity at treatment facilities; therefore, this registry is considered incomplete. There are plans to improve the usability of this sytstem. However, in the meantime, the best source of RR-TB registry data is an offline electronic database at each facility. This is in the form of an Excel file in which RR-TB clinicians enter data directly from patient charts or laboratory reports. Clincians update this file each time new information is reported about a patient. Updates are sent from facilities and compiled at least biannually at the national level where the master RR-TB register is held. The data from this registry are used for surveillance, to develop national annual reports and has been used for previous publications of the RR-TB cohort in Botswana[87, 107-112]. This Excel file RR-TB registry wil be referred to as the RR-TB registry in this thesis. The RR-TB registry inclues data on all patients who were referred to an RR-TB treatment center; some patients did not initiate treatment (died before treatment initiation or clinical decision not to initiate treatment) and are identified as not initiating treatment in the RR-TB registry. The RR-TB registry includes patient identifying information, demographics and clinicial information. The RR-TB registry has been in use since 2006.

III. The National Tuberculosis Reference Laboratory (NTRL) laboratory database

The Laoratory Information System (LIS) used by the NTRL is the DisaLab system[113]. The DisaLab system is a windows based system which interfaces multiple workstations and testing instruments through the network. The server, workstations and testing instruments are all co-located in the NTRL. Data is entered directly into the LIS by laboratory technicians or is imported directly from laboratory equipment (eg. mycobacteria growth indicator tube [MGIT]). Patients are given a unique laboratory number which automatcially links the patient with the result from the laboratory equipment. The LIS using DisaLab was first implemented in 2009 and includes patient identifying information and laboratory data per patient (specimen details and results).

IV. Patient medical records

Medical records are kept in paper format at the RR-TB treatment facilities. All patient information, including patient history from the referring facility, testing results and treatment information is kept in a folder at the treatment facility. At each patient visit (monthly while on treatment), the RR-TB clinican types clinic notes describing any updates in the patient condition. These typed notes are printed and kept in the patients medical records. The RR-TB treatment card is also kept in the patient files. There were some patients for whom paper charts were unavailable, and it is not clear why this is. These were collected directly from the RR-TB treatment

facilities, so it is likely this was impacted by poor filing and retention practices.

V. Xpert MTB/RIF data sets

Each Xpert testing instrument is accompanied by a computer. The GeneXpert Dx System software is installed on the computers, and this software automatically archives all test results as .gxx files on the computer. Data included in the archived Xpert files includes patient identifying information and testing results data. This data is stored at each testing facility and backed up by the NTRL staff (or CDC staff during the CDC study) on CDs or hard-drives during lab monitoring visits. Backed up records are stored at the NTRL.

3.2.2 Access to existing data sources

A data sharing agreement was developed with the BNTP, specifically for this research, to ensure that data was collected in agreement with program policies and procedures. This data sharing agreement was incorporated into the protocol and approved by ethical review boards as well. Additionally, the Program Manager of the BNTP provided an official letter to all facilities visited as part of this research to ensure facilities were aware of the approval for access to data.

Based on the data sharing agreement, data was provided to the researcher as follows. The ETR data, covering the years of 2013-2014, were exported to an Excel file and provided to the researcher on an encrypted USB drive. The RR-TB Registry, covering patients registered for treatment in the years 2006-2014, was provided to the researcher on an encrypted USB drive. The LIS data, covering the years of 2013-2014, were exported to an Excel file and provided to the researcher on an encrypted USB drive. The Xpert data (.gxx files), covering the years 2013-2014, were extracted from archived files directly from the Xpert instruments. These files were extracted and placed on an encrypted USB drive by the researcher or by a collaborator from the MoHW. Xpert software version 4.0 was used to access and combine test results at a central location, and results were exported to an Excel spreadsheet. Additional data was extracted directly from paper patient files and entered into a password protected database. All files were password protected, as was the computer on which they were stored.

3.2.3 New data collection

Data from qualitative interviews were captured in both written and verbal recording formats. Recordings were stored on the researcher's computer, and written interview notes were transferred into word documents and stored on the researcher's computer. All files were password protected, as was the computer on which they were stored.

3.3 Development of study databases

This section will describe how existing data were used to create the databases for this research. Each study database has been given a name in this section and will be referred to by this name throughout the thesis. The methods for creating the database for the published systematic review are included in the systematic review chapter.

Previous TB treatment database

The previous TB treatment database was created from three existing data sources: the ETR, the LIS and the Xpert datasets. Initially, all previously treated TB patient data was extracted from the ETR to create a database of previously treated patients only, registered January 1, 2013 to November 30, 2014. The cutoff of November 30, 2014 is due to a lab closure at this time, which interrupted submission of samples for testing at the NTRL. The ETR extraction of previously treated patients was reviewed for duplicates, and any duplicates were removed. Each data source had the following patient identifying information: name (first and last name) and omang (national identity number); date of birth (DOB) was available for the ETR and the LIS. The ETR data were manually matched against the national LIS records and the Xpert dataset by national identity number, name and, where available, by date of birth to determine if the patient had a sample submitted for culture or Xpert testing. Manual methods included using spelling variations for names in searching for matches; any names identified by a spelling variation were confirmed by another variable as well (date of birth or omang). Any discrepancies between the databases were resolved; if two databases had the same data and one differed, the data confirmed by two would be retained. If this could not be resolved by majority, the data from the ETR was retained as it was determined by the researcher to be more complete and accurate. Only data from samples submitted for testing within the following timeframe were considered: within three months prior to first-line TB treatment initiation and up to one month after treatment initiation. The rationale for the time frame is described in Chapter 4. The testing results data from the LIS or Xpert datasets were merged into the previous treatment database. Results data included test results as well as dates (date of sample receipt at lab [LIS only], date of test conducted and date of result reviewed). In instances when multiple results were available per patient, all results were included in the merge and were reviewed manually. For analysis, when more than one sample was submitted per patient during the specified time frame, all results were reviewed for completeness, i.e. both culture and DST results. For example, in the LIS if one sample had only culture results available and another sample for the same patient was also submitted, during the time frame for analysis, with both culture and DST results available, the results and date of sample submission for the latter sample would be included in analysis. The main outcome of the analysis this database was used for was having a sample submitted for culture; however DST results were also described in this analysis making it important to include the most

complete information for each patient. Xpert data was also reviewed for duplicate tests per patient, and no duplicate results were identified. A unique study ID was assigned by the researcher to each patient; once all matching was complete, all identifying information was deleted from the database. The coded age variable, calculated from date of birth, and the district of residence remained in the database. All analyses were conducted on the de-identified database. RR-TB patient database

The RR-TB patient database was created from four existing data sources: the national RR-TB registry, the LIS, patient medical records (paper) and the Xpert dataset. The national RR-TB registry formed the base of the study database, and additional data was added to this database from the other three sources. Each data source had the following patient identifying information: name (first and last name) and omang (national identity number); date of birth (DOB) was available for the RR-TB registry, patient medical records and the LIS. Matching methods described in the previous section were also used in the development of this database. Each data source was reviewed for quality and completeness. In review of the data, the researcher did identify missing data for some variables (radiology results, smear results, etc.) and some illogical dates. These are highlighted as limitations in the respective chapters. It was clear that some dates were entered in different formats. Some dates were entered in the MM/DD/YY format, while others were entered in the DD/MM/YY format. These were manually corrected to all be in the same format, and where available these dates were checked against the LIS records (however, LIS was only available for the years 2012-2014). Specific data definitions and analytic methods are described in detail in the respective chapters. This database was used in Chapter 4 to describe confirmation of drug resistance patterns; data for this analysis came mainly from the RR-TB register and the Xpert dataset which did not have specimen collection date data; therefore these findings are presented in terms of when the test result was recorded in these data sources (result available date). This database was also used in Chapter 5 and additional data cleaning and merging were conducted to make the database useful for the sub-analysis of patients initiating treatment between 2012 and 2014. For these patients, matching with the LIS and Xpert datasets was conducted to confirm testing data. Additionally, patient charts were reviewed for these patients and variables were added for the data from these reviews (weight, side effects, etc.). A unique study ID was assigned by the researcher to each patient; once all matching was complete, all identifying information was deleted from the database. The coded age variable, calculated from date of birth, and the district of residence remained in the database. All analyses were conducted on the de-identified database.

Xpert database

The Xpert database was created from the original Xpert datasets (.gxx files directly from testing instruments), the LIS and the RR-TB registry. The Xpert dataset formed the base of this study database and included the results from all tests conducted by Xpert in 2012-2014. Tests conducted for quality assurance or training purposes were

identified in the dataset and were excluded from the study database. A broad analysis was conducted on the full Xpert database to describe all testing conducted in the study time period.

Further data cleaning and matching was conducted for a subset of this database. This subset included all tests with a result of rifampicin resistance detected or rifampin resistance indeterminate. For all tests with a result of rifampicin resistance or rifampicin resistance indeterminate by Xpert, these were reviewed by name and omang (national ID number) for duplicates, and all duplicates were removed. Some patients had multiple tests performed within the same week. If there were multiple tests for the same patient, only one result was retained for the analysis. In the case that the result was the same, the date of the first result was retained. In the case that results were different, any positive result was retained. Manual matching, using name and omang was conducted with the LIS for NTRL test results for this subset of the database. Data was organized by patient, and results from the LIS (results and dates of results) were added to the data for the corresponding patients. The RR-TB register was also matched with this subset of the database, and data was added for corresponding patients. The data from the RR-TB register included demographic data (sex, age) and treatment data (start date, outcome). Any patient with a result of RR-TB by Xpert who was not located in the RR-TB registry was followed up further. The researcher called the RR-TB facilities to determine why the patient was not started on treatment, and this information is included in Chapter 7.

Additional data was added to this database for patients who initiated RR-TB treatment based on results from the NTRL. This data was added as a comparison group to patients who initiated RR-TB treatment based on Xpert, to compare time to treatment among these two groups. To add this data, the RR-TB registry was matched with the LIS to confirm testing dates and results for patients who had initiated treatment in 2012-2014. Any patient who initiated treatment without a test result available at the time of treatment initiation was excluded. Data for patients who did initiate treatment based on results from the NTRL was added to the database, including patient characteristics (gender and age), treatment information (start date and outcome) and testing data (result data and dates of specimen collection and result available date). The specific data definitions and analyses are described in Chapter 7. A unique study ID was assigned by the researcher to each patient; once all matching was complete, all identifying information was deleted from the database. The coded age variable, calculated from date of birth, and the district of residence remained in the database. All analyses were conducted on the de-identified database.

Qualitative data

Qualitative data was collected using standardized interviews (Appendix B). Interviews were recorded, transcribed and translated into word documents. Interview transcripts were read through to identify patient and provider experiences with RR-TB treatment, themes were uncovered and transcribed on to note cards which

included specific quotes, participant ID numbers and thematic codes. Summarized themes and quotations were entered into an Excel database for further organization and review. A unique study ID was assigned by the researcher to each patient; all identifying information was deleted from the database. The coded age variable, calculated from date of birth, and the GIS coordinates for village of residence (not unique to any one patient) remained in the database. All analyses were conducted on the de-identified database. Specific methods for data collection (Section 8.4), review and analysis are described in Chapter 8.

Data analysis:

Specific methods for data analysis are described in individual chapters. Common to all analyses, efforts were made to reduce type 1 errors. The p-value set for significance was 0.05. In addition, factors included in models were carefully selected and minimized, only including factors with clinical or public health reasons to suspect there may be an association, increasing the confidence that type 1 errors were minimized.

3.4 Ethical review

Ethical approval for this research was given by the University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee; U.S. Centers for Disease Control and Prevention; and Botswana Ministry of Health and Wellness. Informed consent was provided by each of the study participants participating in the qualitative interviews (Appendix B). Informed consents were translated into Setswana and Basarwa verbally at the time of the interview. Back translations of the consents, as well as any questions and responses were performed verbally and recorded (written and verbal recordings).

Chapter 4 - Assessment of RR-TB case detection in Botswana

4.1 Chapter overview

Two main analyses will be described in this chapter. The first section will describe an assessment of culture testing and first-line DST for previously treated TB patients registered January 1, 2013 to November 30, 2014 in Botswana. The second section will describe an analysis of first- and second-line DST for patients registered for RR-TB treatment from January 1, 2006 to December 31, 2014. The chapter begins with a background and overview of current policies regarding case detection in Botswana, relevant to both sections.

4.2 Hypotheses, aims and objectives

Hypothesis 1: Case detection of RR-TB is suboptimal in Botswana

Aim: Conduct an assessment of access to TB culture and first-line drug susceptibility testing (DST) according to global and national guidelines

Objectives:

To determine the proportion of previously treated TB patients, registered January 1, 2013 to November 30, 2014, with samples submitted for culture and first-line DST within 1 month of first-line TB treatment initiation

To identify risk factors associated with not having a sample submitted for culture and first-line DST for previously treated TB patients

Hypothesis 2: There are gaps in confirmed diagnosis of patients initiating second-line treatment in Botswana

Aim: Conduct an assessment of first and second-line DST for patients initiating second-line treatment

Objective:

To determine the proportion of patients registered for RR-TB treatment from 2006 to 2014 with first-line and second DST results available.

4.3 Background/Policy review

The WHO has published recommendations to address improvements in case detection of RR-TB[27]. The WHO recommends universal access to DST for all patients with signs and symptoms of TB and defines universal access to DST as rapid DST for at least rifampicin[27]. The WHO guidance acknowledges the difficulty of accomplishing this in certain settings and suggests that, at a minimum, patient groups with the highest risk of RR-TB should

receive culture DST. These high risk groups include previously treated TB patients, contacts of RR-TB patients, and those patients who do not culture convert after three months of TB treatment[114].

Globally, 3.5% of new TB patients and 18% of previously treated TB patients are estimated to have RR-TB[13]. Based on the last drug resistance survey (DRS) for Botswana conducted in 2008, 2.5% of new TB patients and 6.6% of previously treated TB patients were estimated to have MDR-TB (confirmed resistance to isoniazid and rifampicin)[17]. Any resistance to rifampicin (with or without isoniazid resistance) was reported for 3.6% of new TB patients and 13% of previously treated TB patients in 2008[17], in line with the current estimates from the WHO for Botswana[13]. The first section of this chapter assesses culture and DST among previously treated patients in Botswana as a group at risk of developing RR-TB. Previously treated TB patients were selected as the major group to monitor testing among high risk groups, because it is large and easily identifiable.

Ideally, all patients initiating RR-TB treatment should also have second-line DST for at least fluoroquinolones (which are used in the country) and at least one of the three second-line injectable agents[114]. The second section of this chapter assesses the first and second-line DST practices for patients initiating RR-TB treatment in Botswana.

There is one laboratory facility in Botswana with the capacity to conduct TB culture and phenotypic DST, the National Tuberculosis Reference Laboratory (NTRL), located in Gaborone. Laboratory capacity has been affected by two NTRL closures. In 2011, the laboratory closed for renovations and once complete in 2012, capacity remained limited due to lack of reagents. The NTRL fully opened by 2013 but was closed again from the end of 2014 through 2016. With the exception of these closures, the NTRL has been conducting culture testing since approximately 2000, and first-line solid DST was introduced in the early 2000s (exact date unknown). There was an additional TB research laboratory established in 2011, which was owned and managed by the US CDC until 2017, used for research study related testing. This research laboratory was a separate containerized TB laboratory collocated with the NTRL, and was not routinely used for testing non-study participants. In 2017, this containerized laboratory was transferred to the MoHW; it continues to be used for TB research as well as serving as a backup for the NTRL.

During the time of the analyses described in this chapter, culture and first-line DST were primarily performed with Mycobacteria growth indicator tube (MGIT) or Lowenstein-Jensen solid media (LJ), with a low proportion of samples tested using line probe assays (LPA). Samples were processed with GB Mycoprep (Becton Dickinson, Sparks, Maryland, United States of America) which consists of 1% N-acetyl-L-cysteine (NALC), 4% sodium hydroxide and 2.9% sodium citrate. Routine practice at the NTRL was to conduct first-line DST for all culture positive samples, including those submitted for monitoring purposes. LPAs were first introduced in 2012 but were not routinely used for all patients during the time of these analyses. The capacity for second-line DST was

not available in Botswana during the time of these analyses. From 2006 to 2010, samples were sent to South Africa for second-line DST. However, this stopped almost completely after 2010, and the country did not develop capacity for second-line DST until 2014.

Citing costs and limited capacity, the Botswana National TB Program does not recommend culture and DST for all TB patients in Botswana[16]. However, culture and first-line DST is recommended for patient groups in whom there is a higher risk of drug resistance or lower sensitivity of smear microscopy[16]. These patient groups are listed together in the 2011 TB Program Manual as follows; they are not separated by their reasons for testing (i.e. risk of drug resistance or lower sensitivity of smear microscopy):

- HIV positive individuals with presumptive TB with 2 negative sputum smear results
- New TB patients who remain or become smear positive at month 3 of treatment
- All previously treated TB patients regardless of reason (failure, relapse, or loss to follow-up)
- All children < 5 years of age with presumptive TB
- Patients who develop TB during or after isoniazid preventive therapy
- Symptomatic individuals at higher risk of MDR-TB: laboratory workers, MDR-TB contacts, health care workers

According to the 2009 National Guidelines for Management of DR-TB, all patients microbiologically diagnosed with RR-TB and initiating second-line treatment and those initiating treatment empirically should have a baseline culture and first-line DST[48]. Patients with presumptive or laboratory confirmed RR-TB are placed on a standardized second-line TB regimen. Additionally, patients are to be monitored throughout second-line treatment with monthly smear and culture testing[48].

There is inconsistent guidance regarding second-line DST. While the most recent TB program manual (2011) states that all confirmed MDR patients should receive second-line DST[16], the 2009 National Guidelines for Management of DR-TB states that only those who remain culture positive after four months of treatment should receive second-line DST[48]. Both were current guidelines in use during the time of the study; while it is possible that these were inconsistent because the guidelines were changing over time, it is unclear which guidelines were meant to be adhered to.

Xpert was first introduced in Botswana through an operational research study (XPRES), which was being conducted within the programmatic setting of TB care in Botswana from the years 2012-2014. Some patients included in these analyses received Xpert testing through this study; however, national policies regarding Xpert use were not fully developed and implemented until 2016. While Xpert was used during the time of this research, it was not intended to replace routine practices in the country. Any patient who would have had a

sample sent to the NTRL for testing should still have had a sample sent to the NTRL, regardless of Xpert result. During the time of this study, any patient with a positive Xpert test should have received confirmatory culture and first-line DST performed at the NTRL.

TB diagnosis and care is managed through a network of health facilities at six levels: national referral hospitals (3), general district hospitals (15), primary hospitals (17), clinics (288), health posts (350) and mobile clinics (900)[12]. All facilities in a health district are overseen by District Health Management Teams (DHMTs). All facilities have the capacity to collect and transport sputum for TB testing. Peripheral laboratories (36) are available throughout the country and have the capacity to conduct smear microscopy testing. Sputum samples are sent to the NTRL by all facilities via the peripheral laboratories throughout the country. However, based on personal communication from members of the national TB program, poor coordination of transportation from some health posts and particularly from mobile clinics limits the ability of these facilities to collect and submit sputum for TB testing[11]. The program reports 100% geographical coverage of the WHO recommended Directly Observed Therapy Short Course (DOTS) for drug sensitive TB treatment, and direct observation is provided at local health facilities (hospitals, clinics, health posts) or through community volunteers[16]. Because mobile posts are not open every day, they do not provide DOT but do support the community volunteers providing DOT in these areas.

4.4 Section 1: Assessment of culture and first-line DST among previously treated TB patients in Botswana

4.4.1 Methods (Section 1)

Study population

The study population included all patients initiating first-line TB treatment registered as previously treated patients in the Electronic TB Registry (ETR) in 2013 and 2014. All analyses use data for patients registered between January 1, 2013 through November 30, 2014. This did not extend beyond November 2014 because of a laboratory closure in December 2014, which would have affected sample submission and testing. The methods for development and description of this database are included in the Chapter 3. Previously treated patients included the following categories[16]:

- Retreatment after previous successful treatment: A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with TB.
- Retreatment after treatment failure: A patient who is started on a retreatment regimen after having previous treatment failure.
- Retreatment after loss to follow-up: A patient who is started on a retreatment regimen following interruption of treatment for two or more consecutive months.

- Smear-negative PTB and EPTB patients are also classified as new and retreatment after relapse, failure and loss to follow-up.

Measured variables

This analysis aims to assess if previously treated patients are being monitored for drug resistance as recommended. In order to be monitored for drug resistance, patients must have a sample submitted for culture testing. Therefore, this analysis measures the proportion of patients with a sample submitted to either the NTRL or an Xpert testing facility. Sample submission is used as a marker for recommended monitoring. For the purpose of this analysis, patients are considered as having samples submitted for monitoring if they had a sample submitted at treatment initiation (defined as within three months before and up to one month after first-line TB treatment initiation). Specimens submitted within three months before treatment initiation were classified as pre-treatment samples. Patients were considered as being monitored as recommended if a sample was submitted, regardless of whether or not results became available or were positive. Having a sample submitted does not necessarily mean that first-line DST would have been conducted. DST may or may not have been conducted for samples submitted for culture depending on initial culture result. In addition to describing sample submission for culture testing, DST will be described separately.

Data analysis

Proportions, medians and interquartile ranges were produced to describe patient characteristics, sample submission and testing results. Univariate and multivariate logistic regression were used to analyze associations between collected variables and sample submission (as the dependent variable). Univariate and multivariate regression were also used to identify factors related to culture positivity. Odds ratios, 95% confidence intervals (CI) and p-values were calculated for all variables included in the univariate and multivariate regressions. P-values of <.05 were considered statistically significant.

All analyses were conducted using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) or Excel for basic charts and graphs.

ArcGIS was used to create maps, displaying spatial variation in sample submission and availability of DST results by health district. A separate map displaying population density by health district was created. Population density was calculated for each health district using the following formula:

Population density = population of the district / square kilometers of the district

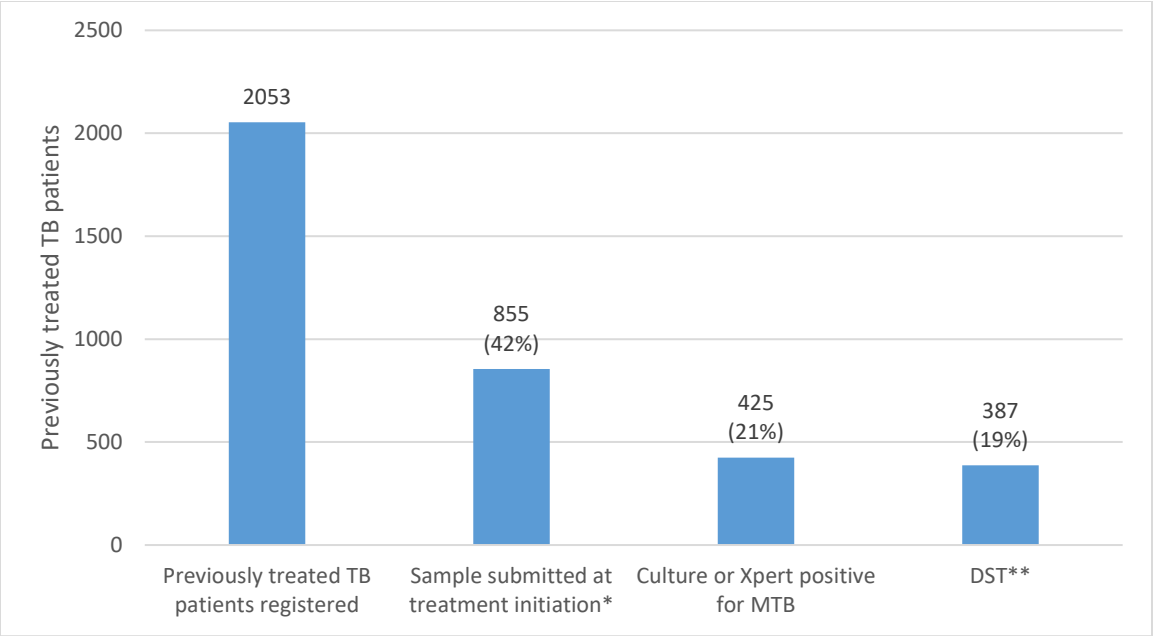
Population by district was obtained from the 2011 national census[6], and square kilometers were obtained from the shape files of each district[115]. All maps displaying results per district were created using shape files provided by the Botswana National Statistics Office[115].

Additional district level data was compiled. Health facilities per district were obtained from the 2012 Ministry of Health and Wellness Health Facilities Report[12]. Health facilities per population was calculated using the 2011 census population data[6].

4.4.2 Results (Section 1)

Among 13,411 registered TB patients between January 1, 2013 and November 30, 2014, 2,053 (15%) were recorded as previously treated. The 2,053 patients represent the total after the duplicates (n=16) were removed. Figure 4.1 describes the testing and diagnosis cascade for the 2,053 previously treated TB patients. Only 855/2,053 (42%) patients had a sample submitted at treatment initiation; 70 of these had samples submitted for Xpert testing only. Only 425 patients had at least one culture positive for MTB and/or Xpert positive result; representing 21% of the entire cohort of previously treated patients. Among the entire cohort, 387/2,053 (19%) had a DST result available from samples submitted at treatment initiation (between 3 months prior to treatment initiation and up to one month after treatment initiation). Each level of the cascade is explored in two main sections of results:

A. Sample submission
B. Testing results (culture positivity and DST results)



* Sample submitted to the NTRL or district level Gene Xpert laboratory for testing

** DST refers to rifampicin resistance testing at a minimum

Figure 4.1. Diagnosis and treatment cascade for previously treated patients in Botswana registered 2013-2014

A. Sample submission

Table 4.1 describes the characteristics of previously treated patients and the proportion of patients with a sample submitted per characteristic.

	Total previously treated patients	Sample submitted at treatment initiation
	N =2053	N = 855
Factors	n	n (% per characteristic)
Gender		
Female	820	357 (44%)
Male	1233	498 (40%)
Age Group		
≤18	92	35 (38%)
19-29	270	117 (43%)
30-44	853	371 (43%)
45+	838	332 (40%)
Median (IQR)	41	40 (32-52)
Urban/Rural (Diagnosing facility)		
Urban	485	291 (60%)
Rural	1568	564 (36%)
Facility type		
Clinic	1301	576 (44%)
Health Post	555	210 (38%)
Hospital	179	62 (35%)
Unknown	18	7 (39%)
HIV Status		
Negative	635	254 (40%)
Positive	1277	541 (42%)
Unknown	141	60 (43%)
Smear Status		
Negative	425	183 (43%)
Positive	977	463 (47%)
Not done	651	209 (32%)
Treatment Category		
Previous successful treatment	1836	765 (42%)
Previous treatment failure	77	44 (57%)
Previous treatment lost to follow-up	140	46 (33%)
Year of registration		
2013	1149	464 (40%)
2014	904	391 (43%)

Table 4.1. Patient characteristics and sample submission, previously treated TB patients, 2013-2014

Multivariate analysis

Given the overall low level of sample submission among prevously treated patients, both univariate and multivariate analyses were conducted to further assess if certain clinical or demographic factors were associated with having a sample submitted (Table 4.2). Factors which were significantly associated with increased likelihood of sample submission included any smear result (positive or negative) compared to no smear conducted. Of all previously treated patients, 756 (37%) had a smear test only (at the diagnosing facility), 646 (31%) had both smear and culture testing, 209 (10%) had culture testing only, and 442 (22%) had neither smear nor culture testing (Figure 4.2). Patients with a smear positive result (aOR 1.9) were slightly more likely to have a sample submitted than those with a smear negative result (aOR 1.5). Living in an urban area and a previous TB outcome of treatment failure were also significantly associated with increased likelihood of sample submission. Being diagnosed in an urban area had the largest effect on sample submission; those in an urban area were almost three times more likely to have a sample submitted than those diagnosed in a rural area.

Compared to being diagnosed at a health post, being diagnosed at a clinic was associated with increased likelihood of having a sample submitted in the univariate model but not in the multivariate model. Crosstabulations revealed an association between living in an urban area and being diagnosed at a clinic. Urban patients were more likely to be diagnosed in a clinic (93%), compared to rural patients (54%).

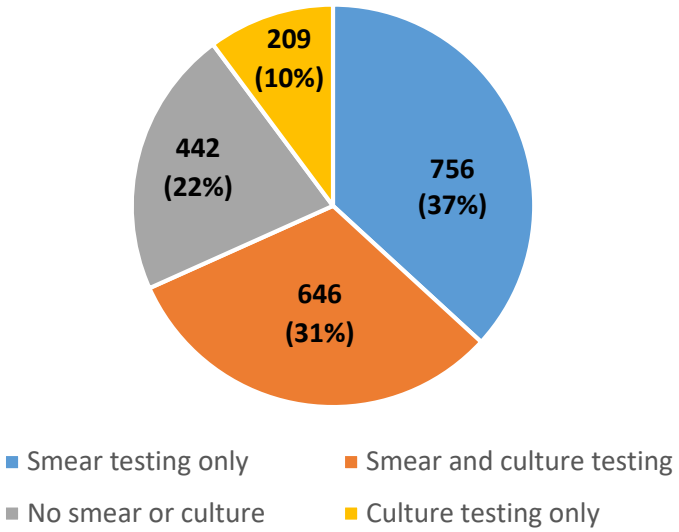


Figure 4.2. Culture and/or smear testing among previously treated TB patients in Botswana, 2013-2014, N=2053

	Total N=2053	Sample submitted N=855		Univariate analysis					Multivariate analysis			
Factors	N	n	%	p-value	OR	CI Lower	CI Upper		P-value	aOR	CI Lower	CI Upper
Facility type												
Health Post	555	210	38%	reference					reference			
Clinic	1301	576	44%	**0.010**	**1.305**	**1.065**	**1.600**		0.742	0.964	0.773	1.202
Hospital	179	62	35%	0.441	0.871	0.612	1.238		0.475	0.877	0.612	1.257
Unknown	18	7	39%	0.928	1.045	0.399	2.739		0.854	1.098	0.406	2.969
HIV Status												
Negative	635	254	40%	reference					reference			
Positive	1277	541	42%	0.323	1.103	0.908	1.338		0.299	1.113	0.910	1.361
Unknown	141	60	43%	0.576	1.111	0.768	1.608		0.391	1.183	0.806	1.735
Smear Status												
Not done	651	209	32%	reference					reference			
Positive	977	463	47%	**0.000**	**1.905**	**1.549**	**2.343**		**0.000**	**1.876**	**1.514**	**2.324**
Negative	425	183	43%	**0.000**	**1.599**	**1.242**	**2.059**		**0.002**	**1.515**	**1.166**	**1.969**
Urban/Rural												
Rural	1568	564	36%	reference					reference			
Urban	485	291	60%	**0.000**	**2.670**	**2.167**	**3.291**		**0.000**	**2.717**	**2.162**	**3.415**
Gender												
Female	820	357	44%	0.157	1.138	0.952	1.361		0.137	1.156	0.955	1.399
Male	1233	498	40%	reference					reference			
Age Group												
≤18	92	35	38%	0.316	0.798	0.513	1.241		0.788	.938	0.589	1.495
19-29	270	117	43%	0.963	0.993	0.754	1.309		0.916	1.016	0.760	1.357
30-44	853	371	43%	reference					reference			
45+	838	332	40%	0.106	0.852	0.702	1.035		0.917	0.989	0.806	1.214
Category												
Previous treatment success	1836	765	42%	reference					reference			
Previous treatment failure	77	44	57%	**0.008**	**1.867**	**1.177**	**2.959**		**0.020**	**1.768**	**1.095**	**2.855**
Previous treatment lost to follow-up	140	46	33%	**0.042**	**0.685**	**0.476**	**0.987**		0.282	0.811	0.554	1.188
Year of registration												
2013	1149	464	40%	reference					reference			
2014	904	391	43%	0.191	1.125	0.943	1.343		0.205	1.126	0.937	1.353

Table 4.2. Logistic regression: factors associatied with sample submission among previously treated TB patients in Botswana 2013-2014

Spatial analysis

Examining the data spatially highlights wide variation in sample submission throughout the 24 health districts in the country. Figure 4.3 displays the proportion of patients with samples submitted per health district, an overall proportion of 42%, ranging from as low as 6% to 78% per district. Maps showing population density and road systems in Botswana are included for comparison. Figure 4.4 displays the proportion of patients with first-line DST results available per health district, an overall proportion of 19% ranging from 2-36% per district. Both maps (Figures 4.3 and 4.4) indicate that lower rates are concentrated on the eastern side where population density is higher. Because this is the opposite of what would be expected, additional district level factors were explored in an attempt to identify factors influencing sample submission rate.

The NTRL is located in Gaborone in the southeastern corner of the country. While Gaborone has the highest percent of sample submission at 78%, it appears there are additional factors beyond distance from the NTRL, contributing to the variation in sample submission and availability of DST results. Table 4.3 describes characteristics of each district listed in order from lowest to highest rates of sample submission. Six out of 24 total health districts have a sample submission rate ≤ 30%. The following characteristics are summarized for each district to determine if any may have an effect on sample submission: population, TB case notification rate, number of TB laboratories (defined as having at least smear microscopy capability), number of health facilities, and health facilities per population.

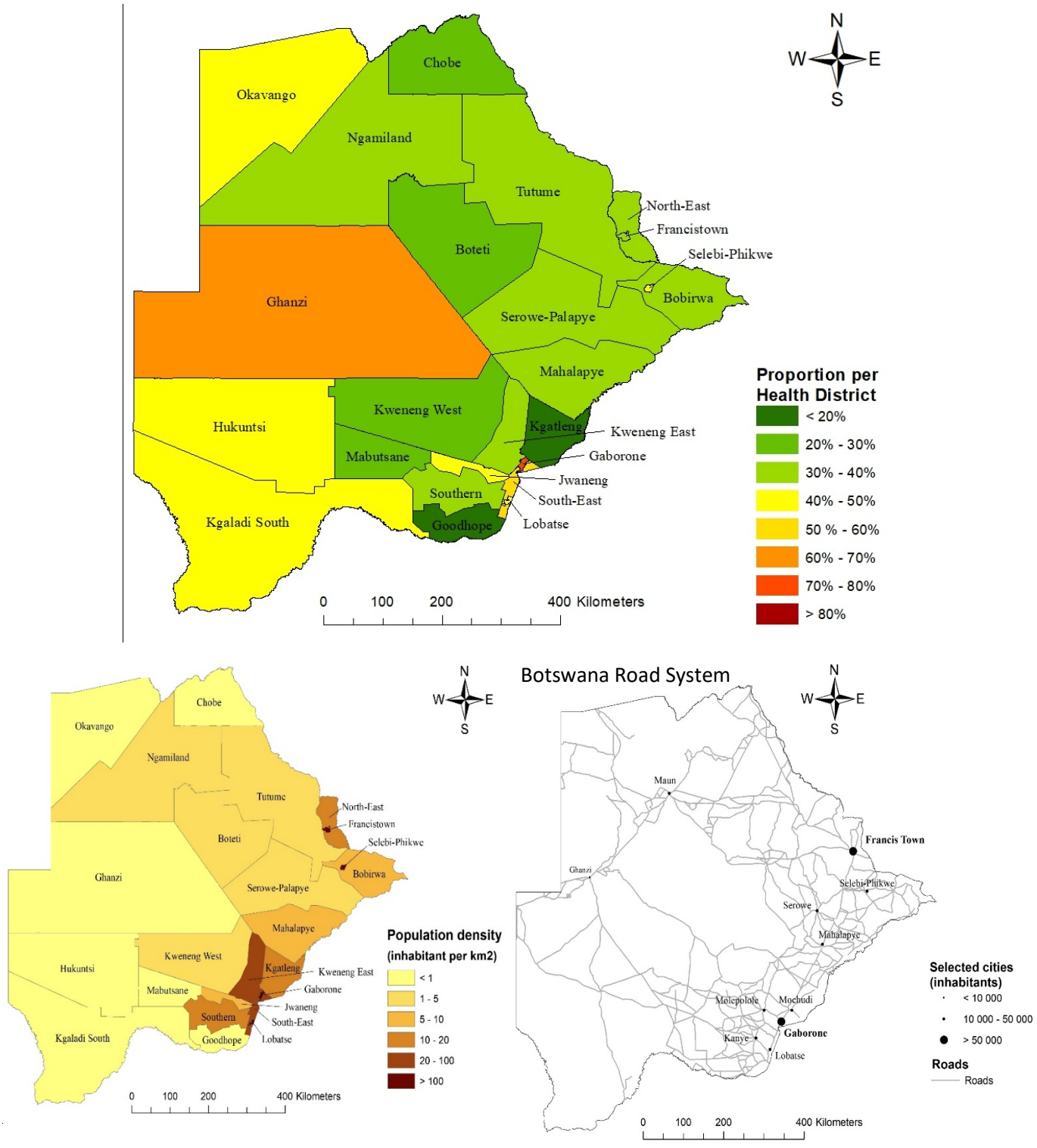


Figure 4.3. Proportion of previously treated TB patients with sample submission per district – and comparison maps of population density and road systems

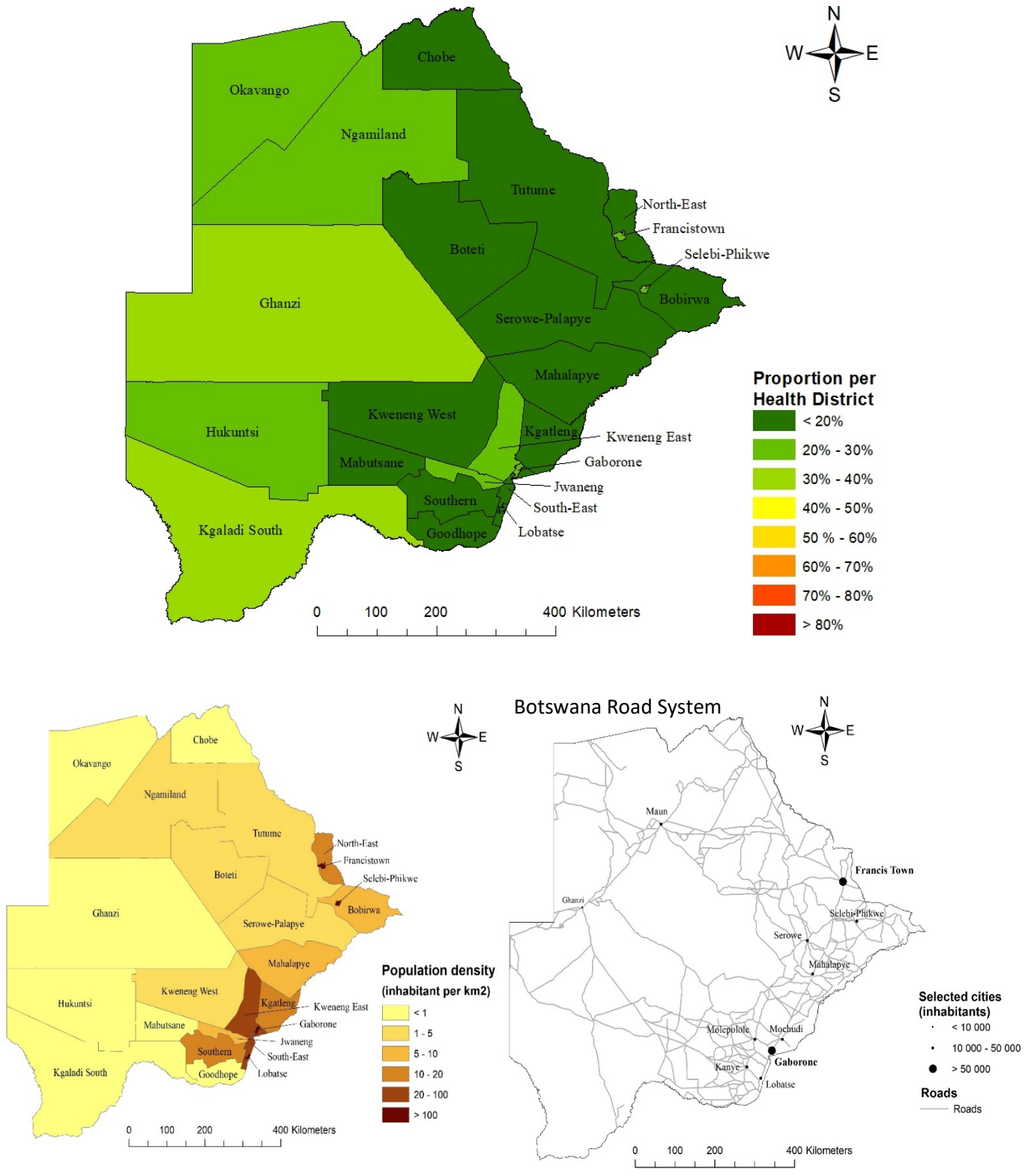


Figure 4.4. Proportion of previously treated TB patients with first-line DST results available per district – and comparison maps of population density and road systems

Districts	Sample submitted	Population [6]	TB Case Notification [14]*	TB Labs [12]**	Referral hospital [12]	General hospital [12]	Primary hospital [12]	Clinics [12]	Health Posts [12]	Mobile Posts[12]	Total Health Facilities[¥] [12]	Population per health facility[6, 12]
KGATLENG	6%	91660	333	0		1		14	16	33	31	2957
GOODHOPE	13%	6362	302	1			1	10	25	14	36	177
CHOBE	23%	23347	243	1			1	3	12	2	16	1459
KWENENG WEST	24%	47797	271	0			1	8	16	26	25	1912
BOTETI	26%	66907	356	3		1	2	12	12	66	27	2478
MABUTSANE	29%	2386	428	0				4	5	3	9	265
SOUTHERN	30%	189019	222	1		1		13	21	13	35	5401
BOBIRWA	34%	71936	196	0			2	8	13	22	23	3128
SEROWE/PALAPYE	35%	180500	309	2		1	1	22	31	53	55	3282
NORTH EAST	35%	60264	223	1			1	12	25	12	38	1586
NGAMILAND	35%	149755	267	1		2		14	20	73	36	4160
TUTUME	36%	150975	233	3			2	12	18	21	32	4718
FRANCISTOWN	37%	98961	314	3	1			25	13	19	39	2537
MAHALAPYE	38%	118875	228	2		1	1	15	28	27	45	2642
KWENENG EAST	39%	256752	370	3		2	1	18	21	42	42	6113
LOBATSE	40%	29007	345	2	1	1		10	1	4	13	2231
OKAVANGO	41%	2529	223	1			1	11	17	30	29	87
JWANENG	42%	18008	520	0		1		7	5	12	13	1385
KGALAGADI NORTH	44%	20476	517	1			1	2	13	3	16	1280
KGALAGADI SOUTH	49%	30016	438	1			1	6	16	14	23	1305
SELEBI PHIKWE	50%	49411	228	1		2		11			13	3801
SOUTH EAST	52%	85014	302	2		1		7	2	36	10	8501
GHANZI	60%	43355	800	1			1	7	15	362	23	1885
GABORONE	78%	231592	284	6	1	1		37	5	13	44	5263

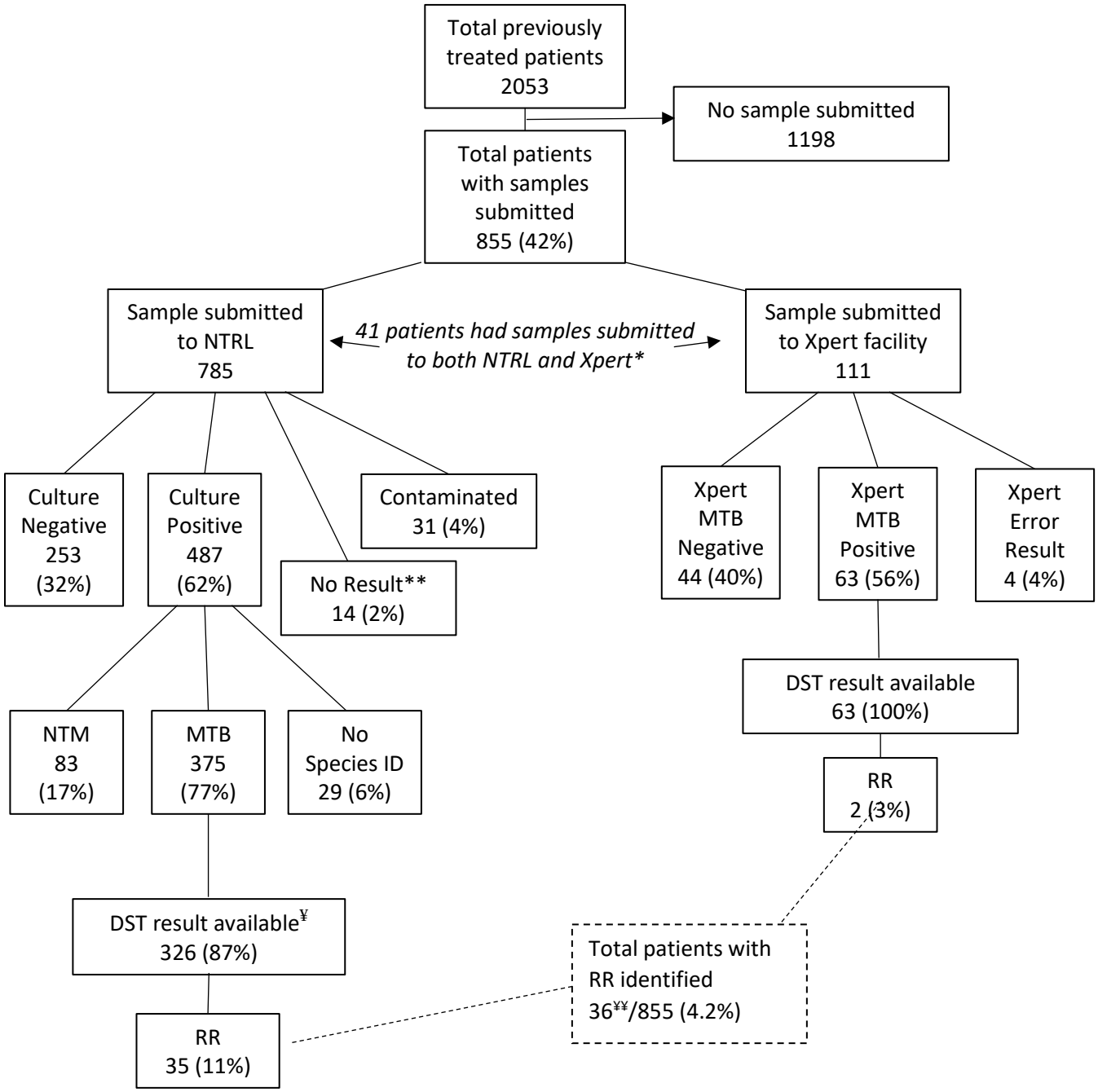
*TB Case Notification – per 100,000 population (2014); **TB laboratory = smear microscopy capability at minimum; [¥]Total health facilities includes hospitals, clinics and health posts

Table 4.3: Characteristics of districts in Botswana

B. Testing results

Figure 4.5 describes the overall testing results of the samples submitted for this cohort. Of 855 patients with samples submitted to any laboratory, 785 had samples submitted directly to or transported to the NTRL, and 111 had samples submitted to an Xpert testing facility; samples were submitted to both the NTRL and an Xpert facility for 41 patients. DST results were available for 326 patients with samples submitted to the NTRL, and these results are from a combination of LJ solid media DST, MGIT liquid media DST and LPA DST (Figure 4.5). Some patients had samples tested by more than one method, therefore there is overlap; any patient with an RR positive result by any one method was considered as diagnosed with RR-TB. Thirty-five patients with RR-TB were identified among samples tested at the NTRL. Because Xpert testing is inclusive of testing for RR, all Xpert positive patients (n=63) are considered to have a first-line DST result available. Two patients with RR were identified among all samples tested by Xpert. One of these patients identified with Xpert as having RR-TB, was also identified through a sample submitted to the NTRL. Therefore, the total number of patients with RR-TB identified was 36, representing 4.6% of all patients with samples submitted. Samples were not submitted for testing for 1,198 patients.

An estimation of the number of patients potentially missed due to inadequate monitoring can be made based on past DRS data for Botswana. Based on the most recent DRS (2008), 13% of previoulsy treated patients in Botswana have RR-TB[17]. Using this estimate, one would expect to diagnose 266 RR-TB patients among this cohort of 2053 previously treated patients included in this analysis. In contrast, only 36 (2% of the total 2053) RR-TB patients were identified through the monitoring efforts described in this analysis indicating that over 200 RR-TB patients may have gone undiagnosed.



* Table 4.4 describes testing results for the patients with samples submitted to both the NTRL and Xpert facility
** No result indicates no culture result was entered into the LIS
¥DST conducted by solid LJ method (207), by MGIT liquid method (110), and/ or by LPA (37)
¥¥The total patients with RR identified is 36 (one patient had RR results at both Xpert facitily and the NTRL)

Figure 4.5. Testing results of previously treated patients (2013-2014) with samples submitted to the NTRL and/or Xpert facility

Table 4.4 describes a comparison of Xpert testing results to results from the NTRL. Of the 63 total Xpert MTB positive tests, 44 (70%) had no sample submitted to the NTRL for culture and DST. Because of the small numbers submitted to the NTRL and the fact that these tests are not from the same sample or necessarily the same day, limited conclusions can be drawn about correlation of tests.

	Xpert testing results (N=111)			
	Xpert MTB (No RR) n=61	Xpert MTB+RR n=2	Xpert Negative n=44	Xpert Error n=4
NTRL testing results				
MTB, Rifampicin Susceptible	9	0	0	2
MTB, DST not conducted	2	1	0	0
MTB+RR	0	1	0	0
NTM* or no species test conducted	2	0	5	0
Negative	4	0	12	0
Contaminated	0	0	2	1
No culture or DST	44	0	25	1

* Non-tuberculosis mycobacteria

Table 4.4. Comparison of Xpert results to the NTRL culture results, 2013-2014

Assessment of culture positivity rates

To assess if any factors (such as transport time) were influencing culture positivity and therefore ability to conduct DST, Table 4.5 explores culture positivity rates and factors for possible association with culture positivity. This analysis includes only samples submitted to the NTRL and does not include samples tested by Xpert only. Having a salivary sample was associated with lower culture positivity in the univariate analysis but not in the multivariate analysis. Additionally, smear status (smear negative), from smear tests conducted at the NTRL, was significantly associated with lower culture positivity. Those with a smear positive sample were 33 times more likely to have a positive culture compared to smear negative samples. It is surprising that neither having a sample submitted post treatment or transport time over one week significantly affected culture positivity.

	Total N= 785	Culture positive N=487		Culture negative N=253		Contaminated N=31		Univariate analysis					Multivariate analysis			
		n	%			n	%	p-value	Odds Ratio	CI Lower	CI Upper		P-value	Odds Ratio	CI Lower	CI Upper
Time of sample submission																
Pre-treatment	246	143	58%	85	35%	14	6%	reference					reference			
Post-treatment (within 1 month)	539	344	64%	168	31%	17	3%	.113	1.287	.942	1.759		.513	1.147	.761	1.730
Smear status at the NTRL																
Smear negative	370	122	33%	217	59%	26	7%	reference					reference			
Smear positive	356	334	94%	16	4%	4	1%	**.000**	**33.263**	**20.158**	**54.889**		**.000**	**33.452**	**20.132**	**55.585**
Not recorded	59	31	53%	20	34%	1	2%	**.000**	**2.940**	**1.622**	**5.331**		**.000**	**3.226**	**1.758**	**5.919**
Sputum appearance																
Salivary	154	81	53%	62	40%	8	5%	reference					reference			
Mucoid	83	61	73%	19	23%	2	2%	**.003**	**2.480**	**1.375**	**4.472**		**.036**	**2.244**	**1.054**	**4.776**
Mucopurulent	497	315	63%	154	31%	18	4%	**.018**	**1.563**	**1.081**	**2.261**		.119	1.463	.907	2.362
Blood stained	34	20	59%	12	35%	1	3%	.486	1.313	.610	2.830		.357	1.568	.603	4.081
Not recorded	17	9	53%	6	35%	2	12%	.937	.960	.352	2.622		.238	2.000	.632	6.329
Time to specimen receipt at lab																
More than 7 days	116	82	71%	26	22%	7	6%	reference					reference			
Within one week (7 days)	547	339	62%	181	33%	19	3%	.089	.682	.439	1.059		.893	1.041	.579	1.872
Not recorded	122	66	54%	46	38%	5	4%	**.019**	**.521**	**.302**	**.898**		.964	.984	.481	2.009

Table 4.5. Univariate and multivariate analysis for culture positivity

4.4.3 Discussion (Section 1)

This study revealed a low rate of monitoring for drug resistance among previously treated TB patients in Botswana; only 42% of patients had samples submitted for culture and fewer still had DST conducted, leading to low RR-TB case detection. Factors which were associated with lower monitoring for drug resistance included not having a smear test at the diagnosing facility, living in a rural area and having a treatment category of previous treatment success. A wide variation in sample submission rates was seen among health districts. However, none of the measured factors completely explain the low access to recommended testing. Poor compliance with the guidelines appears to be the main contributor to inadequate monitoring for this group of at-risk patients.

Sputum culture is the most sensitive test for TB and detects more cases than smear microscopy[116]. Because culture is more costly and time-consuming than microscopy and requires a specialized laboratory and skilled personnel, it is not routinely recommended for all patients[20]. However, culture is essential for certain patient groups in whom the risk of drug-resistance is high or the sensitivity of sputum smear microscopy is low[13]. The Botswana national guidelines do recommend culture testing for high-risk patients, and all previously treated patients should have had a sample submitted for culture and DST[16]. This analysis showed that a low proportion of patients had samples submitted for culture and DST; furthermore, 442 (22%) had neither smear nor culture testing. This analysis highlighted that not having a smear test done was associated with a significantly lower rate of having a sample submitted for culture and DST, indicating that for many patients no sample was collected. Reasons for that may include health care workers not prioritizing the collection of sputum for some patients (i.e. not following recommended guidelines) or patient inability to produce sputum.

All patients in this analysis had previously been treated for TB. Among these, previous successful TB treatment was significantly associated with a lower likelihood of having a sample submitted for culture and DST, as compared to unsuccessful treatment outcomes. Those with a previous treatment outcome of treatment failure were more likely to have a sample submitted for testing, indicating that many clinicians wait for treatment failure before monitoring for drug resistance. However, even among those with previous treatment failure, 43% were not monitored for drug resistance. A study in Peru showed that 94% of patients with TB treatment failure had MDR-TB[117], making this a very important group to monitor for drug resistance.

Receiving TB treatment in a rural setting was significantly associated with lower likelihood of having a sample submitted for culture and DST. This was potentially due to logistical difficulties in transportation of samples to laboratories. The health districts in Botswana are large, and most contain both rural and urban settings. Other district level factors should also be explored, including training of health staff, support from the national level (financial and mentoring), and overall performance of district health management teams.

Given the wide variation in drug resistance testing among districts as highlighted by the spatial analysis, this analysis investigated factors that may explain this variation including: road systems, laboratory and clinical infrastructure, population density and TB case notification rate. None of these factors clearly explained the rates of drug resistance monitoring per district. Population is most concentrated on the eastern side of the country, and in general there are lower rates of drug resistance monitoring along the eastern side of the country (with the exception of the smaller urban districts such as Gaborone and Selebi Phikwe). This is the opposite of what one would expect, and this was also not explained by exploring whether or not there was adequate infrastructure per population. There also appear to be adequate roads for sample transportation throughout the eastern side of the country. Areas with less road infrastructure were able to achieve medium to high rates of sample submission (Okavango, Ghanzi, Hukuntsi and Kgalagadi South).

Of the six districts with sample submission rates below 30%, three had no TB laboratory, which was likely a contributor. The two districts with the lowest rates of sample submission, Kgatleng and Goodhope, are rural districts. Particularly Kgatleng appears to have limited infrastructure (laboratories and health facilities) in comparison to other districts with similar population levels, such as Francistown and South East. However, there were other districts with low or high submission rates with no clear correlation to population, road systems or infrastructure. Therefore, the spatial and district analysis unfortunately did not provide clarity into this variation among districts. The districts of Gaborone and Ghanzi have the highest rates of sample submission. It should be noted that two large TB research studies were being conducted in these districts during the time of this current analysis; therefore it is possible that these districts have higher compliance to the recommended testing because of the research studies and the additional research staff who were placed in these districts.

A positive culture test is needed in order to perform phenotypic DST. Therefore, to determine if there were any areas to improve culture positivity rates (i.e. time to specimen receipt, NTRL practices), an assessment was conducted to determine if any modifiable factors were associated with culture positivity. The culture positivity rates observed in this analysis were consistent with the rates observed in the most recent DRS[17] (2008), as well as the WHO reports. The WHO mycobacteriology laboratory manual[118] reports that more than 90% of smear positive samples should be culture positive. In the most recent DRS, culture positivity was presented separately for smear negative and smear positive previously treated patients. Among smear positive patients from the DRS, 87% were culture positive[17] consistent with the findings of this analysis, which reported, culture positivity among 94% of smear positive patients. Among smear negative patients from the DRS, 28% were culture positive[17], consistent with this analysis' finding that 33% of smear negative patients were culture positive. A study in Uganda also reports low culture positivity (23%) among smear negative HIV positive TB patients[119]. Smear negative pulmonary TB disease has been documented to be more prevalent among HIV infected patients in sub-Saharan Africa[120] and is harder to diagnose[121]. Culture positivity rates among this cohort were what would

be expected, and among those that were culture positive, 91% had DST. Time to specimen receipt in the lab or the NTRL sample preparation and testing practices do not seem to contribute to the low case detection observed in this analysis.

In the whole WHO African region, only 43% of previously treated TB patients are tested for rifampicin resistance[13]. Some African countries are able to monitor over 50% of previously treated patients, including Congo (57%), Kenya (52%), Nigeria (61%) and South Africa (68%). Outside of Africa, other high burden countries are shown to monitor high rates including India (82%) and Philippines (83%)[13]. Other research reports a wide range of monitoring for drug resistance among previously treated TB patients. In Nepal, RR-TB is also poorly detected, and a study revealed that only 15% of previously treated patients had samples submitted for culture and DST[122]. In Sri Lanka, 79% of previously treated TB patients had samples submitted for culture and DST[123].

The most recent 2017 TB country profile for Botswana indicated that only 5% of previously treated patients are monitored for RR-TB, indicating that the problem in Botswana may be getting worse. Botswana is an upper-middle income country with an overall small population and presumably should be able to achieve monitoring similar to other upper-middle income countries. However, the 19% of previously treated patients with DST in this analysis (and the even lower proportion (5%) of patients in the most recent WHO report) is lower than other countries with the same income status, including South Africa (68%), China (69%) and Gabon (40%)[13]. In Algeria and Equatorial Guinea (upper middle income countries), 14% and 29%, respectively, of previously treated patients are estimated to have RR-TB; both countries achieve 100% monitoring for RR-TB among previously treated patients[13]. It is surprising that Botswana's rate of monitoring is so low and appears to be worsening, given the implementation of Gene Xpert machines in Botswana. However, Chapter 8 will highlight challenges being experienced with the Xpert implementation in Botswana as well as ongoing challenges of the NTRL closures.

As a result of inadequate monitoring for drug resistance, patients with drug resistance are likely to remain undiagnosed. These patients may be detected with TB drug resistance during subsequent TB treatment episodes, but in the meantime they are likely to develop more severe disease, and remain infectious for longer[117] possibly transmitting drug-resistant tuberculosis in the community and at the health centers where they are seeking care. However, many patients, particularly those with HIV infection are likely to die during TB treatment if their TB drug resistance remains undiagnosed. Among patients receiving first-line TB treatment in Botswana in 2014, a total of 9% died; among HIV negative patients, 6% died, compared to 10% of HIV positive patients and 15 % of patients with unknown HIV status[14]. Some of these patients may have been diagnosed later after treatment failure, but this may lead to resistance amplification[124] as well as higher risk of mortality[125]. It

should also be noted that the last DRS in Botswana was conducted in 2008; it is possible that drug resistance has increased, and the gap in case detection may be underestimated.

None of the factors investigated in this analysis clearly explain the low rates of sample submission, and it appears that poor compliance with the guidelines may be the main contributor. A previous study in Botswana reported that guidelines for diagnosing smear negative pulmonary TB disease were not well followed in Botswana[126]. Clinicians were interviewed as part of this previous study and reported reasons for non-adherence to guidelines including inability of patients to produce sputum and frustration with long laboratory delays in releasing sputum results[126]. The current TB guidelines in Botswana were last updated in 2011, and there is lack of clarity in some of the guidance. For example, the recommendations for who should receive culture and DST include a list of patient groups who are 'at risk' and does not separate or identify the reasons for testing these groups of patients (i.e. risk of drug resistance or lower sensitivity of smear microscopy). Mohr, et al identified missed opportunities for early diagnosis of RR-TB due to noncompliance with diagnostic algorithms; specifically, this study reported that 18% of patients were screened incorrectly at some point while seeking care in the 6 months before the eventual RR-TB diagnosis[127]. Other research highlighting noncompliance with guidelines suggests that inconsistencies with training and distribution of guidelines contributes to noncompliance[70].

The study did have limitations. Some important information that may influence adherence to guidelines was not available including staffing levels at facilities, training of staff in districts, availability of guidelines in the facilities and other indicators of district level performance. Submission of samples was determined by matching two databases, the electronic TB registry and the national laboratory information system. Matching was done manually by name and ID number, and it is possible that some matches were missed due to mis-entering of names or ID numbers in either database. This analysis only examined one group of patients at increased risk of drug resistance, and it would be important to assess performance of recommended testing among other groups of at risk patients.

To address the low rate of monitoring for drug resistance and the wide range of variability among districts, it is crucial that the TB program focus on disseminating clear education and guidance to health facilities at all levels (from hospitals to mobile posts) regarding testing for this and other high-risk groups of patients. Program supervision and monitoring are needed to ensure guidelines are followed consistently. Ensuring adequate resources at all facilities in the districts (rural and urban) is essential. Greater access to Xpert through decentralized laboratories has the potential to reduce gaps and improve RR-TB case detection if it could be implemented effectively and if the high priority groups are targeted for testing with Xpert.

4.5 Section 2: Confirmation of drug resistance profile for patients initiating second-line treatment

4.5.1 Methods (Section 2)

Study population

The study population included all patients registered for second-line treatment in the RR-TB register between January 1, 2006 and December 31, 2014. Patients registered for treatment more than once were considered as separate patients. The full methods for development and description of this database are included in the Methods chapter.

Definitions

The primary outcome of this analysis is confirmation of drug resistance profile. Confirmation of first-line drug resistance profile is defined for this analysis as having DST results (for at least rifampicin) available in the RR-TB treatment register. Confirmation of second-line drug resistance is defined as having second-line DST results (for at least fluoroquinolones and/or injectable drugs) available in the RR-TB treatment register. While the DST results are recorded in the RR-TB treatment register, it is not always known if the result is from a baseline sample (specimen collection date is not recorded). Therefore, for this analysis the resistance profile categories were not assumed to be from baseline DST. Patients are considered to have confirmation of drug resistance if they have a DST result recorded in the treatment register, regardless of date of DST. Patients with Xpert DST results only were included as having confirmation of first-line drug resistance. Patients were categorized as presumptive RR-TB patients if they never had a confirmed first-line drug resistance profile recorded in the register throughout treatment.

Data analysis

For patient characteristics and primary outcome data, categorical variables were summarized using frequencies and proportions, and continuous variables were summarized using median values and interquartile ranges (IQR). A graph was created to describe confirmation of drug resistance over time among this cohort.

Using the date that second-line DST was recorded in the RR-TB register (defined as the date the result is available), time to second-line DST from treatment initiation was calculated, producing median and IQR. Patients with second-line DST results available before treatment initiation were given a time to DST of 0 days. A Kaplan Meier curve was created for time to second-line DST; patients were censored at date of DST or date of treatment end. Time to second-line DST result was defined as time from second-line treatment initiation to the time a second-line result was reviewed at the laboratory.

All analyses were conducted using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) or Excel (for basic charts and graphs).

4.5.2 Results (Section 2)

Figure 4.6 displays the number of RR-TB patients registered by year and the TB (drug sensitive) case notification by year. The TB case notification rate has declined over the study time period. On the other hand, the number of patients registered as RR-TB patients has been variable over time with no clear trend.

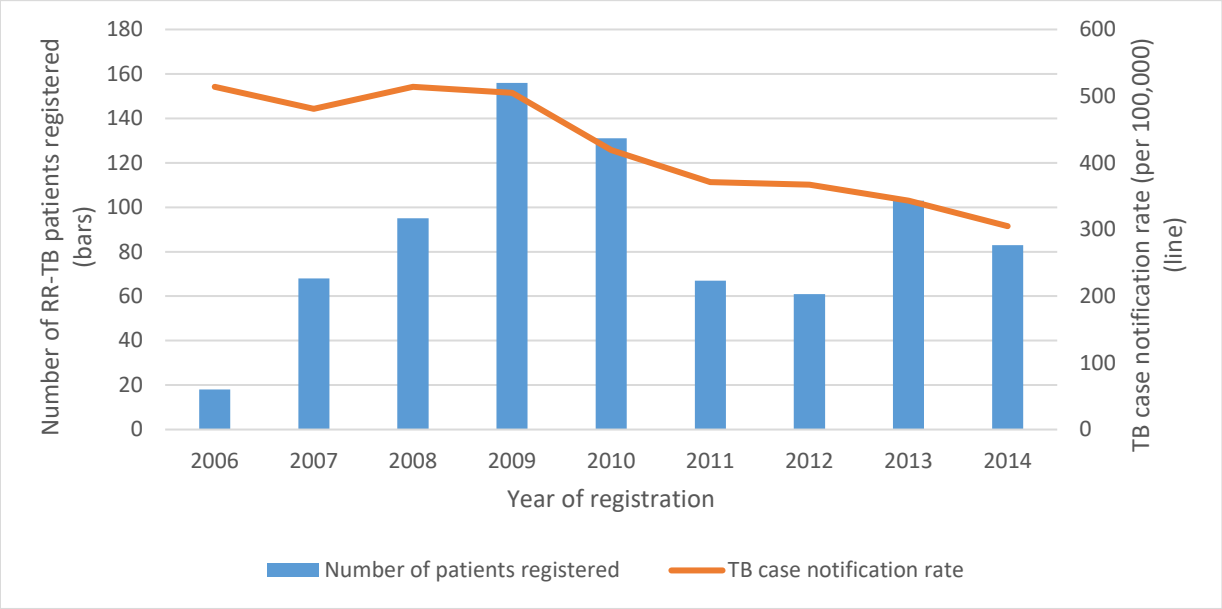


Figure 4.6. RR-TB patients registered and TB case notification by year

Of 785 patients in the treatment register, 665 (85%) had a first-line DST result available and were therefore bacteriologically confirmed RR-TB patients. Among these 665 patients 190/665 (29%) had a second-line DST result available in the RR-TB treatment register (Figure 4.7).

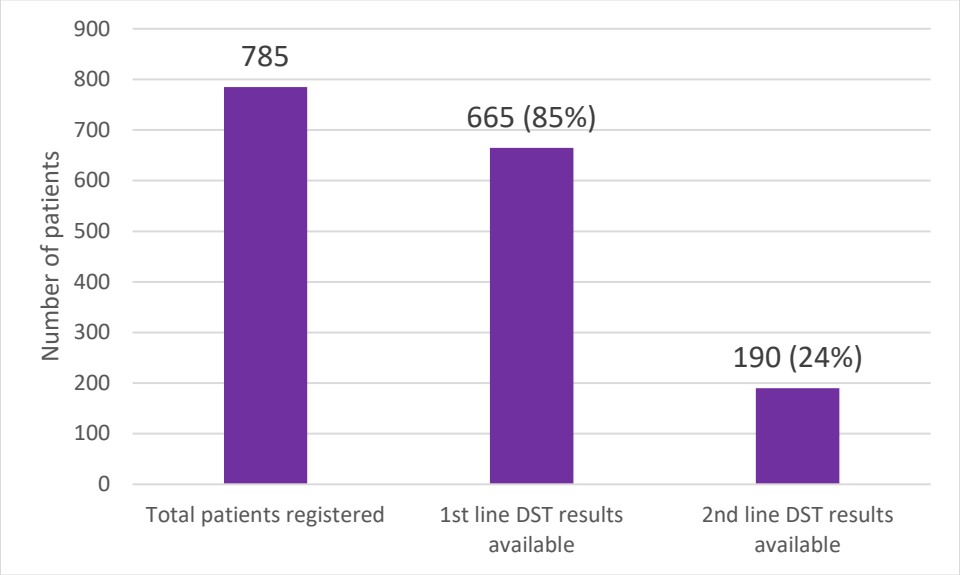


Figure 4.7. Diagnosis cascade for patients registered for RR-TB treatment 2006-2014

Patient characteristics

Table 4.6 describes the characteristics of patients included in the RR-TB treatment register between January 1, 2006 and December 31, 2014 and the proportion of patients with confirmed drug resistance profiles per characteristic. Overall, 85% of patients had confirmation of first-line drug resistance but this was much lower among younger patients, particularly those aged 5 years and under. Confirmation of first-line drug resistance profile was also lower among patients with no previous TB treatment, those with unknown HIV status and those with extrapulmonary TB (including those with both pulmonary and extrapulmonary disease). Overall, only 24% of patients had confirmation of second-line drug resistance profile, and this was particularly low in recent years. There were no patients with confirmation of second-line drug resistance profile who did not also have confirmation of first-line drug resistance profile.

Of the 785 registered patients, 120 (15%) had no confirmation of first or second-line drug resistance profile and are classified as presumptive RR-TB patients. Among these 120 patients, 41 (34%) were female, 73 (61%) were HIV positive, and the median age was 38 (IQR 19-51).

Characteristic	Total Cohort	First-line DST results available among entire cohort		Second-line DST results available among those with first-line DST	
	n	n (%)		n (%)	
TOTAL	785	665 (85%)		190	24%
Age					
≤5	20	5	25%	1	20%
6 to 18	53	39	74%	8	21%
19-29	164	152	93%	56	37%
30-44	328	290	88%	78	27%
45+	202	165	82%	47	28%
Not recorded	18	14	78%	0	0%
Median (IQR)	36 (28-46)				
Gender					
Female	361	320	89%	98	31%
Male	424	345	81%	92	27%
HIV Status					
HIV negative	254	210	83%	56	27%
HIV Positive on ART*	449	389	87%	131	34%
HIV Positive not on ART	37	30	81%	3	10%
HIV Positive ART unknown	34	28	82%	0	0%
HIV status unknown	11	8	73%	0	0%
Smear at treatment start					
Negative	220	179	81%	40	22%
Positive	427	372	87%	140	38%
Not recorded	138	114	83%	10	9%
Baseline radiology					
Non-cavitary	285	243	85%	65	27%
Cavitary	252	216	86%	78	36%
Not recorded	248	206	83%	47	23%
Registration Category					
New TB (no previous TB treatment)	65	49	75%	9	18%
Previous cure or completed treatment	15	14	93%	4	29%
Treatment after failure	622	536	86%	170	32%
Not recorded	83	66	80%	7	11%
TB site					
Pulmonary	695	601	86%	169	28%
Extrapulmonary and both	73	55	75%	21	38%
Not recorded	17	9	53%	0	0%
Treatment facility					
NRH	230	205	89%	61	30%
LIIMH	64	52	81%	14	27%
GPH	57	49	86%	13	27%

PMH	341	281	82%	89	32%
SMH	93	78	84%	13	17%
Year of registration					
2006	18	14	78%	2	14%
2007	68	59	87%	29	49%
2008	95	81	85%	34	42%
2009	156	137	88%	46	34%
2010	131	104	79%	55	53%
2011	67	48	72%	17	35%
2012	61	51	84%	1	2%
2013	103	93	90%	3	3%
2014	83	78	94%	3	4%
Year not recorded	3	0	0%	0	0%

Table 4.6. Characteristics of patients in the RR-TB treatment register, 2006-2014

Confirmation of first and second-line drug resistance over time

Figure 4.8 describes the number of patients in the treatment register with a confirmed first-line drug resistance profile per year, and Figure 4.9 describes the proportion of patients with a confirmed second-line drug resistance profile per year. These figures do not represent a diagnostic cascade; rather they display the gap that exists between empiric treatment and diagnostic confirmation. Overall, the proportion of patients with first-line DST results is 85% and this has remained consistent throughout the years. On the other hand, the proportion of patients with second-line DST results has been consistently low and has dropped in recent years.

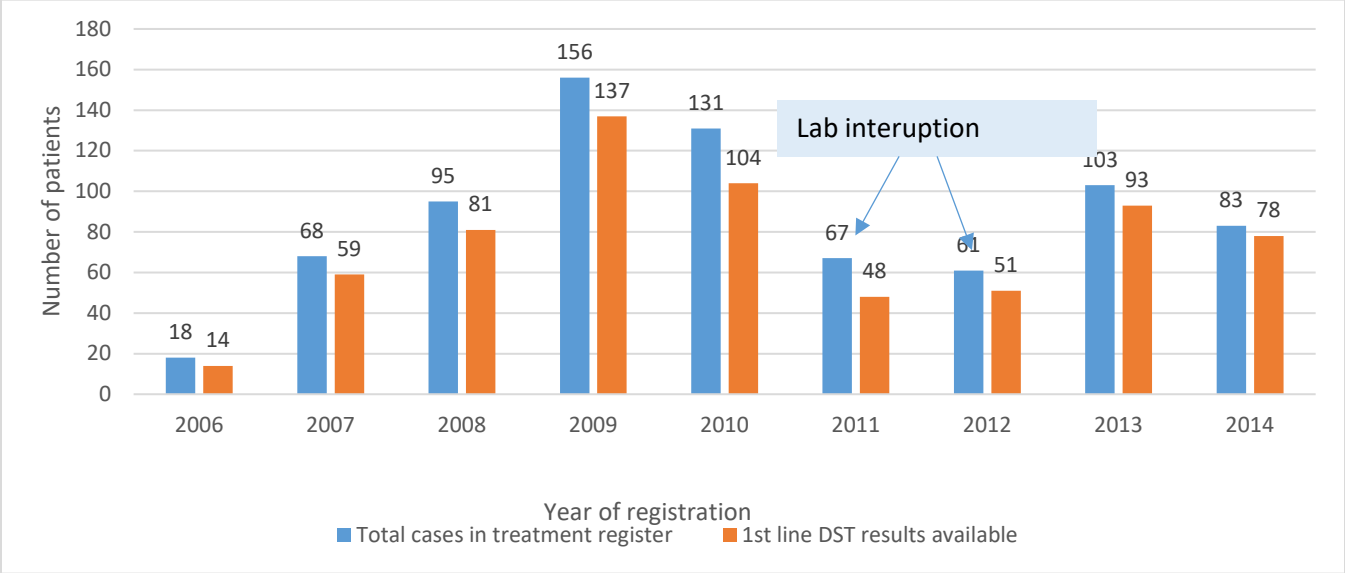


Figure 4.8. Number of registered RR-TB patients with confirmed first-line drug resistance profile, by year

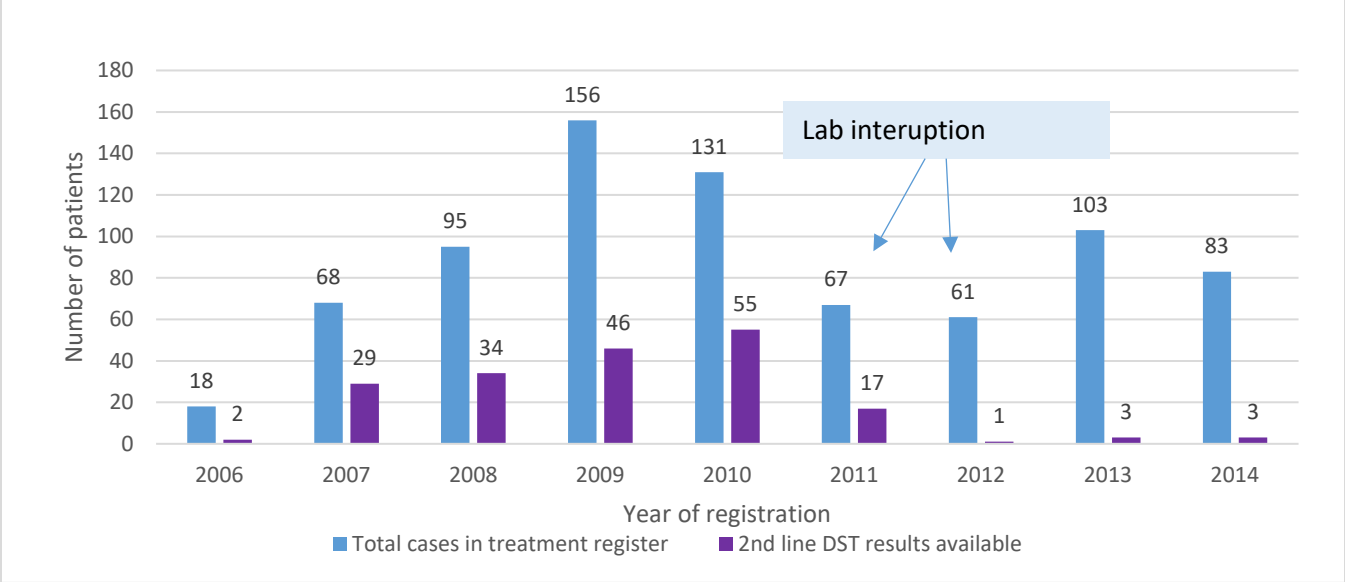


Figure 4.9. Number of registered RR-TB patients with confirmed of second-line drug resistance profile, by year

Time to second-line DST

A total of 190 patients had second-line DST results available in the RR-TB register; 14 (7%) had no date of DST result in the RR-TB register and were excluded from the time to DST analysis. Of the 176 patients with a second-line DST result and date, the median time to second-line DST results from initiation of second-line treatment was 63 days (IQR 0-174). Patients with DST results available before treatment initiation were given a time to DST of 0 days. Figure 4.10 displays the curve for time from treatment initiation to second-line DST result (event of interest). All patients who initiated treatment and had a known date of event or date of treatment stop were included in this analysis (704), and patients were censored at time of event (DST result available) or treatment stop. Patients remained in the analysis until time of event or treatment stop. At day 500 after treatment initiation, 295 patients remained in the analysis, at day 600, 190 patients remained, and at day 700, only 25 patients remained in the analysis. Among these 25 patients, two received subsequent second-line DST due to treatment failure, explaining the rise in the curve at this point.

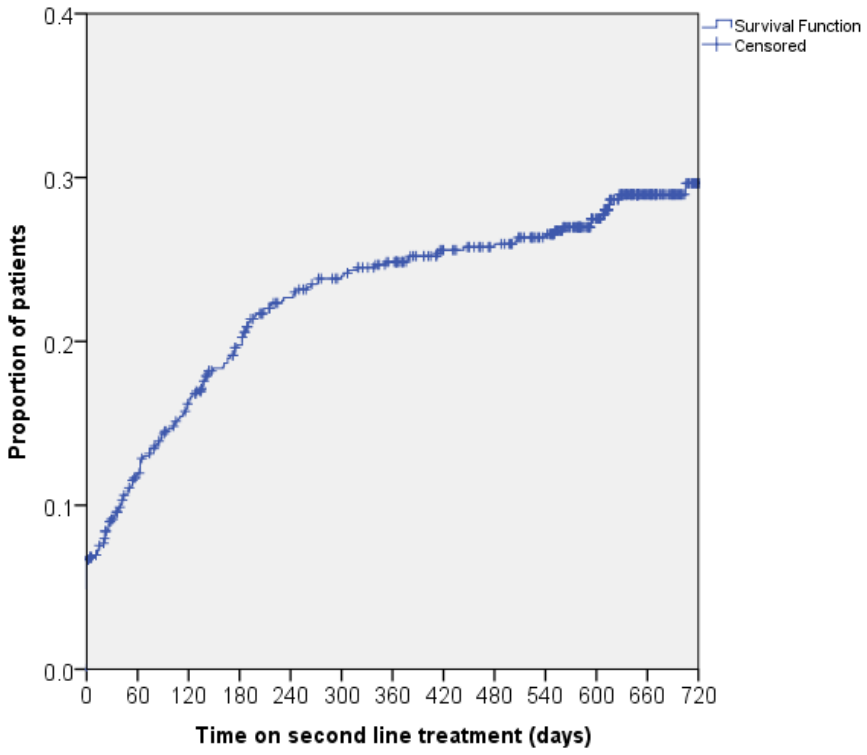
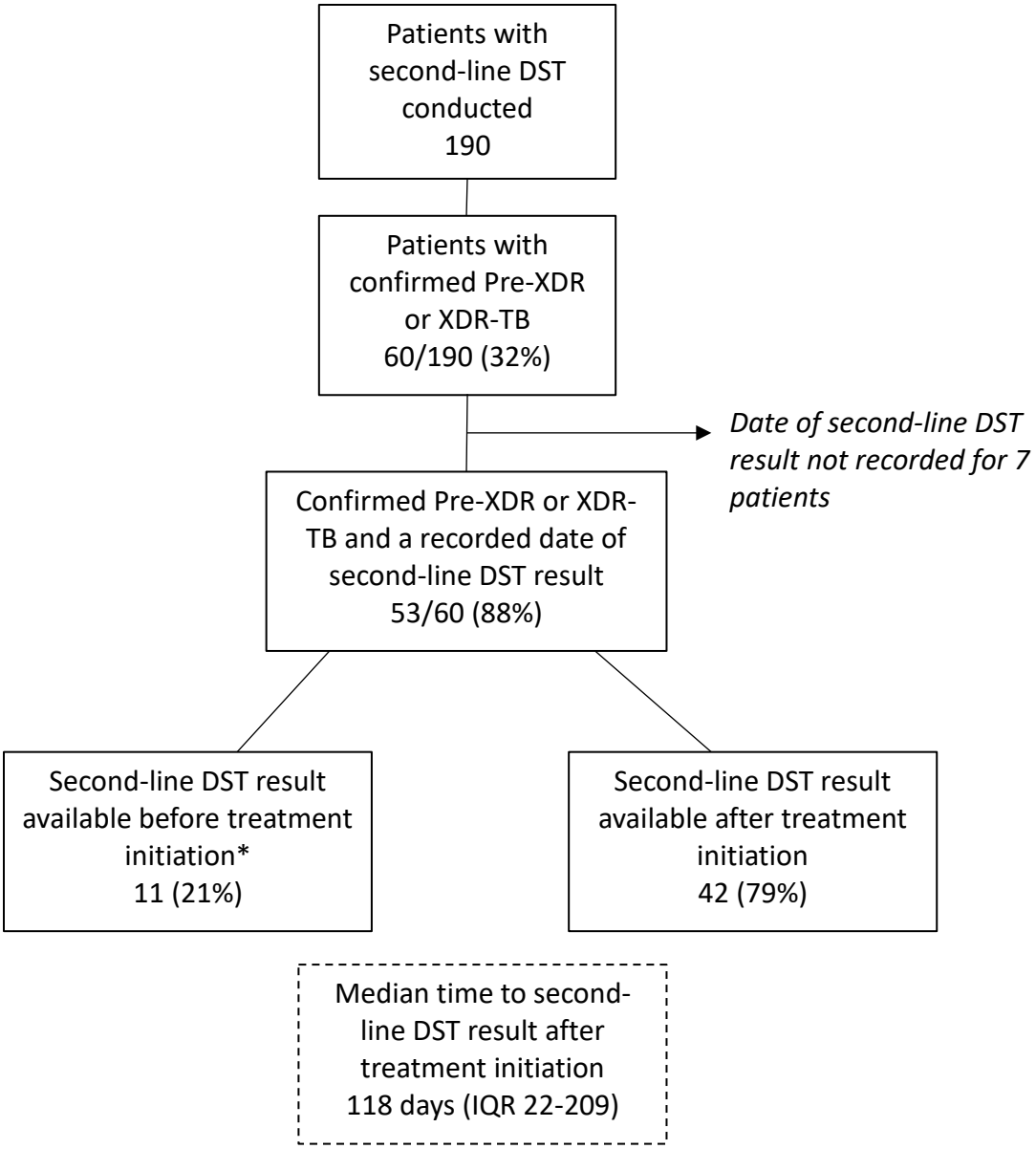


Figure 4.10. Time from treatment initiation to second-line DST results available, Kaplan Meier

Second-line DST results for patients with confirmed Pre-XDR or XDR-TB

Of the 190 patients with second-line DST results, a total of 60 (32%) patients had laboratory confirmed Pre-XDR or XDR-TB, and 53 had a known second-line DST result date. Among these 53, 11 (21%) had second-line DST results available at the time of second-line treatment intiiation, while 42/53 (79%) had second-line DST results available after inititiating second-line treatment (Figure 4.11). These results were available a median of 118 days after treatment initiation; this time extended beyond 1 year for 6 of these patients.



* Patients with DST results available before treatment initiation were given a time to DST of 0 days

Figure 4.11. Pre-XDR or XDR-TB patients and timing of second-line DST

4.5.2 Discussion (Section 2)

RR-TB case registration has varied considerably over time. For patients initiating RR-TB treatment, the first-line drug resistance profile was confirmed for 85%, and this proportion has remained consistent over time. There were 120 patients with presumptive RR-TB, who received second-line treatment with no information about resistance available at any point during treatment. Notably, many younger patients did not have access to first-line DST, likely due to the challenges of sample collection from younger patients[128, 129]. Second-line DST was available for few patients (24%) and has been impacted by changing practices (not sending samples to South Africa for testing) and no in-country laboratory capacity.

There is a range of laboratory confirmation of RR-TB patients reported for other countries. In the Middle East where drug-resistant TB cases are underreported, a study reports that limited laboratory capacity leads to under-diagnosis of drug-resistant TB; in Iran 48/53 (91%) patients started on MDR-TB treatment were laboratory confirmed, and this was well under the total estimated MDR-TB cases (131) in the country[130]. A study in India reported that 45/58 (78%) HIV positive, presumptive MDR-TB patients on treatment were confirmed[131]. Based on the WHO country profiles of high burden TB countries, many countries appear to achieve laboratory confirmation for most or all of the RR-TB patients. For example, Angola reports laboratory confirmation for 100% of patients initiating treatment, Mozambique reports laboratory confirmation for 95% of patients initiating treatment, and South Africa reports laboratory confirmation for more patients than have initiated treatment (15,986 patients with laboratory confirmation, with 10,259 patients initiating treatment)[13]. It should be noted that for many countries this is still well under the estimated RR-TB cases in the country, and for countries like South Africa there appear to be challenges with linking bacteriologically confirmed patients to care[42]. However, for the purposes of comparing the proportion of RR-TB patients on treatment with laboratory confirmation, it is clear that with the 85% of RR-TB patients with laboratory confirmation in Botswana, many countries are performing much better than Botswana.

The effect of interrupted laboratory services was highlighted in this analysis. In 2011 and 2012, the national laboratory had limited capacity overall due to renovations (2011) and limited reagent availability (2012), therefore all diagnosis numbers dropped during these years. Testing for some priority patients with known or presumed RR-TB was still conducted with the assistance of the US CDC TB research laboratory in Gaborone. However, the research laboratory was not able to cover all testing needs during this time frame, and only select patients identified by the government as high priority received testing. While the proportion of patients with confirmed RR-TB did not decrease during this time, the overall numbers of patients identified with rifampicin resistance did decrease. Many patients are likely to have been missed during these years and may have died or entered treatment very late leading to increased transmission risk in the communities.

Additionally, laboratory infrastructure for second-line DST testing suffered a major interruption after 2010. Until 2010, Botswana followed guidelines to send samples to South Africa for second-line DST. In 2010, the country began to move forward with plans to develop laboratory capacity to locally conduct second-line DST. However, due to laboratory interruption and lengthy validation processes, the country did not have the local capacity to conduct second-line DST until 2014. During this gap, 2010-2014, few samples were sent to South Africa for testing, per personal communication[11]. As a result, patients with Pre-XDR or XDR-TB may have not been identified, and consequently many patients may have received ineffective second-line treatment.

Examining time to second-line DST is important to understand how long patients may be on ineffective therapy if additional second-line resistance is present. For the patients with second-line DST, the results were available a median of 63 days after second-line treatment initiation. Among those who were eventually confirmed to have Pre-XDR or XDR-TB, these confirmatory results were available a median of 118 days after treatment initiation, with a delay of more than one year for some patients; therefore, it is difficult to discern whether second-line resistance was present at treatment start or developed during treatment. The low proportion of patients with access to second-line DST and the delay among some of those who do have access contributes to potentially ineffective regimens for many patients.

This study had limitations. Firstly, DST results were reported in the RR-TB register, but the timing of specimen collection was not reported; only the date the DST result is recorded in the RR-TB register is available. Therefore, this analysis used a definition of confirmation of drug resistance profile based on results available at any point during treatment. Therefore, the analysis did not address when that resistance may have developed (pre-existing or during treatment) and the length of time patients may have been receiving potentially ineffective treatment. The program should focus on improving data quality and also further exploration around timing of DST to guide treatment. Secondly, guidelines regarding second-line DST were inconsistent; while the 2011 TB program manual recommended second-line DST for all patients receiving RR-TB treatment, the 2009 National Guidelines for Management of DR-TB recommended second-line DST only for patients who remained culture positive after four months of treatment. Both were current guidelines in use during the time of the study; while it is possible that these were inconsistent because the guidelines were changing over time, it is unclear which guidelines were meant to be adhered to. Therefore, the research cannot draw specific conclusions about compliance with guidance since the guidance is unclear. Regardless, there are clear gaps in access to both first- and second-line DST in Botswana.

Several factors influence the varied case detection over time observed in Botswana, including inadequate screening of at risk patients identified in Section 1 of this chapter. Furthermore, once patients are identified, it is crucial to confirm drug resistance profile to ensure effective treatment. Recommendations for the program

would include ensuring updated guidance is clear and fully disseminated to all health facilities. The program should focus on consistent laboratory capacity and reducing interruptions, which affect case detection and confirmation.

Chapter 5: Risk factors for mortality during treatment of rifampicin-resistant TB in Botswana

5.1 Chapter overview

This chapter will include two sections, describing analysis of two cohorts. The first section describes analysis of RR-TB patients initiating second-line treatment from 2006-2014 inclusive (Cohort 1). The Cohort 1 section explores risk factors for mortality over time. The second cohort is a subset of Cohort 1 for which additional information was collected through medical record review (Cohort 2). Cohort 2 includes patients from 2012-2014 inclusive, and this section will add to findings of the first section by further exploring the frequency and impact of disease severity and drug side effects on mortality during treatment. The chapter begins with an overview of background and policies regarding RR-TB management in Botswana, relevant to both sections.

5.2 Hypotheses, aim and objectives

Hypothesis 1: Mortality among patients initiating RR-TB treatment is associated with identifiable risk factors, some of which are modifiable

Hypothesis 2: Time to mortality is affected by specific risk factors.

Aim: To identify and determine risk factors for mortality among RR-TB patients in Botswana

Objectives:

To describe the proportion of patients initiating treatment who have died and risk factors for mortality

To describe time to mortality and factors associated with early and late mortality

To describe the frequency of co-morbidities and side effects and their impact on mortality

5.3 Background/Policy review

Globally, mortality as a treatment outcome among RR-TB patients who initiated treatment in 2015 is reported as 15%; success (cured or completed treatment) among this same cohort is reported as 55%, and the remaining have outcomes of treatment failure (8%), lost to follow-up (14%) or no outcome information (7%)[13]. In comparison, Botswana has reported mortality as a treatment outcome for 17%, treatment success for 78%, lost to follow-up for 2% and treatment failure for 2% among the cohort that will be described in this chapter (patients initiating treatment from 2006-2014). In Botswana, in contrast to other settings and globally, lost to follow-up and treatment failure rates are low, and mortality during treatment is the main contributor to poor

outcomes. Therefore, reducing mortality is the main area in which the Botswana TB program should focus efforts to improve treatment outcomes for RR-TB patients. Hence, this analysis was planned in collaboration with the Botswana National TB Program (BNTP) to try to better understand the factors associated with mortality and to identify modifiable risk factors for potential interventions.

RR-TB in Botswana is managed at specialized centers with both inpatient and outpatient care. RR-TB care has been decentralized from two referral hospitals in 2006 to five facilities by 2010. Currently, all presumptive and confirmed RR-TB patients are referred to one of five specialized government RR-TB treatment centers located around the country[16]. These five centers are managed by a team including physicians and nurses who have received specific training in RR-TB care. All national guidance up to the most recent 2011 TB Program Manual suggest that all RR-TB patients are initially started on a standardized treatment regimen[16], and this is retained in the 2017 updated national guidelines for management of drug-resistant TB (still in draft, 2019)[92]. Based on the 2007 TB Program Manual, the standardized regimen at that time was composed of amikacin, ethionamide, pyrazinamide and ciprofloxacin[132]. The standardized regimen was updated by 2009 to be composed of amikacin, levofloxacin, ethionamide, cycloserine, pyrazinamide and P-aminosalicylic acid (PAS)[48]. According to the 2009 National Guidelines for Management of DR-TB, the recommended duration of treatment is 18 months after culture conversion[48]. All national guidelines have suggested that individualized regimens may be provided for patients based on DST results or patients who do not culture convert after four months of treatment. As of 2008, additional drugs available for individualized regimens included linezolid, clarithromycin, clofazimine, capreomycin and augmentin[104]. Based on the 2011 TB Program Manual, RMR-TB patients are treated with isoniazid, ethambutol, levofloxacin and at least two months of pyrazinamide; minimum treatment duration is 12-18 months[16]. The 2017 draft (unreleased) updated national guidelines for the management of drug-resistant TB suggest that the program is considering moving to the short course MDR regimen for RMR-TB patients. General recommendations for treatment of pre-XDR or XDR-TB (i.e. use an injectable for which the strain is susceptible and extend duration) are included in the treatment guidelines, and providers are advised to liaise with national level consultants in developing the regimen for patients with Pre-XDR or XDR-TB[48].

Some patients are hospitalized for the intensive phase of treatment; and reasons for hospitalization are discussed further in Chapter 8. National guidelines suggest that RR-TB patients on ambulatory treatment should receive directly observed treatment (DOT), provided by health facilities (hospitals, clinics, health posts) or by trained community volunteers[48]. Throughout the entire course of treatment, patient-held treatment cards are supposed to be signed every day by a DOT provider to record adherence, and ambulatory patients are seen at the specialized RR-TB treatment facilities once a month for monitoring[48].

National guidance suggests that all RR-TB patients should have a baseline culture and first-line DST[48] (2009 National Guidelines for Management of DR-TB). Patients are to be monitored throughout second-line treatment with monthly smear and culture testing[48]. There is conflicting guidance regarding second-line DST. While the most recent TB program manual (2011) states that all confirmed RR-TB patients should receive second-line DST[16], the 2009 National Guidelines for Management of DR-TB states that only those who remain culture positive after four months of treatment should receive second-line DST[48]. As described in Chapter 4, capacity for first- and second-line DST in Botswana was affected by laboratory closures (2011-2012, 2014-2016) and changes in practices whereby the program stopped sending samples to South Africa for second-line DST after 2010. At monthly consultations, patients should also be monitored for side effects, and the 2009 guidelines provide recommendations for laboratory testing (frequency and type of tests)[48]. For example, serum creatinine is to be monitored at baseline and monthly while receiving an injectable drug.

5.4 Section 1: Mortality among RR-TB patients initiating treatment 2006-2014

5.4.1 Methods (Section 1)

Study population and definitions

This analysis included patients registered in the RR-TB treatment register from 2006-2014 (Cohort 1). The development of the study database from the RR-TB treatment register is described in detail in Chapter 3 (Data/Methods Chapter). Patients were excluded from this analysis if they were registered but did not initiate treatment or if they had an unknown treatment outcome date.

The primary outcome of this analysis was mortality during treatment (death as a treatment outcome), defined as death from any cause. Treatment outcomes were assigned by clinical staff in the RR-TB treatment register, defined based on the World Health Organization (WHO) guidelines[13] as follows:

- Cured: Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
- Treatment Completed: Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
- Treatment Failure: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:
    - Lack of conversion by the end of the intensive phase OR
    - Bacteriological reversion in the continuation phase after conversion to negative OR

    - Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs OR
    - Adverse drug reactions
- Death: A patient who dies for any reason during the course of treatment
- Lost to follow-up: A patient whose treatment was interrupted for 2 consecutive months or more
- Treatment success: The sum of cured and treatment completed

The resistance profile for each patient was defined by DST results available at any point during treatment. If there was more than one resistance profile available per patient, any profile that showed resistance was included in the analysis. While the resistance profile was recorded in the RR-TB treatment register, it was not always known if the result was from a baseline sample or during treatment (as the specimen collection date is not recorded). Therefore, for this analysis the resistance profile categories were not assumed to be from baseline DST. Patients listed as presumptive RR-TB were patients that never had a confirmed drug resistance profile recorded in the database and were assumed to have had unknown drug resistance profile throughout treatment.

Data analysis

For patient characteristics and treatment outcomes, categorical variables were summarized using frequencies and proportions, and continuous variables were summarized using median values and interquartile ranges (IQR). Median time from treatment initiation to outcome date was calculated for each outcome. The outcome date was recorded by RR-TB clinicians in the RR-TB registry.

Cox proportional hazards regression was used to determine associations between potential risk factors and mortality over time. Potential risk factors, including demographic and clinical characteristics and selected other characteristics, were used in both univariate and multivariate analyses. Unadjusted hazard ratios (HR) and adjusted hazard ratios (aHR) with 95% confidence intervals (CI) and p-values for time to mortality were calculated. A p-value < 0.05 was considered statistically significant. Cases (patients) were censored at outcome date. Survival curves were produced from the adjusted model and plotted by each characteristic of interest. Survival curves were scaled to show survival from treatment initiation to two years. Kaplan Meier curves were created to show overall mortality. A cumulative hazard curve was produced from the adjusted model to explore changes in hazard over time.

Binary logistic regression was conducted at two time points (death within 6 months and death after 6 months) to separately examine risk factors for early and late mortality. Odds ratios with 95% confidence intervals and p-values were calculated. A p-value < 0.05 was considered statistically significant. All analyses were conducted

using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) or Excel (for basic charts and graphs).

5.4.2 Results (Section 1)

Of the 785 patients registered in the RR-TB treatment register from 2006-2014, 704 were included in this analysis. Nineteen patients were excluded because they did not initiate treatment, seven of whom died before treatment initiation. An additional 62 patients were excluded because they had an unknown treatment outcome date, of whom 20 (32%) had an outcome of death. As will be shown throughout this analysis, missing information for patients is common; among those excluded due to missing information, the majority of patients were treated at Nyangabwe Referral Hospital (NRH). Patient characteristics are described in Table 5.1 for patients initiating RR-TB treatment, both for those included in the analysis as well as for those excluded due to unknown outcome date to assess potential limitations of excluded patients for this reason. Only Table 5.1 includes results from excluded patients; all other analyses are only presented for the 704 patients meeting the inclusion criteria. Of the 704 patients, 46% are female, median age is 36 (IQR 28-46), and 471 (67%) are HIV positive.

	Included in this analysis N=704		**Excluded from this analysis (missing outcome date) N=62**
	n (%/IQR)		n (%/IQR)
Gender			
Male	379 (54%)		36 (58%)
Female	325 (46%)		26 (42%)
Age groups			
Median age	36 (28-46)		39 (29-47)
≤18	66 (9%)		6 (10%)
19-29	150 (21%)		11 (18%)
30-44	294 (42%)		26 (42%)
45+	181 (26%)		17 (28%)
Not recorded	13 (2%)		2 (3%)
Miner			
Miner	72 (10%)		2 (3%)
Not miner	632 (90%)		60 (97%)
HIV ART			
HIV negative	229 (33%)		18 (29%)
HIV Positive on ART*	423 (60%)		19 (31%)
HIV Positive not on ART	29 (4%)		6 (10%)
HIV Positive ART unknown	19 (3%)		14 (23%)
HIV status unknown	4 (1%)		5 (8%)
Smear at treatment start			

Positive	407 (58%)		16 (26%)
Negative	208 (30%)		4 (7%)
Not recorded	89 (13%)		42 (68%)
Baseline radiology			
Cavitary	243 (35%)		7 (11%)
Non-cavitary	266 (38%)		10 (16%)
NA	195 (28%)		45 (73%)
Registration category			
New TB (no previous anti-TB treatment)[¥]	59 (8%)		4 (7%)
Previous cure or completed treatment[¥¥]	14 (2%)		1 (2%)
Treatment after failure[¥¥]	584 (83%)		29 (47%)
Not recorded	47 (7%)		28 (45%)
Resistance profile			
Presumptive RR-TB	105 (15%)		12 (19%)
Rifampicin mono-resistance	51 (7%)		8 (13%)
MDR, second-line susceptible	129 (18%)		0
MDR, 2nd Line DST not conducted**	360 (51%)		42 (68%)
Pre-XDR or XDR-TB	59 (8%)		0
Treatment facility***			
GPH	56 (8%)		0
LIIMH	50 (7%)		13 (21%)
NRH	196 (28%)		33 (53%)
PMH	322 (46%)		7 (11%)
SMH	80 (11%)		9 (15%)
Year of registration			
2006-2008	161 (23%)		17 (27%)
2009-2011	327 (46%)		16 (26%)
2012-2014	216 (31%)		29 (47%)
TB site			
Pulmonary	623 (88%)		56 (90%)
Extrapulmonary and both	69 (10%)		3 (5%)
Not recorded	12 (2%)		3 (5%)

* ART at treatment initiation

[¥] New TB = No previous history of first or second-line treatment

[¥¥] Outcome from first-line treatment

** Includes Xpert only

*** NRH = Nyangabwe Referral Hospital (Francistown), LIMH = Letsholathebe Memorial Hospital (Maun), GPH = Ghanzi Primary Hospital (Ghanzi), PMH = Princess Marina Hospital (Gaborone), SMH = Sekgoma Memorial Hospital (Serowe)

Table 5.1. Patient characteristics RR-TB patients initiating treatment 2006-2014

Treatment outcomes

Table 5.2 shows median time to outcome for patients initiating RR-TB treatment, by outcome category. Overall, 17% of patients initiating treatment had an outcome of died, and median time to mortality from treatment initiation was 144 (IQR 57-343) days (4.7 months). Mortality among those patients who were lost to follow-up or had treatment failure is unknown.

Treatment outcome	n (%)	Time to outcome (days) median (IQR)
Completed	375 (53%)	637 (575-700)
Cured	176 (25%)	644 (592-731)
Treatment Success	*551 (78%)*	
Lost to follow-up	15 (2%)	305 (172-376)
Treatment failure	16 (2%)	404 (172-629)
Died	122 (17%)	144 (57-343)
Total	704 (100%)	610 (468-691)

Table 5.2. Time to treatment outcome for patients initiating RR-TB treatment, 2006-2014

To assess treatment outcomes over time, Figure 5.1 displays the proportion of patients per treatment outcome by year. Overall, treatment success is high across the years, ranging between 70-86%. There are low rates of treatment failure and loss to follow-up. However, mortality remains high (19% or higher for 5 out of 9 years) over time, though proportionally mortality has decreased in 2013 and 2014.

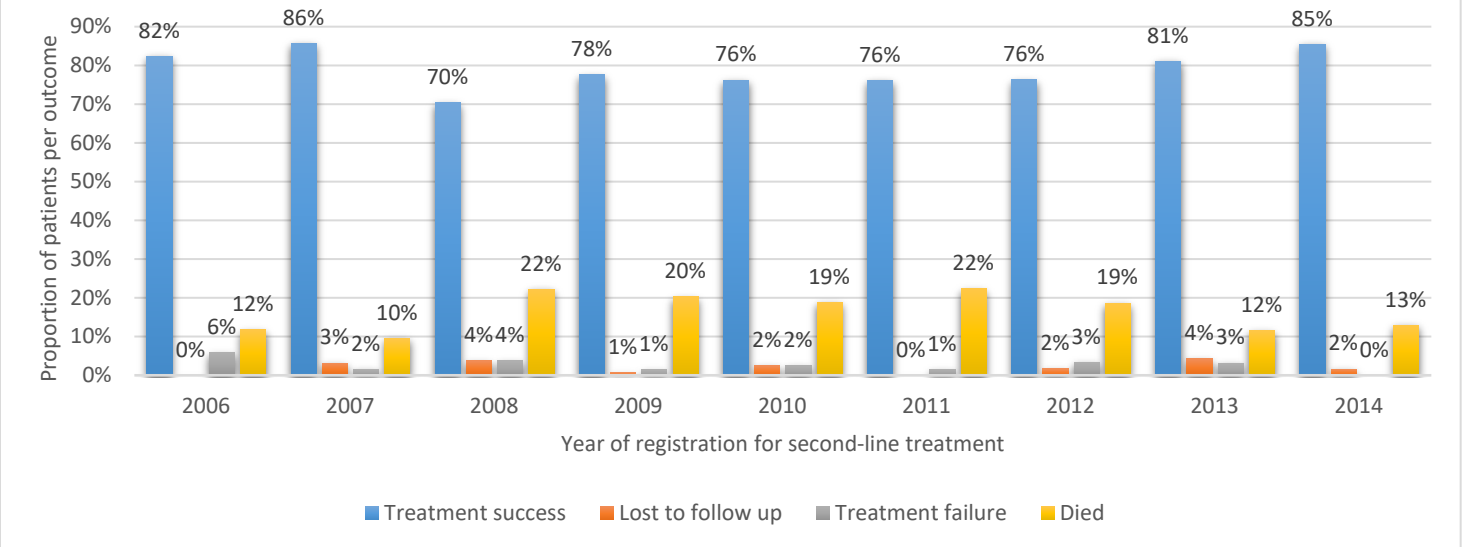


Figure 5.1. Proportion of patients per treatment outcome by year, N=704

As previously described, the median time to mortality was 144 (IQR 57-343) days. While mortality was more rapid in the first 3 month of treatment, patients continue to die throughout treatment, as shown in Figure 5.2. Risk factors for mortality during treatment will be further explored throughout this chapter, including risk factors for early mortality and late mortality.

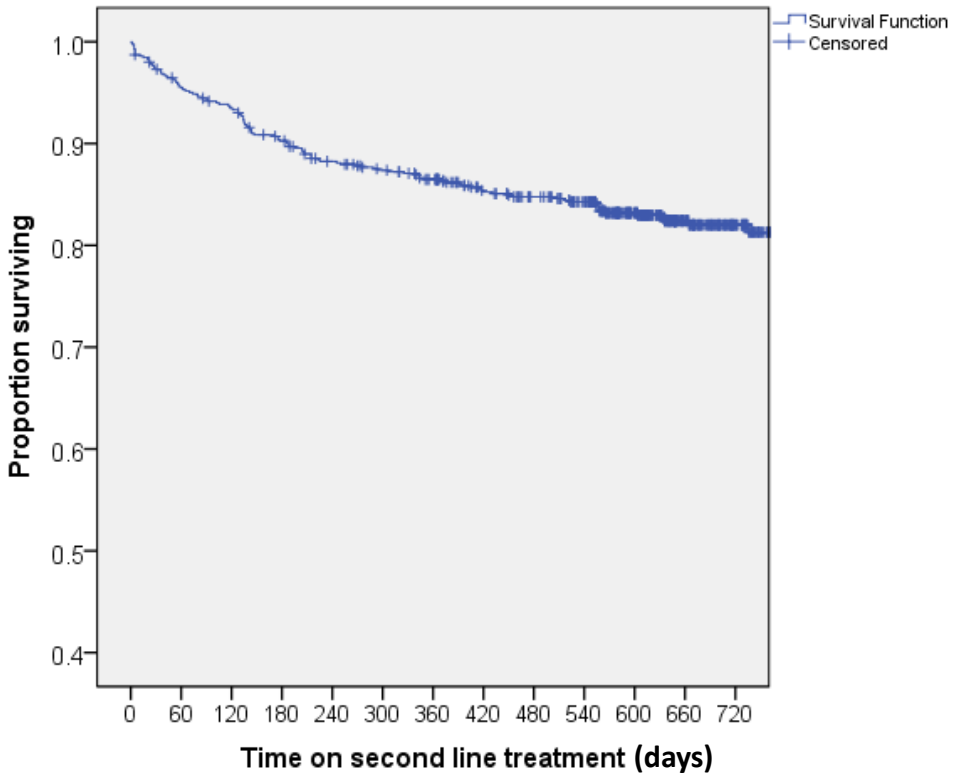


Figure 5.2. Survival of patients on second-line treatment, Kaplan Meier

Cox proportional hazard regression

Both univariate and multivariate survival analyses were conducted to assess if certain clinical or demographic factors were associated with time to mortality (Table 5.3). Factors which were significantly associated with increased mortality risk over time in the multivariate model included: age ≥ 45 years, HIV positive patients not on ART at treatment initiation, unknown HIV status, smear positive patients at treatment initiation, baseline radiology not recorded, registration category not recorded, unknown drug resistance profile (presumptive RR-TB), Pre-XDR or XDR-TB, treatment at Princess Marina Hospital, treatment at Sekgoma Memorial Hospital, and treatment between 2009-2011. Figures 5.3-5.8 display adjusted survival curves, and each of these factors are further discussed along with the respective survival curves.

	Total N=704	Deceased	Univariate Analysis				Multivariate Analysis			
	n	n (%)	p-value	Unadjusted HR	Lower CI	Upper CI	p-value	Adjusted HR	Lower CI	Upper CI
Gender										
Male	379	78 (21%)	**.021**	**1.544**	**1.066**	**2.234**	.861	1.039	.679	1.591
Female	325	44 (14%)	reference				Reference			
Age groups										
≤18	66	3 (5%)	**.026**	**.261**	**.080**	**.850**	**.013**	**.206**	**.059**	**.712**
19-29	150	16 (11%)	.121	.626	.347	1.131	.178	.664	.367	1.205
30-44	294	48 (16%)	reference				Reference			
45+	181	52 (29%)	.528	1.177	.709	1.956	**.026**	**1.726**	**1.068**	**2.791**
Not recorded	13	3 (23%)	.442	1.581	.492	5.079	.981	.985	.274	3.536
Miner										
Miner	72	25 (35%)	**.000**	**2.426**	**1.562**	**3.767**	.780	1.086	.610	1.932
Not miner	632	97 (15%)	reference				reference			
HIV ART										
HIV negative	229	28 (12%)	reference				reference			
HIV Positive on ART*	423	78 (18%)	**.041**	**1.568**	**1.018**	**2.415**	.244	1.322	.826	2.115
HIV Positive not on ART	29	10 (34%)	**.000**	**3.695**	**1.794**	**7.612**	**.001**	**3.633**	**1.674**	**7.885**
HIV Positive ART unknown	19	2 (11%)	.849	.870	.207	3.653	.163	.309	.059	1.608
HIV status unknown	4	4 (100%)	**.000**	**43.650**	**14.790**	**128.823**	**.000**	**22.415**	**6.853**	**73.313**
Smear at treatment initiation										
Positive	407	88 (22%)	**.000**	**2.616**	**1.575**	**4.344**	**.000**	**2.787**	**1.636**	**4.747**
Negative	208	18 (9%)	reference				reference			
Not recorded	89	16 (18%)	**.020**	**2.229**	**1.136**	**4.371**	.299	1.547	.679	3.522
Baseline radiology										
Cavitary	243	37 (15%)	.865	1.040	.661	1.636	.606	.883	.550	1.417
Non-cavitary	266	38 (14%)	reference				reference			
Not recorded	195	47 (24%)	**.008**	**1.787**	**1.165**	**2.741**	**.001**	**2.483**	**1.456**	**4.236**
Registration category										
New TB[¥]	59	3 (5%)	reference				reference			
Previous cure or completed[¥¥]	14	5 (36%)	**.006**	**7.559**	**1.806**	**31.641**	.133	3.122	.706	13.812

Treatment after failure	584	103 (18%)	**.028**	**3.620**	**1.148**	**11.410**	.138	2.425	.752	7.818
Not recorded	47	11 (23%)	**.012**	**5.103**	**1.424**	**18.293**	**.009**	**6.655**	**1.591**	**27.831**
Resistance profile										
Presumptive RR-TB	105	31 (30%)	**.000**	**3.301**	**1.755**	**6.209**	**.002**	**2.851**	**1.461**	**5.564**
Rifampicin monoresistance	51	4 (8%)	.772	.849	.279	2.580	.659	.764	.232	2.522
MDR, second-line susceptible	129	14 (11%)	reference				reference			
MDR, second-line DST not conducted**	360	58 (16%)	.103	1.626	.907	2.915	.057	1.837	.981	3.437
Pre-XDR or XDR-TB	59	15 (25%)	**.009**	**2.657**	**1.282**	**5.509**	**.019**	**2.468**	**1.163**	**5.241**
Treatment facility***										
GPH	56	5 (9%)	.475	.703	.267	1.850	.580	1.343	.473	3.815
LIIMH	50	1 (2%)	.072	.160	.022	1.182	.214	.278	.037	2.095
NRH	196	23 (12%)	reference				reference			
PMH	322	74 (23%)	**.003**	**2.032**	**1.271**	**3.246**	**.001**	**2.594**	**1.463**	**4.600**
SMH	80	19 (24%)	**.029**	**1.972**	**1.073**	**3.623**	**.015**	**2.266**	**1.174**	**4.372**
Year of registration										
2006-2008	161	26 (16%)	reference				reference			
2009-2011	327	66 (20%)	.177	1.368	.868	2.155	**.004**	**2.200**	**1.287**	**3.761**
2012-2014	216	30 (14%)	.745	.917	.542	1.551	.218	1.486	.791	2.795
TB site										
Pulmonary	623	102 (16%)	reference				reference			
Extrapulmonary and both	69	17 (25%)	.134	1.481	.886	2.476	.083	1.661	.936	2.947
NR	12	3 (25%)	.305	1.824	.578	5.753	.860	1.132	.285	4.488

* ART at treatment initiation

¥ New TB = No previous history of first or second-line treatment

¥¥ Outcome from first-line treatment

** Includes Xpert only

*** NRH = Nyangabwe Referral Hospital (Francistown), LIMH = Letsholathebe Memorial Hospital (Maun), GPH = Ghanzi Primary Hospital (Ghanzi), PMH = Princess Marina Hospital (Gaborone), SMH = Sekgoma Memorial Hospital (Serowe)

Table 5.3. Univariate and multivariate analysis of risk factors for mortality among patients initiating RR-TB treatment, 2006-2014

Adjusted survival curves were produced from the Cox proportional hazards regression. This next section further describes risk factors for mortality along with survival curves.

HIV and smear status both revealed associations with mortality (Figure 5.3). Being HIV positive without ART at RR-TB treatment initiation was associated with an almost four-fold increase in risk, as compared to HIV negative persons. Unknown HIV status was also associated with increased risk though the n is small (n=4, and all died within 6 months of treatment); HIV positive individuals on ART at RR-TB treatment initiation had a high mortality risk over time compared to HIV negative individuals in the univariate model only. HIV positivity with unknown ART status has the lowest mortality rate; however, the n is small (19), and this effect is not statistically significant. Being smear positive at treatment initiation was associated with a three-fold increase in risk as compared to smear negative, in the multivariate model.

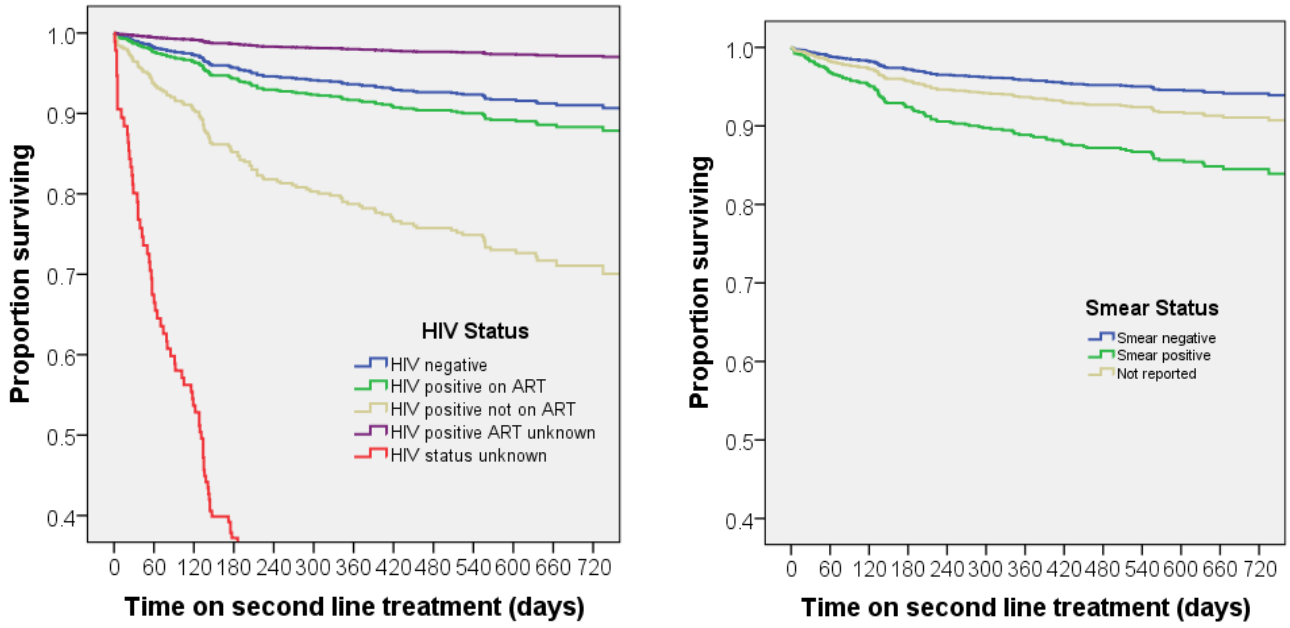


Figure 5.3. Mortality by HIV status and baseline smear result, adjusted survival curves

Older age, over 45, was significantly associated with a higher risk of mortality, while younger age, 18 years or less, was shown to be protective (Figure 5.4).

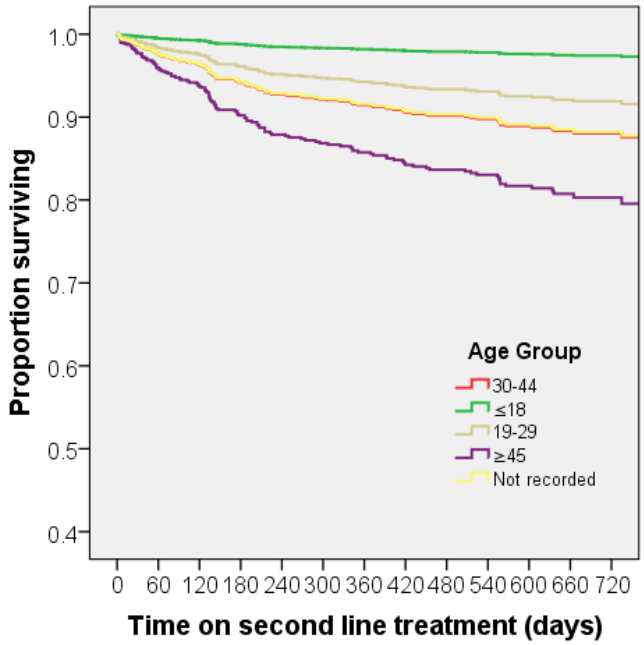
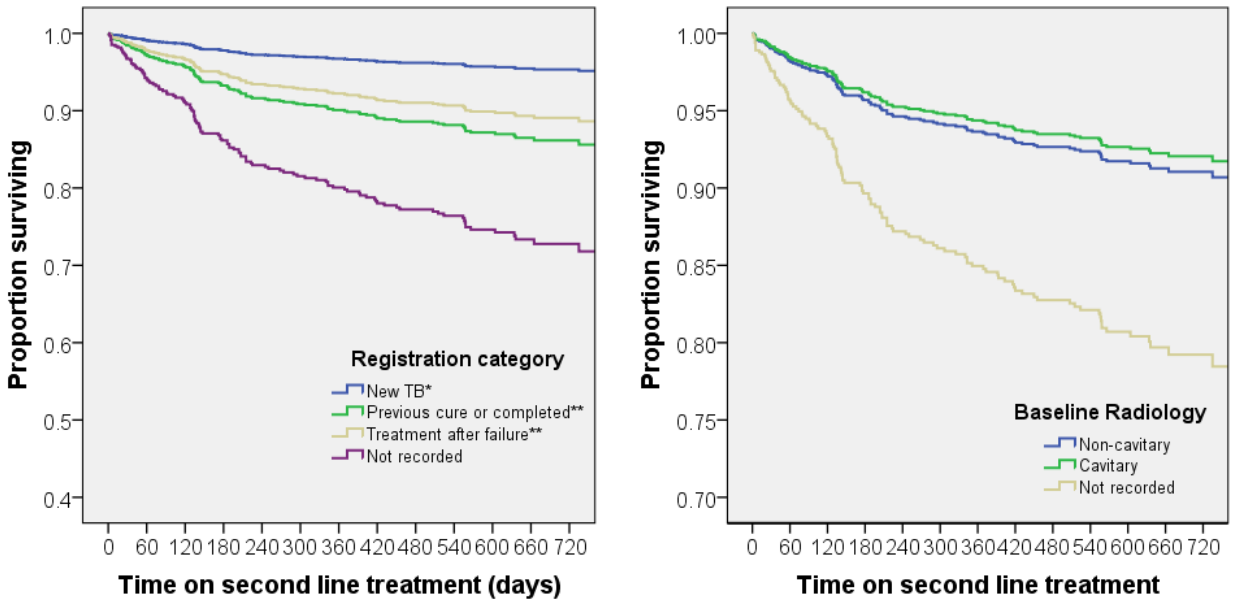


Figure 5.4. Mortality by age group, adjusted survival curve

Increased mortality was associated with missing patient information for both registration category and baseline radiology (Figure 5.5). A result of 'not recorded' indicates there was no information available in the RR-TB registry. The RR-TB registry is completed from the patient medical records at the RR-TB treatment facilities; therefore, if information is missing in the registry, it can be assumed that the clinicians did not have access to this data to take into account for patient management.

Missing baseline radiology results are associated with a higher risk of mortality, and a large proportion of patients were missing these results (195/704, 28%). It is possible that patients who are smear positive are not further referred for chest x-ray. Cross tabulations revealed that those with unknown radiology results were more likely to be smear positive (90/195, 46%) than smear negative (37/195, 19%), with 35% (68/195) having both missing radiology and smear results.

Registration category refers to previous first-line TB treatment and provides information about a patient's history of exposure to TB medications. Having previous TB treatment was associated with a higher risk of mortality in the univariate model for both those with a previous outcome of cure or completed and those with an outcome of treatment failure. However, in the multivariate model only those with missing data on registration category had a significantly higher risk of mortality.



* New TB = No previous history of first or second-line treatment; ** Outcome from first-line treatment

Figure 5.5. Mortality by registration category and baseline radiology, adjusted survival curves

Other findings also indicate that missing patient information was associated with mortality. Unknown HIV status was associated with a higher risk of mortality as described above (Figure 5.3), as well as unknown smear status (in the univariate model only) (Figure 5.3). In an effort to identify if missing patient information is more common at any of the treatment facilities, these results are displayed by treatment facility in Table 5.4. Nyangabwe Referral Hospital (NRH), in Francistown (the second largest city in Botswana) has consistently higher proportions of missing information than other facilities.

Characteristic	NRH N=196	LIMH N=50	GPH N=56	PMH N=322	SMH N=80
Radiology – not recorded	77 (39%)	7 (14%)	16 (29%)	70 (22%)	25 (31%)
Smear – not recorded	48 (25%)	4 (8%)	5 (9%)	22 (7%)	10 (13%)
Registration – not recorded	36 (18%)	2 (4%)	0	4 (1%)	5 (6%)
HIV positive, ART unknown	14 (7%)	2 (4%)	0	0	3 (4%)
HIV status unknown	2 (1%)	0	0	2 (1%)	0

*** NRH = Nyangabwe Referral Hospital (Francistown), LIMH = Letsholathebe Memorial Hospital (Maun), GPH = Ghanzi Primary Hospital (Ghanzi), PMH = Princess Marina Hospital (Gaborone), SMH = Sekgoma Memorial Hospital (Serowe)

Table 5.4. Proportion of patients with missing information by facility***

As has just been described, missing patient information was associated with increased mortality. Further supporting this finding, missing drug resistance information was also associated with increased mortality. Missing both first and second-line DST (presumptive RR-TB) was associated with a three-fold increase in mortality. Additionally, having first-line DST results confirming RR but no second-line DST also suggested increased risk (not statistically significant) (Figure 5.6). Overall, 15% of patients were classified as presumptive RR-TB. Certain groups were more likely to have a presumptive RR-TB classification, including children (38%) and HIV positive persons with unknown ART (32%). No facility had a higher proportion of patients with presumptive RR-TB classification; the proportion of presumptive RR-TB per facility ranged from 11-17%

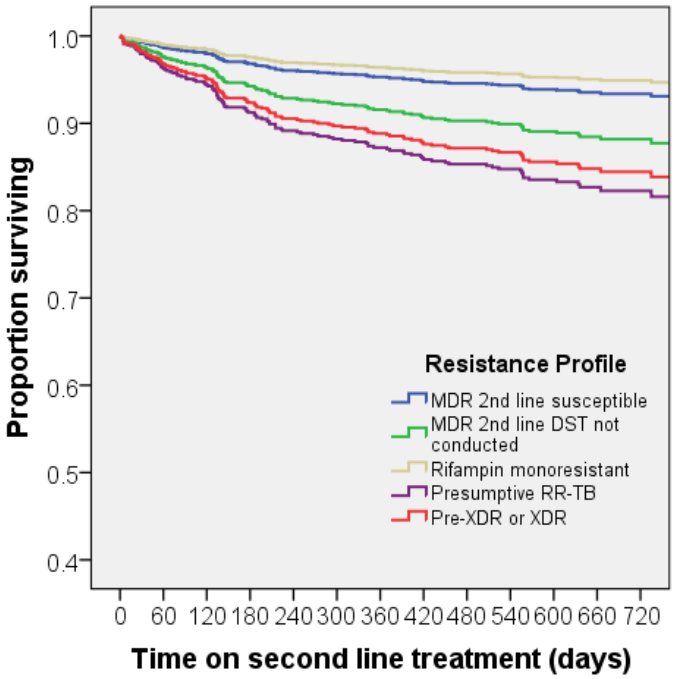
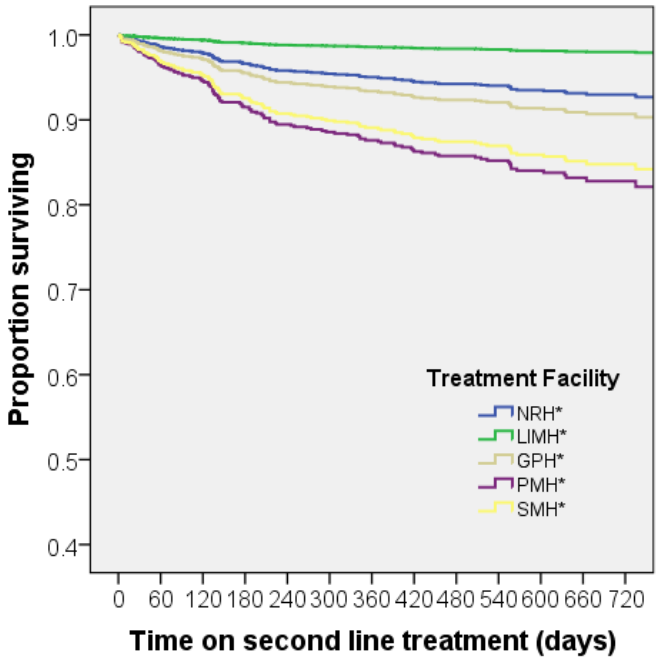


Figure 5.6. Mortality by drug resistance profile, adjusted survival curve

Increased risk of mortality was associated with receiving treatment at two of the five treatment facilities in Botswana: Princess Marina Hospital (PMH) and Sekgoma Memorial Hospital (SMH) (Figure 5.7). Table 5.5 describes select patient characteristics per treatment facility. PMH is located in the capital city (Gaborone) and treated the highest number of RR-TB patients. PMH appears to have received patients with more severe disease; there are higher rates of smear positive patients and patients with documented cavitary disease. However, LIMH also has high rates of cavitary disease, and there is a high rate of unreported radiology results among all sites. Smear and baseline radiology results were similar in Serowe compared to other facilities. There was a slightly higher rate of HIV positive patients not on ART in Serowe (7.5% compared to 4-5% at other sites). However, all of these factors were adjusted for in the multivariate model; therefore, there remain un-identified factors influencing mortality at these treatment facilities.



* NRH = Nyangabwe Referral Hospital (Francistown), LIMH = Letsholathebe Memorial Hospital (Maun), GPH = Ghanzi Primary Hospital (Ghanzi), PMH = Princess Marina Hospital (Gaborone), SMH = Sekgoma Memorial Hospital (Serowe)

Figure 5.7. Mortality by treatment facility, adjusted survival curve

	NRH N=196 n (%)	LIMH N=50 n (%)	GPH N=56 n (%)	PMH N=322 n (%)	SMH N=80 n (%)
HIV status					
HIV negative	41 (21%)	17 (34%)	32 (57%)	115 (36%)	24 (30%)
HIV positive on ART	129 (66%)	31 (62%)	24 (43%)	192 (60%)	47 (59%)
HIV positive not on ART	10 (5%)	0	0	13 (4%)	**6 (8%)**
HIV positive ART uknown	14 (7%)	2 (4%)	0	0	3 (4%)
HIV status unknown	2 (1%)	0	0	2 (1%)	0
Smear Status					
Smear negative	47 (24%)	18 (36%)	27 (48%)	87 (27%)	29 (36%)
Smear positive	101 (52%)	28 (56%)	24 (43%)	**213 (66%)**	41 (51%)
Not recorded	48 (25%)	4 (8%)	5 (9%)	22 (7%)	10 (13%)
Baseline radiology					
Noncavitary	62 (32%)	21 (42%)	27 (48%)	123 (38%)	33 (41%)
Cavitary	57 (29%)	**22 (44%)**	13 (23%)	**129 (40%)**	22 (28%)
Not recorded	77 (39%)	7 (14%)	16 (29%)	70 (22%)	25 (31%)

Table 5.5 Select patient characteristics per treatment facility

Increased mortality was significantly associated with being registered in the years 2009-2011, the time period with the highest number of patients (Figure 5.8). Between 2009 and 2011, 327 patients initiated treatment, compared to 161 (2006-2008) and 216 (2012-2014).

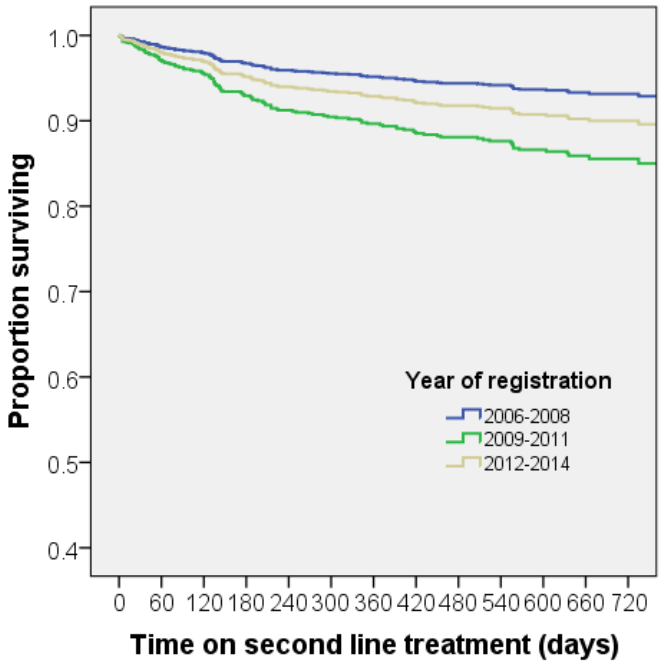


Figure 5.8. Mortality by year of registration, adjusted survival curve

Other categories did not show significant associations with mortality. Male gender was associated with higher risk of mortality in the univariate analysis (HR 1.54, p-value .021), but not in the multivariate analysis. The same was seen for being a miner (HR 2.43, p-value .000) versus not being a miner. Cross tabulations revealed no differences among miners compared to non-miners in regards to HIV status, smear status, baseline radiology results or resistance profile. Miners were more likely to be men (71/72), most were over 45 years (61/72) and most were treated at PMH (63/72) (where more severe cases are referred). Miners may have had more severe disease. In addition, data on silicosis was not available. There were no associations with mortality by site of TB disease in either the univariate or multivariate model.

Figure 5.9 displays the cumulative hazard of mortality over time for RR-TB patients on second-line treatment. The slope of the hazard function decreases over time; therefore the hazard of mortality appears to decrease over time. Specifically, for the first six months the slope is steeper, compared to after six months. Therefore, risk factors for mortality were explored for two time points (death within 6 months and death after 6 months) to separately examine risk factors for early and late mortality.

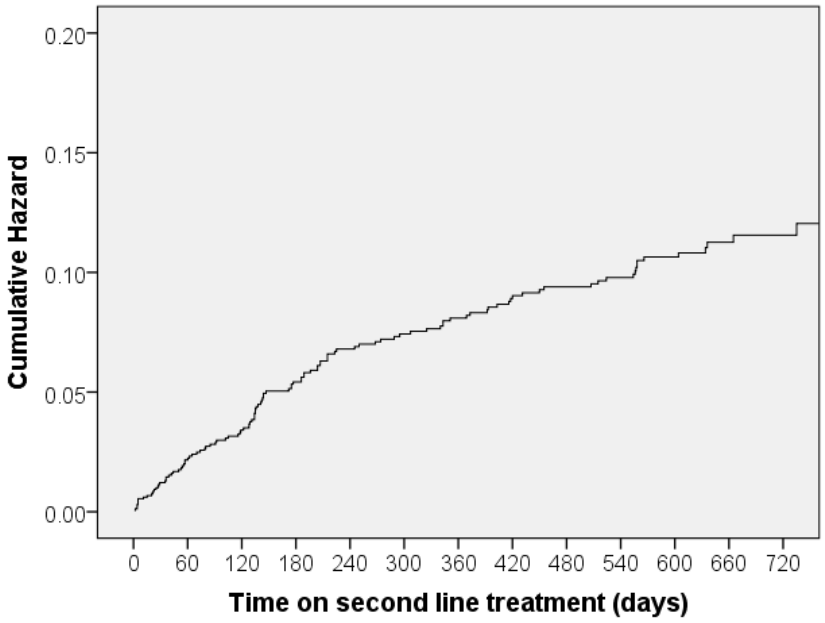


Figure 5.9. Cumulative hazard of mortality over time among RR-TB patients on second-line treatment

Table 5.6 describes a logistic regression for mortality within the first six months of treatment and after six months of treatment. Of the 704 patients initiating second-line treatment, 68 (10%) died within the first six months of treatment; this is 56% of all patients who died at any point during treatment (68/122). Factors which were associated with mortality throughout treatment included smear positivity at baseline, unknown drug resistance profile (presumptive RR-TB), and treatment at PMH. Factors associated with mortality only in the first 6 months include HIV positive persons not on ART, missing baseline radiology results, missing registration category, and year of registration of 2009-2011 or 2012-2014. Although all of the patients with unknown HIV results died in the first six months, the n (4) is too small to produce a significant association in this analysis. Age under 18 years was protective in the first six months of treatment.

Risk factors for mortality after six months of treatment initiation were assessed for the 626 patients who received six or more months of treatment. Those who died in the first six months or otherwise stopped treatment in the first six months were not included in this analysis. Factors contributing to mortality only after six months of treatment included unknown smear results, Pre-XDR or XDR-TB, and receiving treatment at SMH (Table 5.6).

	Death within 6 months							Death after 6 months					
	Total N=704 n	Deceased N=68 n(%)	p-value	OR	Lower CI	Upper CI		Total N=626 n	Deceased N=54 n(%)	p-value	OR	Lower CI	Upper CI
Gender													
Male	379	44 (12%)	.531	1.237	.635	2.410		331	34 (10%)	.812	.918	.454	1.856
Female	325	24 (7%)	reference					295	20 (7%)	reference			
Age groups													
≤18	66	2 (3%)	**.050**	**.162**	**.026**	**1.000**		63	1 (2%)	.155	.213	.025	1.792
19-29	150	9 (6%)	.245	.578	.229	1.458		140	7 (5%)	.182	.514	.194	1.364
30-44	294	26 (9%)	reference					262	22 (8%)	reference			
45+	181	29 (16%)	.214	1.643	.751	3.591		150	23 (15%)	.099	1.952	.882	4.320
Age unknown	13	2 (15%)	.769	.698	.063	7.714		11	1 (9%)	.921	.890	.087	9.107
Miner													
Miner	72	14 (19%)	.498	1.392	.534	3.630		57	11 (19%)	.834	1.112	.412	3.002
Not miner	632	54 (9%)	reference					569	43 (8%)	reference			
HIV ART													
HIV negative	229	13 (6%)	reference					212	15 (7%)	reference			
HIV Positive on ART*	423	40 (9%)	.329	1.461	.682	3.129		377	38 (10%)	.539	1.259	.604	2.628
HIV Positive not on ART	29	9 (31%)	**.000**	**9.740**	**2.951**	**32.151**		20	1 (5%)	.592	.543	.058	5.055
HIV Positive ART unknown	19	2 (11%)	.967	.954	.101	9.049		17	0 (0%)	.998	.000	0.000	
HIV status unknown	4	4 (100%)	.999	1.86E+10	0.000			0	-				
Smear at treatment start													
Positive	407	48 (12%)	**.009**	**2.939**	**1.308**	**6.602**		352	40 (11%)	**.004**	**3.614**	**1.510**	**8.653**
Negative	208	10 (5%)	reference					196	8 (4%)	reference			
Not recorded	89	10 (11%)	.584	.686	.178	2.648		78	6 (8%)	**.045**	**3.816**	**1.033**	**14.096**
Baseline radiology													
Cavitary	243	19 (8%)	.954	.977	.443	2.154		219	18 (8%)	.449	.753	.362	1.568
Non-cavitary	266	17 (6%)	reference					245	21 (9%)	reference			
Not recorded	195	32 (16%)	**.000**	**6.031**	**2.495**	**14.579**		162	15 (9%)	.710	1.178	.497	2.790
Registration category													
New TB	59	2 (3%)	reference					56	1 (2%)	reference			

Previous cure or completed	14	2 (14%)	.978	1.035	.088	12.217		12	3 (25%)	.105	8.198	.645	104.194
Treatment after failure	584	55 (9%)	.500	1.697	.364	7.906		520	48 (9%)	.205	3.878	.477	31.542
Not recorded	47	9 (19%)	**.022**	**11.013**	**1.411**	**85.978**		38	2 (5%)	.336	3.963	.240	65.420
Resistance profile													
Presumptive RR-TB	105	19 (18%)	**.042**	**3.096**	**1.042**	**9.199**		86	12 (14%)	**.041**	**3.036**	**1.049**	**8.788**
Rifampicin monoresistance	51	2 (4%)	.611	.612	.093	4.048		47	2 (4%)	.648	.668	.118	3.780
MDR, second-line susceptible	129	6 (5%)	reference					123	8 (7%)	reference			
MDR, second-line DST not conducted**	360	35 (10%)	.182	1.964	.729	5.288		320	23 (7%)	.316	1.641	.623	4.324
Pre-XDR or XDR-TB	59	6 (10%)	.404	1.761	.467	6.639		50	9 (18%)	**.050**	**3.100**	**.999**	**9.622**
Treatment facility													
GPH	56	4 (7%)	.109	3.056	.779	11.990		52	1 (2%)	.757	.703	.075	6.593
LIIMH	50	0 (0%)	.997	.000	0.000			48	1 ((2%)	.828	.784	.087	7.055
NRH	196	17 (9%)	reference					178	6 (3%)	reference			
PMH	322	42 (13%)	**.006**	**3.561**	**1.451**	**8.741**		274	32 (12%)	**.019**	**3.341**	**1.216**	**9.173**
SMH	80	5 (6%)	.951	.963	.289	3.206		74	14 (19%)	**.000**	**8.307**	**2.696**	**25.597**
Year of registration													
2006-2008	161	10 (6%)	reference					149	16 11%)	reference			
2009-2011	327	42 (13%)	**.000**	**7.399**	**2.805**	**19.517**		281	24 (9%)	.467	.736	.323	1.679
2012-2014	216	16 (7%)	**.012**	**4.066**	**1.357**	**12.187**		196	14 (7%)	.210	.538	.205	1.416
TB site													
Pulmonary	623	57 (9%)	reference					556	45 (8%)	reference			
Extrapulmonary or both	69	8 (12%)	.439	1.478	.549	3.974		61	9 (15%)	.131	2.026	.810	5.064
Not recorded	12	3 (25%)	.617	1.574	.266	9.292		9	0 (0%)	.999	.000	0.000	

* HIV Positive and on ART at RR-TB treatment initiation; ** Includes Xpert only

Table 5.6. Logistic regression for mortality within six months of treatment initiation and after six months of treatment initiation

5.5 Section 2: Mortality among RR-TB patients initiating treatment 2012-2014

The next section describes analyses of Cohort 2, which is a subset of the full cohort (Cohort 1) described in the first section of the chapter. Additional clinical information (baseline weight, drug side effects, symptoms and co-morbidities) was obtained for patients in Cohort 2 through medical record reviews to describe the frequency of reported side effects, comorbidities and factors of disease severity, as well as their relative contribution to mortality.

5.5.1 Methods (Section 2)

Study population

This analysis included patients registered in the RR-TB treatment register from 2012-2014 inclusive, using similar inclusion and exclusion criteria as was used for the full cohort (Cohort 1). Patients were excluded if they were registered but did not initiate treatment, had an unknown treatment outcome date or if their patient chart was not available.

Study variables

Characteristics which did not show a significant association in the analysis of the full cohort were excluded from the Cox regression for this cohort, such as gender and TB site. Some of the risk factors were combined due to the smaller sample size in this three-year cohort. For example, age group is limited to under 45 years and over 45 years. For the multivariate analysis, characteristics to measure disease severity were combined into one composite variable including: baseline weight below 40kg, the presence of cavitary disease, smear positivity and shortness of breath. Likewise, side effects and comorbidities were combined into composite variables and analyzed by the number of events (side effect or comorbidities) reported. These variables are also described individually, separate from the multivariate analysis. Side effects are defined in Table 5.7 below.

Comorbidities refer to diabetes, hypertension and cancer (HIV is included separately). Clinicians make note of comorbidities in the medical charts but do not include laboratory or other clinical values. The presence of a comorbidity was extracted from the medical charts and added to the study database per patient.

Table 5.7 describes the definitions used to characterize side effects included in this analysis. These are the definitions used by clinicians to note the presence of a side effect in the medical charts. Medical charts list the laboratory values where relevant and/or note the presence of the side effect. These details were extracted from the medical charts and added to the study database per patient (with name matching) to indicate the presence of a side effect. Medical charts do not specify the severity of side effects based on these definitions; however, Table 5.7 includes an interpretation of the grade level of reported side effects based on definitions used in

Botswana, Common Terminology Criteria for Adverse Events (CTCAE) v4[133] and normal lab ranges according to Merck Manuals[134]. All reported side effects are Grade 1 or higher.

Side effects	Definitions used by Botswana TB program	CTCAE criteria definition	Normal lab ranges	Interpretation of reported side effects
Anemia	Hemoglobin < 11 g/dL	Grade 1: Hgb <LLN - 10.0 g/dL	14-17 (men), 12-16 (women)*	Grade 1 or higher
Hypokalemia	Potassium < 3.5 mmol/L	Grade 1: K<LLN - 3.0 mmol/L	3.5-5 mmol/L*	Grade 1 or higher
Hypothyroidism	TSH > 9	Grade 1: Asymptomatic; clinical or diagnostic observations only	0.5–5.0 mcIU/mL*	Grade 1 or higher
Renal impairment	Creatinine >104 (male) and> 90 (female) umol/L	Grade 1: Creatinine >ULN - 1.5 x ULN	30–170 U/L*	Grade 1 or higher
Thrombocytopenia	Platelets < 150	Grade 1: <LLN - 75.0 x 10e9 /L	150-350 x 10^3/mcL *	Grade 1 or higher
Hepatitis	ALT > 50 U/L	Grade 1: >ULN – 3.0 x ULN	0-35 U/L*	Grade 1 or higher
Hearing loss	Self-reported hearing loss, confirmed by audiometry when possible.	Grade 1: Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear.	N/A	N/A
Tinnitus	Self-reported ringing in the ears	Grade 1: Mild symptoms	N/A	Grade 1 or higher
Psychiatric disturbances	Self-reported presence of one or more of the following: depression, hallucinations, suicidal attempt, anxiety or psychiatric disturbances.	Grade 1: Mild symptoms	N/A	Grade 1 or higher
Neuropathy	Self-reported numbness, prickling or burning sensations	Grade 1: Asymptomatic; clinical or diagnostic observations only;	N/A	Grade 1 or higher
Gastrointestinal disorders	Self-reported presence of one more of the following: nausea, vomiting, or diarrhea.	Grade 1: Asymptomatic to mild symptoms	N/A	Grade 1 or higher
Visual disturbances	Self-reported disturbances of eyesight.	Grade 1: Asymptomatic to mild symptoms	N/A	Grade 1 or higher
Dizziness	Self-reported experience of dizziness	Grade 1: Mild unsteadiness or sensation of movement	N/A	Grade 1 or higher
Arthralgia	Self-reported pain or stiffness in joints	Grade 1: Mild pain	N/A	Grade 1 or higher

* Laboratory normal values obtained from Merck Manuals

Table 5.7. Definitions used to characterize side effects

Data analysis

For patient characteristics and treatment outcomes, categorical variables were summarized using frequencies and proportions, and continuous variables were summarized using median values and interquartile ranges (IQR). The median time from treatment initiation to outcome date was calculated for each outcome. The treatment outcome date was recorded by RR-TB clinicians in the RR-TB registry. A two proportion z test was used to calculate p-values for mortality among groups with reported characteristics of disease severity and side effects.

Cox proportional hazards regression was used to determine the correlation between potential risk factors and mortality. Potential risk factors included demographic and clinical characteristics, and characteristics were used in both univariate and multivariate analyses. Unadjusted hazard ratios (HR) and adjusted hazard ratios (aHR) with 95% confidence intervals (CI) and p-values for time to mortality were calculated. A p-value < 0.05 was considered statistically significant. Cases (patients) were censored at outcome date. Survival curves were produced from the adjusted model and plotted by each characteristic of interest. Survival curves were scaled to show survival from treatment initiation to two years. Kaplan Meier curves were created to show overall survival.

All analyses were conducted using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) or Excel (for basic graphs and charts).

5.5.2 Results (Section 2)

Of the 245 total patients registered in the RR-TB treatment registry from 2012 to 2014 inclusive, 176 were included in this analysis. During this time frame, there were no patients registered who did not initiate treatment. Patients were excluded if they had an unknown outcome date (29) or if they did not have a patient chart available (40). Of the 69 excluded participants, 14 (20%) died during treatment. A higher proportion of excluded patients had presumptive RR-TB (19%) and were over 45 (32%), compared to the included patients (7% and 18% respectively). Patient characteristics are described in Table 5.8 for patients initiating RR-TB treatment, both for those included in the analysis as well as for those excluded due to unknown outcome date to assess potential limitations of excluding patients. Only Table 5.8 includes results from excluded patients; all other analyses are only presented for the 176 patients meeting the inclusion criteria. Of the 176 patients, 50% were female, the median age was 37 (IQR 30-43), and 118 (67%) were HIV positive. Twelve (7%) had missing first and second-line DST and were classified as presumptive RR-TB. This proportion is smaller than the 18% presumptive RR-TB observed in the full cohort, and this suggests that the program improved practices for obtaining confirmatory DST results for patients initiating treatment in more recent years. However, there are also fewer patients initiating treatment in 2012-2014 as compared to preceding years suggesting patients may have been

missed during this time frame. Furthermore, although Xpert had not been fully implemented in Botswana at this time, it was in use as part of a nationwide operational research study conducted within the programmatic setting of Botswana. Therefore, some patients were diagnosed by Xpert during this time frame; 20/176 patients (11%) were diagnosed by Xpert only, and these were classified as confirmed RR-TB.

The proportion of RR-TB patients with Pre-XDR or XDR-TB also decreased during this time period with 2% of patients diagnosed with Pre-XDR or XDR-TB as compared to 10% in the full cohort. Of the 136 patients with confirmed RR-TB, only five had second-line DST; four had Pre-XDR or XDR-TB and one was susceptible to second-line drugs.

Patient characteristics	Included in this analysis N=176	Excluded from this analysis (missing outcome date or patient file) N=69
	n (%/IQR)	n (%/IQR)
Age Group		
Median (IQR)	37 (30-43)	37 (26-52)
Under 45	138 (78%)	46 (67%)
45+	31 (18%)	22 (32%)
Not recorded	7 (4%)	1 (1%)
Gender		
Male	88 (50%)	36 (52%)
Female	88 (50%)	33 (48%)
HIV ART		
HIV negative	58 (33%)	25 (36%)
HIV Positive on ART at RR-TB treatment initiation	114 (65%)	39 (57%)
HIV Positive not on ART	4 (2%)*	3 (4%)
Unknown HIV Status	0	2 (3%)
Resistance Profile		
Presumptive RR-TB	12 (7%)	13 (19%)
RMR	24 (14%)	7 (10%)
RR-TB (includes Xpert only)	136 (77%)**	48 (70%)
Pre-XDR or XDR-TB	4 (2%)	1 (1%)
Year of registration		
2012	44 (25%)	17 (25%)
2013	79 (45%)	24 (35%)
2014	53 (30%)	28 (40%)

* One person with ART unknown

** One person with confirmed second-line susceptibility

Table 5.8. Characteristics of patients initiating RR-TB treatment 2012-2014

Table 5.9 shows median time to outcome for patients initiating RR-TB treatment, by outcome category. Overall, 23/176 (13%) patients initiating treatment had an outcome of died, and median time to mortality was 116 (IQR 20-289) days in this three year cohort.

Treatment outcome	n (%)	Time to outcome (days) median (IQR)
Completed	124 (71%)	648 (575-713)
Cured	20 (11%)	602 (506-648)
Treatment success	*144 (82%)*	
Stopped treatment	5 (3%)	365 (14-451)
Treatment failure	4 (2%)	378 (283-554)
Died	23 (13%)	116 (20-289)
Total	176 (100%)	609 (481-691)

Table 5.9. Time to treatment outcome for patients initiating RR-TB treatment, 2012-2014, N=176

Reviewing medical charts provided important information about disease severity, side effects and comorbidities, which was not present in the RR-TB registry. This additional information is described individually and then as part of the multivariate analysis. Table 5.10. describes mortality among individual characteristics of disease severity. Higher rates of mortality were observed among all characteristics used to measure disease severity in this analysis, compared to patients without these characteristics; the differences are statistically significant for low baseline weight, cavitary disease and presence of shortness of breath.

Characteristics of Disease Severity	Died	p-value
Baseline weight		
Below 40kgs	9/23 (39%)	<.0001
Above 40kgs	12/148 (8%)	
Baseline radiology		
Cavitary disease	9/57 (16%)	.036
Non-cavitary disease	4/79 (5%)	
Baseline sputum smear		
Smear positive	18/109 (17%)	.080
Smear negative	4/58 (7%)	
Shortness of Breath		
Yes	8/13 (62%)	<.0001
No	15/163 (9%)	

Table 5.10. Mortality by characteristics of disease severity among patients initiating RR-TB treatment, 2012-2014

The following tables describe the proportion of all patients with reported side effects and comorbidities and mortality among those with reported side effects and comorbidities (Tables 5.11 and 5.12). Some side effects are reported among a high number of patients (anemia (39%), hearing loss (44%) and gastrointestinal symptoms (39%)), but none of the side effects appear to be associated with mortality. Among reported comorbidities, hypertension and cancer have high rates of mortality but are only reported among 5% and 1% of all patients, respectively. No single side effect or comorbidity appears to have an association with mortality; the multivariate analysis will explore whether or not the number of reported side effects or comorbidities had an association with mortality. It should be noted that this table describes the comorbidities that are combined into a composite variable for the multivariate analysis. HIV is not included as part of the composite variable but is included separately in the multivariate analysis.

	Number of patients	**Mortality per side effect**	
Reported side effects	N=176	N=23	p-value
Anemia			
Yes	68 (39%)	8/68 (12%)	.684
No	108 (61%)	15/108 (14%)	
Hypokalemia			
Yes	40 (23%)	5/40 (13%)	.903
No	136 (77%)	18/136 (13%)	
Hypothyroidism			
Yes	16 (9%)	2/16 (13%)	.944
No	160 (91%)	21/160 (13%)	
Renal impairment			
Yes	35 (20%)	6/35 (17%)	.424
No	141 (80%)	17/141 (12%)	
Thrombocytopenia			
Yes	9 (5%)	1/9 (11%)	.858
No	167 (95%)	22/167 (13%)	
Hepatitis			
Yes	30 (17%)	3/30 (10%)	.584
No	146 (83%)	20/146 (14%)	
Hearing loss			
Yes	78 (44%)	8/78 (10%)	.323
No	98 (56%)	15/98 (15%)	
Tinnitus			
Yes	57 (32%)	5/57 (9%)	.242
No	119 (68%)	18/119 (15%)	
Psychiatric disturbances			
Yes	22 (13%)	4/22 (18%)	.447
No	143 (87%)	19/154 (12%)	
Neuropathy			
Yes	38 (22%)	7/38 (18%)	.269

No	138 (78%)	16/138 (12%)	
GI symptoms			
Yes	69 (39%)	9/69 (13%)	.994
No	107 (61%)	14/107 (13%)	
Visual disturbances			
Yes	28 (16%)	0/28 (0%)	.025
No	148 (84%)	23/148 (16%)	
Dizziness			
Yes	12 (7%)	2/12 (17%)	.702
No	164 (93%)	21/164 (13%)	
Arthralgia			
Yes	53 (30%)	4/53 (8%)	.154
No	123 (70%)	19/123 (15%)	

Table 5.11. Proportion of RR-TB patients with reported side effects and mortality per side effect, 2012-2014

	Number of patients	**Mortality per comorbidity**	
Reported comorbidities	N=176	N=23	p-value
Diabetes			
Yes	4 (2%)	0/4 (0%)	.433
No	172 (98%)	23/172 (13%)	
Hypertension			
Yes	9 (5%)	2/9 (22%)	.403
No	167 (95%)	21/167 (13%)	
Cancer			
Yes	2 (1%)	1/2 (50%)	.119
No	174 (99%)	22/174 (13%)	

Table 5.12. Proportion of RR-TB patients with reported comorbidities and mortality per comorbidity, 2012-2014

Both univariate and multivariate analyses were conducted to further explore risk factors for mortality among this cohort (Table 5.13). Factors associated with increased mortality included having three or more characteristics of disease severity (aHR 9.8, p-value .004) and unknown drug resistance profile (presumptive RR-TB) (aHR 3.7, p-value .039). Age ≥ 45 years was associated with mortality in the univariate model (HR 3.8 p-value .002) but not in the multivariate mode. Figures 5.10-5.12 display adjusted survival curves, and each of these factors will be further discussed along with the respective survival curves.

	Total N=176	Deceased (n=23)		Univariate Analysis				Multivariate Analysis			
	n	n	%	p-value	Unadjusted HR	Lower CI	Upper CI	p-value	Adjusted HR	Lower CI	Upper CI
Age											
Under 45	138	13	9%	reference				reference			
45+	31	10	32%	**.002**	**3.803**	**1.665**	**8.686**	.177	2.080	.718	6.021
Not recorded	7	0	0%	.982	.000	0.000		.981	.000	0.000	
Side effects											
0 side effects	127	15	12%	reference				reference			
1-3 side effects	25	3	12%	.986	1.011	.293	3.494	.744	1.243	.337	4.586
4- 9 side effects	24	5	21%	.288	1.731	.629	4.767	.100	2.524	.836	7.617
Comorbidities											
0	165	20	12%	reference				reference			
1 or more	11	3	27%	.161	2.382	.708	8.019	.203	2.656	.591	11.943
HIV ART											
HIV negative	58	6	10%	reference				reference			
HIV Positive on ART	114	16	14%	.516	1.365	.534	3.489	.762	1.166	.431	3.154
HIV Positive not on ART*	4	1	25%	.330	2.866	.344	23.857	.117	6.142	.634	59.471
Characteristics of Disease Severity											
none	52	3	6%	reference				reference			
1 characteristic	60	4	7%	.900	1.101	.246	4.920	.721	1.332	.276	6.433
2 characteristics	51	9	18%	.108	2.929	.791	10.855	.294	2.121	.520	8.643
3+ characteristics**	13	7	54%	**.000**	**12.082**	**3.109**	**46.962**	**.004**	**9.801**	**2.058**	**46.665**
Resistance Profile											
Presumptive RR-TB	12	7	58%	**.000**	**7.336**	**2.928**	**18.380**	**.039**	**3.696**	**1.067**	**12.805**
RMR	24	1	4%	.470	.473	.062	3.605	.693	.656	.081	5.334
RR-TB***	136	14	10%	reference				reference			
Pre-XDR or XDR-TB	4	1	25%	.333	2.740	.356	21.105	.144	5.163	.570	46.764
Year of registration											
2012	44	9	20%	.086	2.810	.865	9.125	.644	1.374	.357	5.290
2013	79	10	13%	.366	1.708	.535	5.458	.866	1.116	.314	3.967
2014	53	4	8%	reference				reference			

* One person ART unknown; ** One person with all 4 characteristics; died; *** One person with confirmed 2nd line susceptibility; includes Xpert only

Table 5.13. Univariate and multivariate analysis of risk factors for mortality among patients initiating RR-TB treatment 2012-2014

Characteristics of disease severity included baseline weight below 40 kgs, cavitary disease, smear positivity and shortness of breath. As previously described, having three or more of these characteristics was significantly associated with mortality in the multivariate model and was particularly associated with early mortality based on the curve (Figure 5.10). Having fewer than three characteristics of disease severity was not associated with increased mortality, but the combination of three or more has a very high risk. Of the 13 patients with three or more characteristics, seven (54%) died (aHR 9.8). Only one patient had all four characteristics, and this patient died.

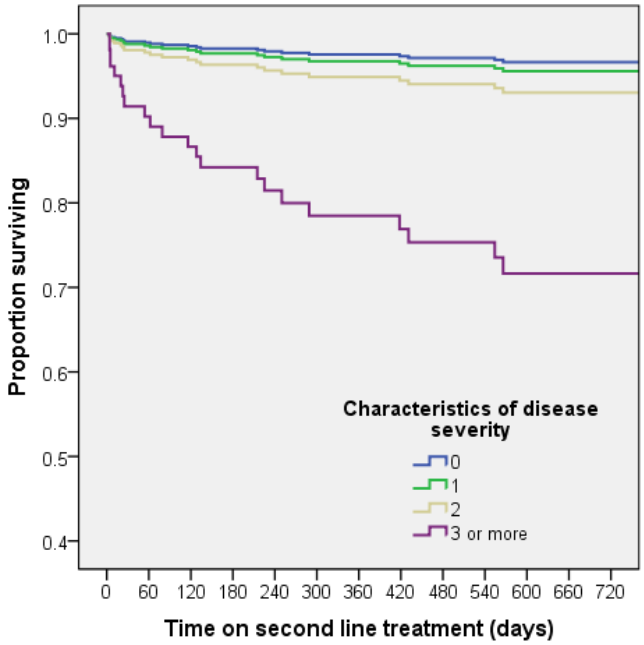


Figure 5.10. Mortality by characteristics of disease severity, adjusted survival curve

Similar to the findings from the 2006-2014 cohort, unknown drug resistance profile (presumptive RR-TB) was significantly associated with mortality (Figure 5.11). The proportion of Pre-XDR or XDR-TB patients who died was high (25%) but this was not statistically significant due to the small number (n=4).

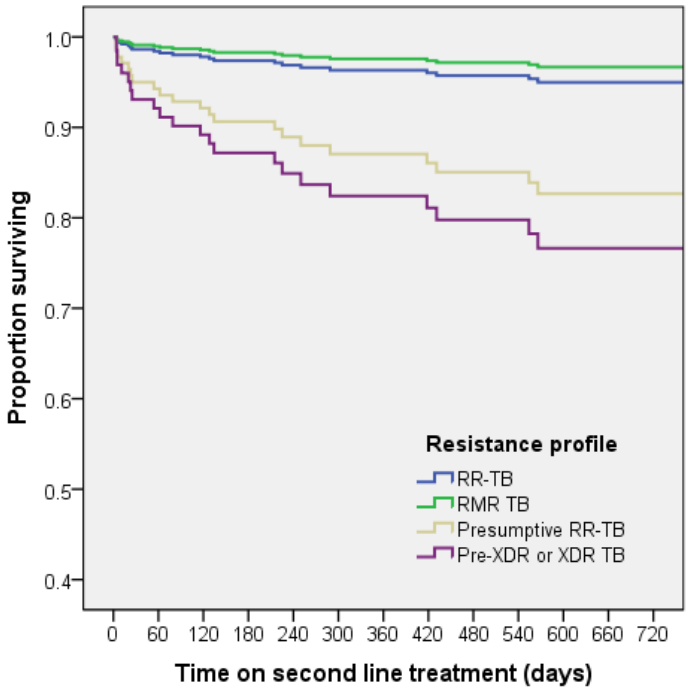


Figure 5.11. Mortality by drug resistance profile, adjusted survival curve

Higher rates of mortality were seen among those with one or more comorbidity (27%) and among those with four or more side effects (21%), but this was not a significant association (Figure 5.12). It is possible that both the presence of drug side effects and comorbidities were under-reported. Only four patients had a recorded comorbidity of diabetes (2%), and no information was included in the medical chart to confirm if others were tested. Comorbidities were more common in those with older age; one or more comorbidities were reported for 16% of those over 45 compared to those under 45 years, in which 4% had one or more comorbidity reported.

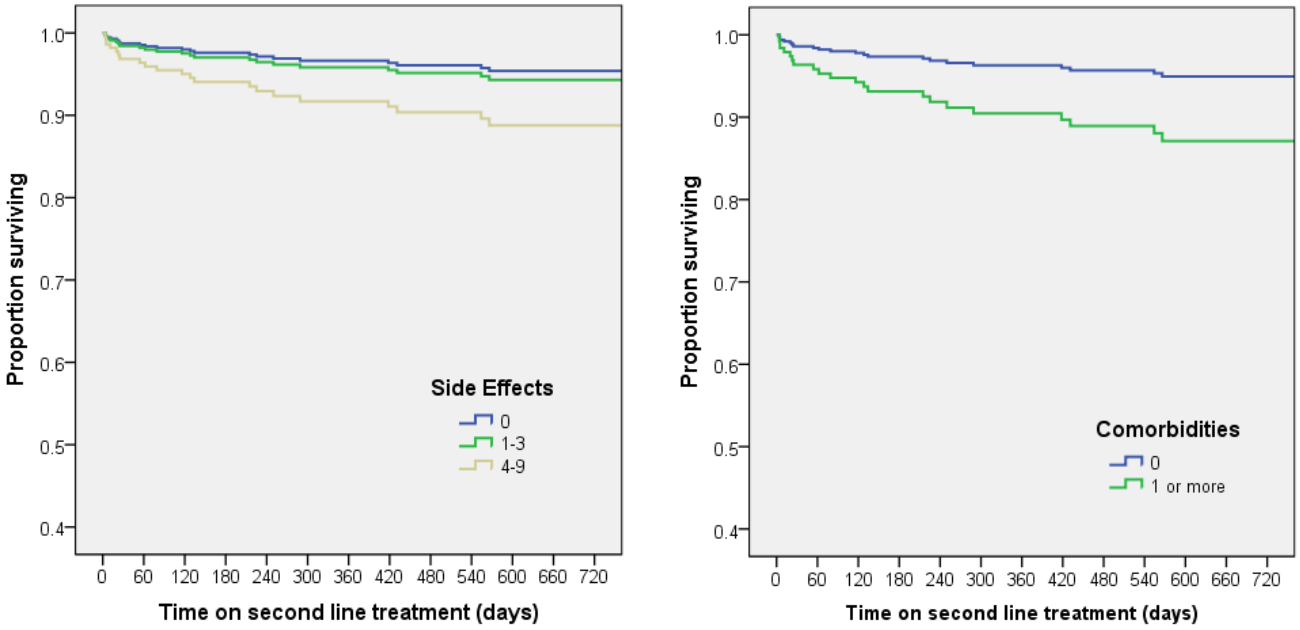


Figure 5.12. Mortality by side effects and comorbidities, adjusted survival curve

5.6 Discussion

Botswana has had continuously high RR-TB treatment success rates, attributed to high ART coverage and close management of patients[87]. Based on personal communication with members of the national RR-TB program, they are very proud of their high levels of treatment success, but also concerned about the consistently high levels of mortality. A common sentiment among those involved in RR-TB management in Botswana is that 'patients are either cured or they die'[11], speaking to the very low rates of treatment failure or lost to follow-up. Almost all patients are recorded with an outcome of either success (treatment completion or cure) or death. The 17% average mortality rate among this cohort is slightly higher than the most recent global mortality rate of 15% among RR-TB patients on treatment, but is similar and even less than some high HIV settings such as Zimbabwe (17%), India (20%) and Mozambique (26%)[13]. For five years of this cohort, the mortality rate was 19% or higher. Although the mortality rate has dropped for the most recent two years, case detection has also declined, and patients are likely to be dying without being identified as having RR-TB.

Several risk factors for mortality were identified in the analysis of the full cohort (Cohort 1), including older age, HIV positivity and not on ART at treatment initiation, unknown HIV status, smear positivity at treatment initiation, baseline radiology not recorded, registration category not recorded, unknown drug resistance profile (presumptive RR-TB), Pre-XDR or XDR-TB, treatment at Princess Marina Hospital, treatment at Sekgoma Memorial Hospital, and treatment between 2009-2011. Analysis of the three year cohort (Cohort 2) supported the finding that older age and unknown drug resistance profile (presumptive RR-TB) were assocated with mortality, although older age was only significant in the univariate model of Cohort 2. The additional elements which were able to be included in Cohort 2 through chart reviews also identified disease severity as associated with mortality. Side effects were also included in the analysis of Cohort 2 and were not shown to be associated with mortality.

Many of the identified risk factors are well established. Other research has shown that older age and being smear positive is associated with mortality among RR-TB patients[76, 135], and this was echoed in this analysis. It is possible that older patients are more ill in general and may have more comorbidities. The model for the full cohort (Cohort 1) adjusts for some indicators of disease severity (smear positivity, cavitation, HIV), but does not take into account other possible comorbidities and conditions that may be more common with older age such as hypertension, cancer and diabetes. Comorbidities were reported and analyzed in Cohort 2 (three year cohort) and the data support the idea that those with older age have more comorbidities. Cohort 2 also included factors of disease severity (low weight, cavitation, shortness of breath, and smear positivity) and identified that a combination of three or more indicators of disease severity was associated with mortality. Due to the small sample size in Cohort 2, a composite variable for disease severity was used. However, other studies have shown

that some of these factors are independently associated with mortality, including low baseline weight[77, 78], cavitary disease[76, 135] and smear positivity as described above, and this current analysis did show a higher proportion of death among these individual factors. Early diagnosis through universal DST could reduce the delay in treatment. If patients who do have RR-TB have DST upfront, they do not have to survive through ineffective first-line treatment, which may increase disease severity.

HIV positivity has been established as a risk factor for mortality during RR-TB treatment[76, 82], particularly among persons with low CD4 counts[85-87]. Other research has shown that ART is protective against mortality for those that are HIV positive[85]. This current analysis is consistent with these findings. HIV positivity was identified as a risk factor in the univariate analysis, and, in the multivariate analysis, HIV positive persons not on ART were shown to be at increased risk of mortality and were more likely to die within the first six months of treatment. This highlights the importance of continuing to push for high ART coverage for all HIV positive persons.

Patients with Pre-XDR or XDR-TB had a higher risk of mortality in this analysis. The risk of mortality among these patients was observed after six months of treatment. Because many of the patients with Pre-XDR or XDR-TB were diagnosed after several months on second-line treatment as reported in Chapter 4, these patients may have received prolonged ineffective treatment (median time from second-line treatment initiation to diagnosis of Pre-XDR/XDR-TB was 153 days and over one year for some Pre-XDR or XDR-TB patients). Additionally, the patients may have had increased risk of resistance amplification. The newer drugs for XDR-TB treatment (delaminid, bedaquiline) were not routinely available and used in this time period. So although these patients were not dying early, the mortality is still impacted by the lack of new, more effective drugs. The proportion of patients with Pre-XDR or XDR-TB decreased in the three year cohort (Cohort 2) with 2% of patients diagnosed with Pre-XDR or XDR-TB as compared to 10% in the full cohort. Globally, the proportion of RR-TB patients with XDR-TB in 2017 was 8.5%[13]; in neighboring South Africa, 4.9% of MDR-TB patients were identified with XDR-TB in a recent survey (2012-2014)[136]. This South African survey indicates an even larger proportion have Pre- XDR-TB, with a total of 13% of RR-TB patients resistant to a second-line injectable and 13% resistant to a fluoroquinolone (ofloxacin)[136]. As shown in chapter 4, second-line DST drastically reduced after 2010; the lack of second-line DST among patients in this cohort may have led to under-diagnosis of Pre-XDR and XDR-TB. Early diagnosis, monitoring for increased resistance and availability of new drugs may improve the outcomes for Pre-XDR and XDR-TB patients.

Botswana has suffered several major interruptions in TB laboratory services throughout the years in this analysis. Reasons for this include necessary but prolonged renovations and lack of reagents (Botswana TB report), and this is further explored in Chapter 8. The finding that patients with unknown drug resistance profile are more likely to die has been shown in other research[137] and indicates that a proportion of patients were likely

to have been receiving ineffective treatment. A recent individual patient level meta-analysis, which included patient data from Botswana, also suggests that treatment with drugs for which there is resistance is associated with mortality[138]. Those with presumptive RR-TB are those that are clinically diagnosed; no DST results are available to guide treatment. They are likely to have been diagnosed and started on second-line treatment after first-line treatment failure, indicating late diagnosis and possibly more severe disease; others may have been diagnosed as contacts of other RR-TB patients. Among the full cohort (cohort 1), 83% of all patients had a result of treatment failure from previous first-line treatment indicating that many patients received ineffective first-line treatment before being referred for second-line treatment. This delay in diagnosis not only has the potential to increase disease severity, but also increases the amount of time patients are infectious and possibly transmitting to others.

The risk of mortality among presumptive RR-TB patients was very similar to those with Pre-XDR or XDR-TB. It is possible that some of the patients with presumptive RR-TB had undiagnosed resistance to first and second-line drugs and were therefore receiving ineffective treatment. A functional laboratory and adherence to the testing guidelines are essential elements for an effective RR-TB treatment program to ensure adequate case detection, known drug resistance profiles of patients on treatment and also to monitor for treatment failure. A study in Peru suggested that rapid DST was associated with a 54% reduction in the odds of death during RR-TB treatment[139]. As discussed in Chapter 4, Xpert has the potential to improve case detection and reduce time to treatment, if implemented and used according to guidelines. With the use of Xpert, confirmatory DST and access to second-line DST remain important.

In addition to unknown drug resistance profile, missing other patient information (registration category and radiology results) were also associated with mortality. This highlights potential problems with data reporting and suggests poorer clinical care for these patients. Chest X-ray (CXR) is important for screening and can also help with diagnosing TB[13]. WHO recommends that CXR is used early in the TB screening and diagnosis process, along with other diagnostic methods[140]. It should be noted that missing radiology results does not necessarily mean that a chest x-ray was not performed for these patients. However, it does indicate that the results may not have been sent to the RR-TB treatment facility when patients were referred for treatment by a primary care health facility or may not have been recorded in the patient's medical files. However, all RR-TB treatment facilities did have the capacity to conduct X-ray, and this should have been done for any patient who was referred with an unknown radiology result. This can be improved through education and intervention at the national level to monitor and identify missing data in time for corrective action. A review of missing data by treatment facility revealed that one facility (NRH) has consistently higher proportions of missing information than other facilities, warranting intervention to further understand and improve data reporting and clinical care at this facility in particular. It should be noted that those with missing radiology and registration category data were more likely

to die within the first six months; therefore, it is possible that if patients did not die, this information would have eventually been obtained and added to the medical charts and patient registry. While an assumption was made in this analysis that missing information may be a marker of poor clinical care, it should also be noted that this may be artefacts of misclassification of specific factors due to missing information, leading to misclassification bias.

Increased mortality was significantly associated with being registered in the years 2009-2011. More patients were diagnosed during this time period, so it is possible that more patients were diagnosed and started on treatment who otherwise would have died without diagnosis, as they may have in the other time periods. In 2006-2008, the RR-TB program was still new, and there were only two RR-TB treatment facilities at that time; the three additional treatment facilities were added in 2010. In 2011 the National TB Reference Laboratory (NTRL) (the only culture facility in Botswana) closed which negatively impacted enrollment from 2011 through 2012; the NTRL opened again in 2013 but was closed again from the end of 2014 through 2016. Therefore, the 2012-2014 time period was greatly impacted by laboratory closures. Therefore, these two time periods (2006-2008 and 2012-2014) had challenges that contributed to lower case detection and potentially patients dying without being diagnosed and initiated on RR-TB treatment.

Receiving treatment at two of the five treatment facilities was associated with increased mortality. Princess Marina Hospital (PMH) is located in the capital city (Gaborone) and treats the highest number of RR-TB patients. Additionally, more severe cases are referred to PMH from other facilities for treatment; potentially explaining the higher mortality rate. The reasons for higher risk of mortality at SMH are not immediately clear. SMH is not a referral hospital, so more severe cases would not be sent to SMH to manage. Treatment at SMH is associated with increased mortality after six months, suggesting poor patient management, including inadequate identification of treatment failure. With laboratory closures and inconsistent testing to monitor patients, particularly for second-line drug resistance, it is possible there is more undiagnosed second-line resistance in this setting contributing to mortality. There are other factors that are known to contribute to mortality which were not addressed in this analyses and may have influenced mortality rates in specific settings; these include unemployment, homelessness, alcohol overuse, imprisonment[135], and low CD4 counts among HIV positive individuals[85, 87]. The National TB program itself speculates that the higher rate of mortality at SMH may be influenced by lack of oversight and mentorship from the national level[11]. This lack of supervision may be influenced by lack of accessibility; all other RR-TB treatment facilities are located in areas with an airport. Because there are no flights to Serowe and it is 310 kilometers from the capital city, SMH receives much fewer oversight and mentoring visits from national level staff. Both facilities should be further evaluated to identify areas for intervention, which may include increased resources, education, monitoring and support.

None of the researched side effects or comorbidities showed a significant associated with mortality. One interesting finding is that hearing loss was reported for 44% of all patients in Cohort 2. Treatment with aminoglycosides (such as amikacin or kanamycin) has been shown to be associated with hearing loss[141, 142]. One study showed increased risk of severe hearing loss among patients using amikacin in comparison to kanamycin[143]. The standardized regimen in Botswana includes amikacin. A previous analysis of hearing loss among RR-TB patients in Botswana has been published and attributes the high rates of hearing loss to the use of amikacin. Modongo, et al reported that, among patients initiating RR-TB treatment in Botswana from 2006-2012, 62% developed hearing loss[110]. Among those with reported hearing loss, 54% had audiometry and others were clinically diagnosed by the treating physician[110]. While the current analysis showed a slightly lower proportion of patients with hearing loss (44%), this remains substantial. A systematic review summarizes results from studies reporting hearing loss among patients receiving treatment with amikacin or kanamycin; the proportion of patients with reported hearing loss ranges from 23% to 64% among studies conducted in South Africa and Namibia[141]. This data is in line with what has been reported for Botswana, and highlights the need for incorporating new, less ototoxic drugs for the treatment of RR-TB.

This analysis had several limitations. Firstly, there were small numbers for some of the variables leading to wide confidence intervals and unclear associations with mortality. Secondly, there were a high number of exclusions. Of patients initiating treatment, 62/766 (8%) were excluded in Cohort 1 and 69/245 (28%) were excluded in Cohort 2 because they had an unknown outcome date or (in Cohort 2 only) because their patient chart was not available for review. Factors such as older age and unknown drug resistance profile which were found to be associated with mortality were higher in the excluded group as compared to the included group. Therefore, bias may be present leading to underestimation of the influence of these factors in the analysis. The analysis identified several areas in which data reporting was sub-optimal, and the high number of exclusions due to missing data further highlights this problem of data reporting. Patient characteristics were reported for patients who were excluded from the analysis highlighting the limitations of excluding these patients. Among those excluded, 32% in Cohort 1 and 20% in Cohort 2 had a treatment outcome of death. There was a high level of missing information among excluded patients, and more than half of excluded patients were treated at Nyangabwe Referral Hospital (NRH). NRH is the facility that was shown to have the highest level of missing information also among the included patients; this further highlights the problem of data reporting and the need to address this nationally and specifically at this facility. Thirdly, DST results were reported in the RR-TB register, but the timing of specimen collection was not reported. Therefore, this analysis used a definition of resistance profile based on DST results available at any point during treatment and did not address when that resistance may have developed (before or during treatment). Fourthly, treatment outcomes were assigned by study clinicians using WHO recommended definitions, but these were not verified in this research by a review of lab

results. Alexy, et al compared programmatic and laboratory based outcomes and reported overall good concordance; however, there is some discordance due to delays and incomplete access to culture[144]. They recommend efforts to improve the accuracy of programmatically determined treatment outcomes[144].

Also a limitation of this study, several of the factors being studied appeared to be under-reported, particularly comorbidities. For example, diabetes was only reported among 2% of the patients in Cohort 2. However, this is not consistent with known rates of diabetes in the country. The prevalence of diabetes is estimated at 6% of the entire population, with 4% of all deaths in Botswana attributed to diabetes[145]. Other studies also suggest higher rates of diabetes among RR-TB patients: 33% in India[146], 11% in Georgia[147] and 27% in the Phillipines[148]. The WHO recommends collaborative care and control of diabetes and TB including screening for diabetes among TB patients, screening for TB among patients with diabetes and closely managing both diseases[149]. Diabetes is associated with poor treatment outcomes in drug-susceptible TB[150]. Recent systematic reviews suggest an association between diabetes and risk of developing RR-TB[151, 152]; one review examined the association with diabetes and poor treatment outcomes among RR-TB patients, and although some individual studies did report unsuccessful outcomes, the review did not identify a clear association[152]. Given the results from the individual studies and recommendations from the WHO, it is important to identify and control diabetes, and other comorbidities, among TB and RR-TB patients.

It is important to note that there may be selection bias present in this analysis due to "survivor" effect[153]. Given that there are low numbers of expected comorbidities (diabetes, hypertension, cancer), it is possible that those who survived to treatment were more resilient / healthy than those who may have died before diagnosed with RR-TB or being diagnosed and receiving treatment This may affect the interpretation and generalizability of these results and in particular may indicate that there is an underestimation of the impact of disease severity on mortality in this analysis.

Further bias can be created by censoring patients at the time point of initial outcome, as was done in this analysis. Brooks, et al reports that bias can be minimized by using a predicted vital status at the end of the cohort period rather than at the time point of initial outcome[154]. The bias inherent in the study design selected is acknowledged.

The Botswana RR-TB program has achieved high treatment success in spite of many challenges. Overall, this analysis highlights several opportunities for improvement to decrease mortality rates. Recommendations for the program include increased access to new TB drugs, such as bedaquiline and delamanid, earlier diagnosis, improvements in data reporting, universal DST for all RR-TB patients, universal ART for HIV positive patients and routine monitoring for treatment failure or increased resistance throughout treatment. This analysis covered the time period of 2006 to 2014; since that time the country has adopted universal ART for all HIV positive persons

and has also begun to include the new TB drug, bedaquiline, into the second-line treatment regimen. Use of delamanid is included in the updated guidelines and has (as of 2019) been received in country but no patients have received it yet. While bedaquiline is being provided by USAID through a donation program, delamanid is being purchased by the government at considerable cost. However, revised guidelines which include these new drugs have not yet been developed and distributed. Chapter 4 described recommendations to improve case detection, which is also essential to ensure cases are detected and treated effectively and aren't dying without having received care. Many of these recommendations are already included in national policies and guidelines, so emphasis on adherence to these recommendations and accountability is needed. Additionally, monitoring, training and financial support from the national level is necessary to ensure that all treatment facilities are well resourced, educated and adhering to guidelines.

Chapter 6: Time to treatment for rifampicin-resistant tuberculosis: a systematic review and meta-analysis (published)

6.1 Chapter overview

This chapter will describe the systematic review and meta-analysis conducted and published by the researcher. As well as published data, additional unpublished data will be included. Unpublished data will be identified in the chapter. The chapter will begin with a summary and background as published.

6.2 Hypothesis, aim and objective

Hypothesis 1: Time to treatment is influenced by diagnostic methods and model of care provided in various setting.

Aim: To conduct a systematic review and meta-analysis assessing time to treatment for RR-TB and variability by diagnostic testing methods and treatment delivery approach.

Objectives:

To assess treatment delay in terms of DST methods, access to ambulatory treatment compared to hospital based treatment, and the proportion of patients who initiate treatment

6.3 Summary

Background: To reduce transmission and improve patient outcomes, rapid diagnosis and treatment of rifampicin-resistant tuberculosis (RR-TB) is required.

Objective: We conducted a systematic review and meta-analysis assessing time to treatment for RR-TB and variability by diagnostic testing methods and treatment delivery approach.

Design: Studies (2000-2015) reporting time to second-line treatment initiation were selected from PubMed and published conference abstracts.

Results: From 53 studies, 83 cohorts (13,034 patients) were included. Overall weighted mean time to treatment from specimen collection was 81 days (95% CI 70-91), shorter with ambulatory (57 days, 95% CI 40-74) than hospital-based treatment (86 days, 95% CI 71-102). Time to treatment was shorter with genotypic susceptibility testing (38 days, 95% CI 27–49) than phenotypic (108 days, 95% CI 98–117). The mean percentage of diagnosed patients initiating treatment was 76% (95% CI 70-83%, range 25-100%).

Conclusion: Time to second-line TB treatment initiation is extremely variable across studies, and often unnecessarily long. Reduced delays are associated with genotypic testing and ambulatory treatment settings.

Routine monitoring of the proportion of diagnosed patients initiating treatment and time to treatment is necessary to identify areas for intervention.

6.4 Background

Multidrug-resistant tuberculosis (MDR-TB) is a global health threat[155]. The World Health Organization (WHO) estimates that 580,000 people developed rifampicin-resistant TB (RR-TB) globally in 2015, accounting for 250,000 deaths[156]. RR-TB, including MDR-TB, (defined as TB resistant to both isoniazid and rifampicin) is more difficult to diagnose and treat than drug-susceptible TB, requiring longer treatment courses. Globally, less than 30% of estimated RR-TB patients are diagnosed and fewer are started on appropriate second-line treatment[157].

For the minority of RR-TB patients who are appropriately diagnosed and receive second-line treatment, delays to treatment initiation are often many months in some settings[37, 57-61]. Such delays are likely to increase mortality and loss to follow-up while waiting for treatment[62, 63]. in addition to potentially poorer treatment outcomes among those who do start treatment[64]. Long delays to treatment are also likely to contribute substantially to transmission, in both community and nosocomial settings[65-67]. Given that the majority of RR-TB patients in high burden settings are likely due to direct transmission,[68] scale up of diagnosis and rapid initiation of effective treatment are required to improve patient outcomes and reduce ongoing transmission[69].

A range of health system factors may influence time from first presentation at a health service to treatment initiation, including access to diagnostic services, complicated referral processes, and availability of second-line treatment. Before the availability of genotypic drug susceptibility testing (DST), resistance testing relied on culture-based (phenotypic) methods, often taking months to receive results. Increased use of polymerase chain reaction (PCR)-based tests such as line probe assays (LPA) and Xpert MTB/RIF (Xpert) have reduced the laboratory time needed to reach a diagnosis of RR-TB and therefore theoretically should reduce delays in treatment initiation. Similarly, the provision of community-based treatment, without mandatory admission to hospital, as recommended by the WHO[158], should both increase access to treatment and reduce delays.

We aimed to conduct a systematic review and meta-analysis to assess time to second-line treatment among RR-TB patients and assess delay in terms of DST methods, access to ambulatory treatment compared to hospital-based treatment, and the proportion of patients who start treatment.

6.5 Methods

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[159]. Using a sensitive search strategy comprised of a combination of MeSH terms and other key terms (Figure 6.1),

we searched PubMed (including Medline) and Scopus for relevant articles published from January 1, 2000 to July 15, 2015, without language restrictions. We reviewed abstract books from the Union World Conference on Lung Health from 2010-2014 for studies that may have been completed but not yet published. Additional articles were identified from bibliographies of articles that underwent full text review. Study protocol is available as Appendix C.

- (((((("tuberculosis" OR "TB"))) AND (("MDR" OR "drug-resistant" OR "multidrug-resistant" OR "resistant" OR "rifampicin resistant" OR "rifampin resistant"))) AND treatment) AND time
- (((((("tuberculosis" OR "TB"))) AND (("MDR" OR "drug-resistant" OR "multidrug-resistant" OR "resistant" OR "rifampicin resistant" OR "rifampin resistant"))) AND treatment) AND delay
- (((((("tuberculosis" OR "TB"))) AND (("MDR" OR "drug-resistant" OR "multidrug-resistant" OR "resistant" OR "rifampicin resistant" OR "rifampin resistant"))) AND treatment) AND outcomes

Figure 6.1. PubMed search strings (unpublished)

Study selection

We included studies reporting time to second-line treatment initiation for RR-TB patients, including MDR-TB and extensively drug-resistant (XDR)-TB. Only studies reporting mean or median times to treatment and standard deviations (or with available data allowing calculation of these figures) were eligible to be included in the meta-analysis. Case reports and studies with small sample size (<10 persons) were excluded. Our intent was not to perform a traditional quality assessment, but to set inclusion and exclusion criteria to identify as many comparable studies as possible while also avoiding low quality studies. Two authors (RB, HC) independently reviewed titles and abstracts to identify potentially eligible articles, which then underwent full review to determine final eligibility status, with the same two authors dividing this effort with overlap. Any discrepancy or uncertainty was resolved by consensus. Abstracts and/or articles in languages other than English were translated. Additional articles published after the defined dates were included only if identified through abstracts published during the initial defined time period.

Data extraction

Two authors (RB, HC) extracted data for each cohort described in the included articles. The following information was sought: study year(s), country, sample size, study design, time to treatment definition, mean and median time to treatment, DST method, model of treatment provision and proportion of patients starting treatment. Attempts were made to contact authors of eligible or potentially eligible studies to provide missing data or clarifications. Study quality and potential bias were assessed by reviewing study design, primary outcomes and availability of adequate time to treatment data.

Definitions

Studies were grouped according to definition of time to treatment. The main categories were defined as either time from date of specimen collected or date of diagnosis. Date of diagnosis included a range of definitions given, including; date of result available or received by clinician, or defined simply as date of diagnosis (unclear definition). Studies that used other definitions of time to treatment are listed in Table 6.1, but were not included in grouped analyses. Diagnostic methods were defined as phenotypic if the DST methods included liquid or solid culture methods and genotypic if based on any genotypic method, such as a LPA or Xpert, even if conducted after a positive culture. The model of treatment provision was defined as hospital-based if patients were hospitalized or relocated close to a hospital for initiating treatment and was defined as ambulatory if patients were able to receive treatment on an ambulatory basis during the full course of treatment. Weighted mean difference (WMD) was defined as the average value after pooling results of individual studies, where the contribution of each study to the mean difference is weighted by sample size.

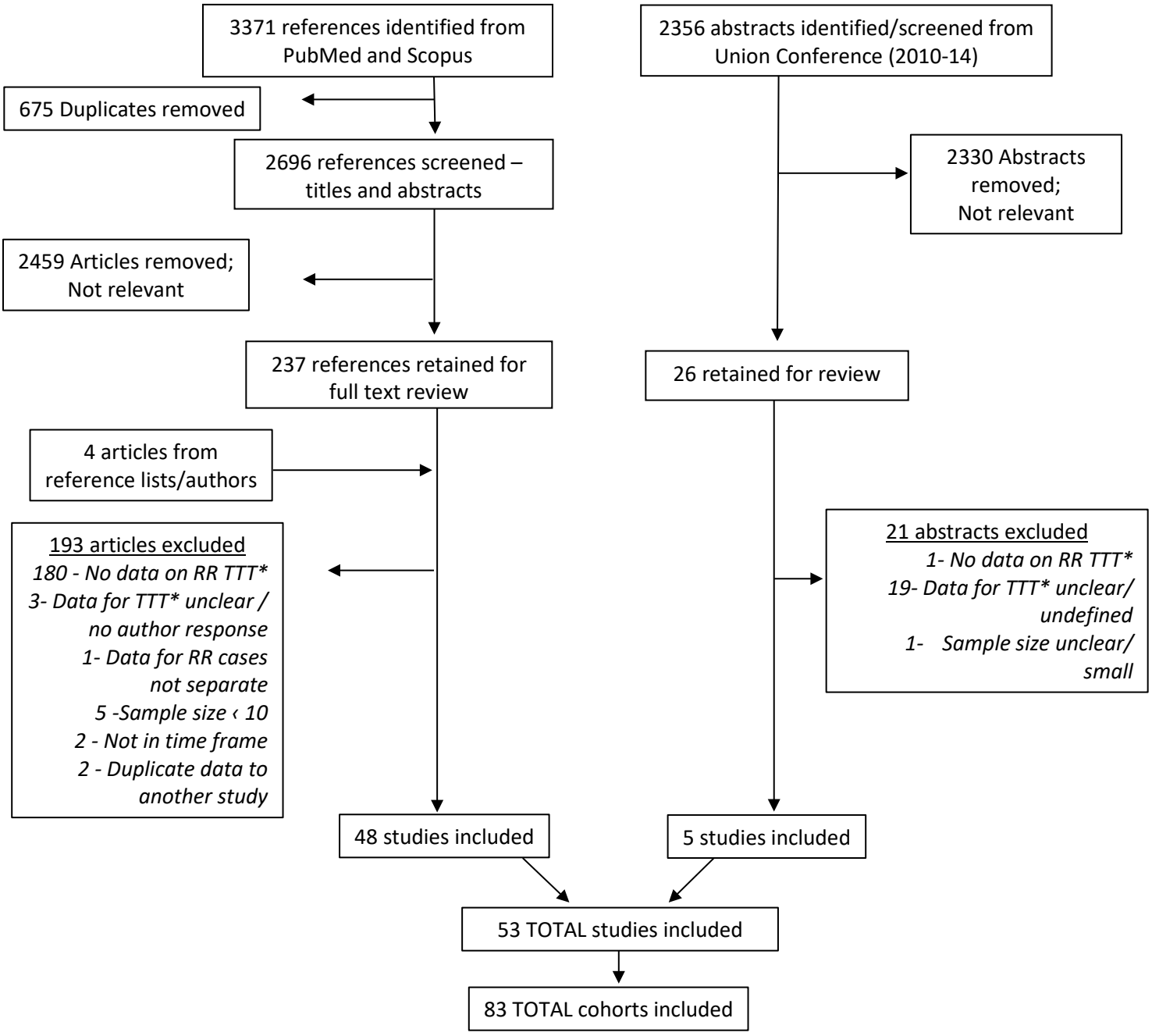
Data analysis

The primary outcome was mean time to treatment. Where this was not reported, means and standard deviations were estimated based on methods described in Wan, et al.[160]. We performed both within-study, comparative meta-analysis as well as analyses across studies to describe the impact of varying DST methods and models of treatment provision. For within-study analysis, any study was eligible to be included irrespective of time to treatment definition used, provided they included two cohorts comparing at least one variable of interest. WMD and corresponding 95% confidence intervals (95%CIs) were calculated to standardize the results of the studies to a uniform scale and to indicate the size of the intervention effect in each study relative to the variability observed in that study. For the across-study analyses, pooled data were stratified by time from specimen collection or from diagnosis; weighted means and corresponding 95% CIs were calculated. Because statistical tests for heterogeneity are not reliable for pooled proportions[161], heterogeneity was assessed by visual inspection of forest plots, with changes in mean time to treatment over time assessed through meta-regression. All analyses were conducted using STATA version 13.0.

6.6 Results

From a screen of 1768 articles and 2356 conference abstracts, a total of 48 published studies and 5 abstracts were included in the systematic review (Figure 6.2). Many studies included more than one patient cohort; these are reported separately. Table 6.1 describes study characteristics, time to treatment definitions, mean and median time to treatment and the proportion of diagnosed patients who were treated.

The studies were from 21 countries and included 83 cohorts, ranging in sample size from 10 to 1063, with a total sample size of 13,034. Twenty-three cohorts were classified as ambulatory, and 58 were hospital-based (2 indeterminable). Phenotypic DST was used for 53 cohorts; 29 used genotypic DST, 12 of which incorporated Xpert (partially or fully) (1 indeterminable). The proportion of diagnosed patients who initiated treatment was reported for 31 cohorts. Study design was prospective for 19 (23%) cohorts and retrospective for 64 (77%) cohorts. Time to treatment was a primary outcome for 26/53 (49%) studies, representing 47/83 (57%) cohorts.



* TTT = Time to Treatment

Figure 6.2. Study selection process flowchart

Author, year	Year of cohort	Location	Laboratory Method	Model of care	Sample size (no. treated)	Median TTT	Mean TTT	SD	Percentage treated (of diagnosed)
From date of specimen collection									
Brust, 2011[162]	2008	South Africa	Phenotypic	Hospital	45	74	75‡	47‡	NR
Cox, 2015[37]	2012	South Africa	Genotypic†	Ambulatory	280	12	27	47	90%
Cox, 2015[37]	2007	South Africa	Phenotypic	Ambulatory	95	76	122	196	NR
Cox, 2015[37]	2003	South Africa	Phenotypic	Hospital	158	71	147	208	NR
Cox, 2015[37]	2007	South Africa	Genotypic	Ambulatory	699	37	51	78	86%
Dlamini-Mvelase, 2014[38]	2011	South Africa	Genotypic†	Hospital	170	20	26	16‡	64%
Dramowski, 2012[163]	2003	South Africa	Phenotypic	Hospital	18	70	94‡	133‡	NR
Fairlie, 2011[57]	2008	South Africa	Phenotypic	Hospital	10	76	154‡	134‡	77%
Francis, 2014[164]	1998	Australia	Phenotypic	Hospital	13	45	52	42‡	81%
Gandhi, 2010[165]	2005	South Africa	Phenotypic	Hospital	46	69	72‡	31‡	37%
Gandhi, 2010[165]	2005	South Africa	Phenotypic	Hospital	35	66	67‡	24‡	25%
Hanrahan, 2012[166]	2007	South Africa	Phenotypic	Hospital	26	78	74‡	32‡	NR
Hanrahan, 2012[166]	2009	South Africa	Genotypic	Hospital	52	62	60‡	41‡	NR
Heller, 2010[58]	2008	South Africa	Phenotypic	Ambulatory	50	84	91‡	32‡	NR
Heller, 2010[58]	2001	South Africa	Phenotypic	Hospital	57	107	150‡	76‡	NR
Jacobson, 2013[167]	2007	South Africa	Phenotypic	Hospital	89	80	81‡	29	NR
Jacobson, 2013[167]	2008	South Africa	Genotypic	Hospital	108	55	57‡	30	NR
Kipiani, 2014[168]	2009	Georgia	Phenotypic	Hospital	72	NR	84	38‡	NR
Kipiani, 2014[168]	2010	Georgia	Genotypic	Hospital	80	NR	18	10‡	NR
Li, 2015[169]	2006	China	Phenotypic	Hospital	81	139	138‡	104‡	88%
Li, 2015[169]	2011	China	Genotypic	Hospital	172	14	15‡	8‡	71%
Loveday, 2015[170]	2008	South Africa	Genotypic	Hospital	736	72	74‡	32‡	NR
Loveday, 2015[170]	2008	South Africa	Genotypic	Hospital	813	92	94‡	38‡	NR
Mpagma, 2013[59]	2009	Tanzania	Phenotypic	Hospital	61	274	301	173‡	NR
Munsiff, 2006[60]	1992	USA	Phenotypic	NR	610	42	198‡	102‡	71%
Naidoo, 2014[39]	2011	South Africa	Genotypic†	Ambulatory	120	17	17‡	6‡	94%
Naidoo, 2014[39]	2008	South Africa	Genotypic	Ambulatory	375	43	43‡	4‡	91%
Narasimooloo, 2012[171]	2010	South Africa	Phenotypic	Hospital	175	NR	87	47‡	94%

O'Riordan, 2008[172]	1982	UK	Phenotypic	Hospital	18	59	60‡	55‡	64%
O'Riordan, 2008[172]	1997	UK	Genotypic	Hospital	14	8	9‡	14‡	100%
Page, 2015[40]	2012	Swaziland	Genotypic†	NR	44	12	12‡	8‡	81%
Rodriguez, 2013[61]	2006	Dominican Republic	Phenotypic	Hospital	289	222	238‡	177‡	NR
Shean, 2012*[173]	2000	South Africa	Phenotypic	Ambulatory	144	77	78	10‡	NR
Shean, 2012*[173]	2000	South Africa	Phenotypic	Hospital	123	62	102	7‡	NR
Shenoi, 2012[174]	2005	South Africa	Phenotypic	Hospital	86	88	90‡	9‡	61%
Smith, 2013*[175]	2011	South Africa	NR	Hospital	365	86	84‡	38‡	NR
van Kampen, 2015 [41]	2012	Indonesia	Genotypic†	Hospital	179	16	22‡	24‡	58%
van Kampen, 2015 [41]	2011	Indonesia	Phenotypic	Hospital	159	88	85‡	48‡	38%
From date of diagnosis									
Charles, 2014[176]	2010	Haiti	Genotypic†	Hospital	110	46	76	42‡	NR
Eliseev, 2016[177]	2009	Russia	Genotypic	Hospital	132	51	53‡	45‡	NR
Eliseev, 2016[177]	2007	Russia	Phenotypic	Hospital	163	99	114‡	70‡	NR
Farley, 2011[78]	2000	South Africa	Phenotypic	Hospital	287	50	64	34‡	NR
Farley, 2011[78]	2000	South Africa	Phenotypic	Hospital	470	54	70	36‡	NR
Gegia, 2013[178]	2009	Georgia	Phenotypic	Hospital	45	16	86‡	71‡	NR
Hoa, 2014[179]	2010	Vietnam	Genotypic	Ambulatory	203	NR	2	12	NR
Hoa, 2014[179]	2010	Vietnam	Genotypic	Hospital	79	NR	13	47	NR
Isaakidis, 2013[180]	2007	India	Genotypic†	Ambulatory	16	7	8‡	3‡	100%
Isaakidis, 2013[180]	2007	India	Phenotypic	Ambulatory	21	8	15‡	38‡	88%
Mitnick, 2003[181]	1996	Peru	Phenotypic	Ambulatory	75	246	909‡	654‡	NR
Odendaal, 2012*[182]	2005	South Africa	Phenotypic	Hospital	224	10	13‡	10‡	NR
Odendaal, 2012*[182]	2005	South Africa	Phenotypic	Hospital	197	37	42‡	34‡	NR
Shao 2013*[183]	2011	Tanzania	Genotypic†	Hospital	44	NR	59	97‡	NR
Shao, 2013*[183]	2011	Tanzania	Phenotypic	Hospital	19	NR	230	186‡	NR
Singla, 2009[184]	2002	India	Phenotypic	Hospital	126	NR	100	49‡	NR
Toshniwal, 2014*[185]	2009	India	Phenotypic	Hospital	44	NR	132	NR	NR
Toshniwal, 2014*[185]	2009	India	Genotypic†	Hospital	71	NR	17	NR	NR
Toshniwal, 2014*[185]	2009	India	Genotypic	Hospital	157	NR	44	NR	NR
Blaya, 2014[186]	2006	Peru	Phenotypic	Ambulatory	134	88	88‡	73‡	NR
Blaya, 2014[186]	2005	Peru	Phenotypic	Ambulatory	132	77	77‡	68‡	NR

Cavanaugh, 2012[187]	2002	Russia	Phenotypic	Hospital	198	NR	466	NR	NR
Ebonwu, 2013[188]	2011	South Africa	Genotypic	Hospital	593	10	12‡	10‡	63%
Gler, 2012[189]	2003	Philippines	Phenotypic	Hospital	1063	76	105‡	216‡	57%
Hossain, 2015[190]	2012	Bangladesh	Genotypic†	Hospital	145	5	7‡	10‡	90%
Narita, 2001[191]	1994	USA	Phenotypic	Ambulatory	31	15	50‡	93‡	100%
Narita, 2001[191]	1994	USA	Phenotypic	Hospital	39	177	696‡	568‡	100%
van Kampen, 2015[192]	2012	Kazakhstan	Genotypic†	Hospital	471	7	9‡	9‡	84%
Other definitions of time to treatment									
Drobac, 2006[193]	1999	Peru	Phenotypic	Ambulatory	38	198	448‡	327‡	NR
Mendoza-Ticona, 2012[194]	2007	Peru	Phenotypic	Ambulatory	11	173	181‡	92‡	NR
Mendoza-Ticona, 2012[194]	2009	Peru	Phenotypic	Ambulatory	13	76	69‡	42‡	NR
Otero, 2014[195]	2008	Peru	Phenotypic	Ambulatory	37	25	31‡	19‡	NR
Belkina, 2014[196]	2013	Uzbekistan	Genotypic†	Hospital	243	8	30	37‡	NR
Banerjee, 2010[197]	2004	USA	Phenotypic	Ambulatory	100	79	84‡	50‡	NR
Banerjee, 2010[197]	2004	USA	Genotypic	Ambulatory	27	38	42‡	32‡	NR
Mirasaeidi, 2005[198]	2000	Iran	Phenotypic	Hospital	17	NR	848	638‡	NR
Natt, 2014[63]	2011	India	Phenotypic	Hospital	67	NR	67	NR	82%
Seddon, 2011[199]	2003	South Africa	Phenotypic	Hospital	105	91	103‡	86‡	95%
Singla, 2014[200]	2009	India	Phenotypic	Hospital	51	157	161	56	61%
Singla, 2014[200]	2009	India	Genotypic	Hospital	83	38	49	37	88%
Skenders, 2011[201]	2003	Latvia	Phenotypic	Hospital	48	40	43‡	34‡	NR
Skenders, 2011[201]	2003	Latvia	Genotypic	Hospital	23	14	14‡	12‡	NR
Otero, 2014[195]	2008	Peru	Phenotypic	Ambulatory	90	25	28‡	25‡	NR
Saravia, 2005[202]	1997	Peru	Phenotypic	Ambulatory	73	268	404‡	199‡	NR
Saravia, 2005[202]	1997	Peru	Phenotypic	Ambulatory	52	55	109‡	72‡	NR

* Union Abstract; † Includes Xpert MTB/RIF; ‡ Figures calculated based on formulas provided in Wan, et al[160]; UK = United Kingdom; USA = United States of America; NR = Not reported

Table 6.1. Study characteristics and results

Time to treatment

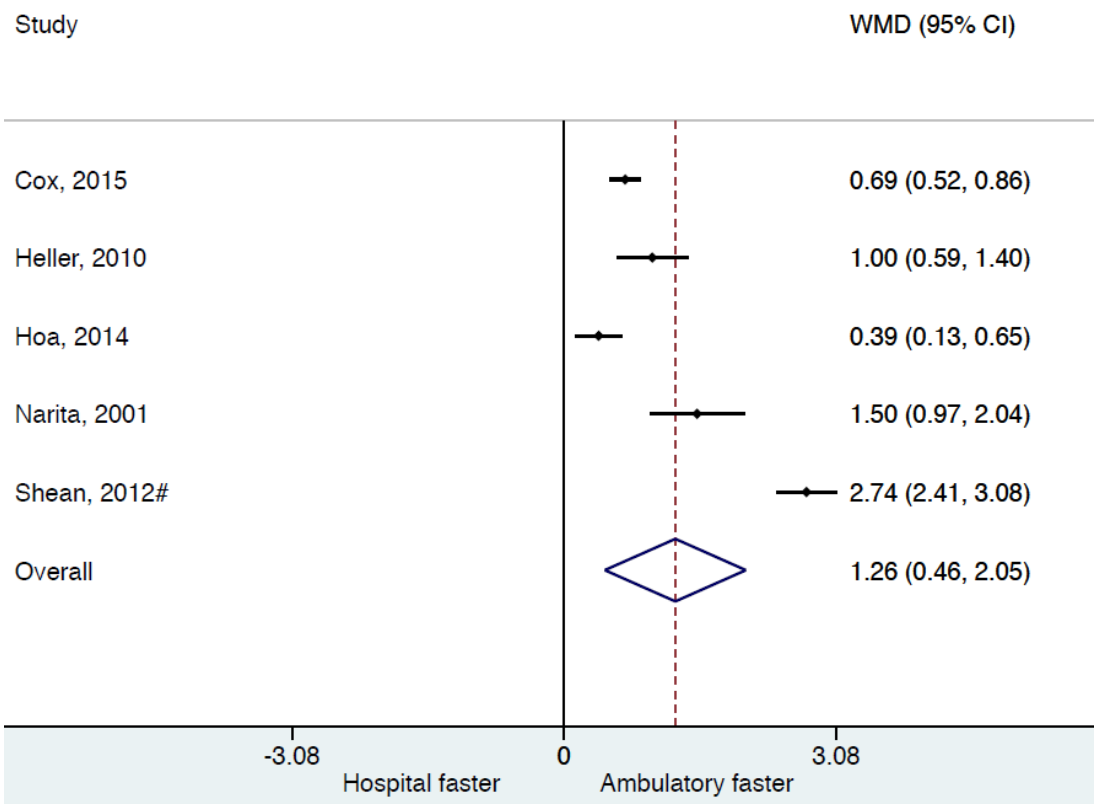
Mean time to treatment was reported for 30 cohorts and calculated for the remaining 53 cohorts. There were insufficient data available to calculate standard deviations for seven cohorts, listed in Table 6.1 but not included in analyses. Time to treatment was most commonly reported as time from specimen collection (38 cohorts), followed by time from diagnosis (28 cohorts) (Table 6.1).

Mean and median times to treatment from specimen collection ranged from 9 days to 10 months and 8 days to 9 months, respectively. Among the 38 cohorts with time to treatment measured from specimen collection, the weighted mean time to treatment was 81 days (95% CI 70-91, range 9-301). Among the 24 cohorts with time to treatment measured from diagnosis, the weighted mean time to treatment was 59 days (95% CI 50-68, range 2-909).

Model of treatment provision

Five studies were included in the within-study comparison of ambulatory versus hospital-based treatment provision (Figure 6.3). All five studies reported faster time to treatment for patients under ambulatory treatment compared to hospital-based treatment; the pooled difference across all studies was significantly in favor of ambulatory treatment (WMD 1.26, 95% CI 0.46-2.05).

There were seven (1,763 patients) cohorts treated under ambulatory based models of care and 29 (4,250 patients) under hospital-based treatment with time to treatment from specimen collection. Mean time to treatment with ambulatory treatment was 57 days (95% CI 40-74, range 17-122) compared to 86 days (95% CI 71–102, range 9-301).

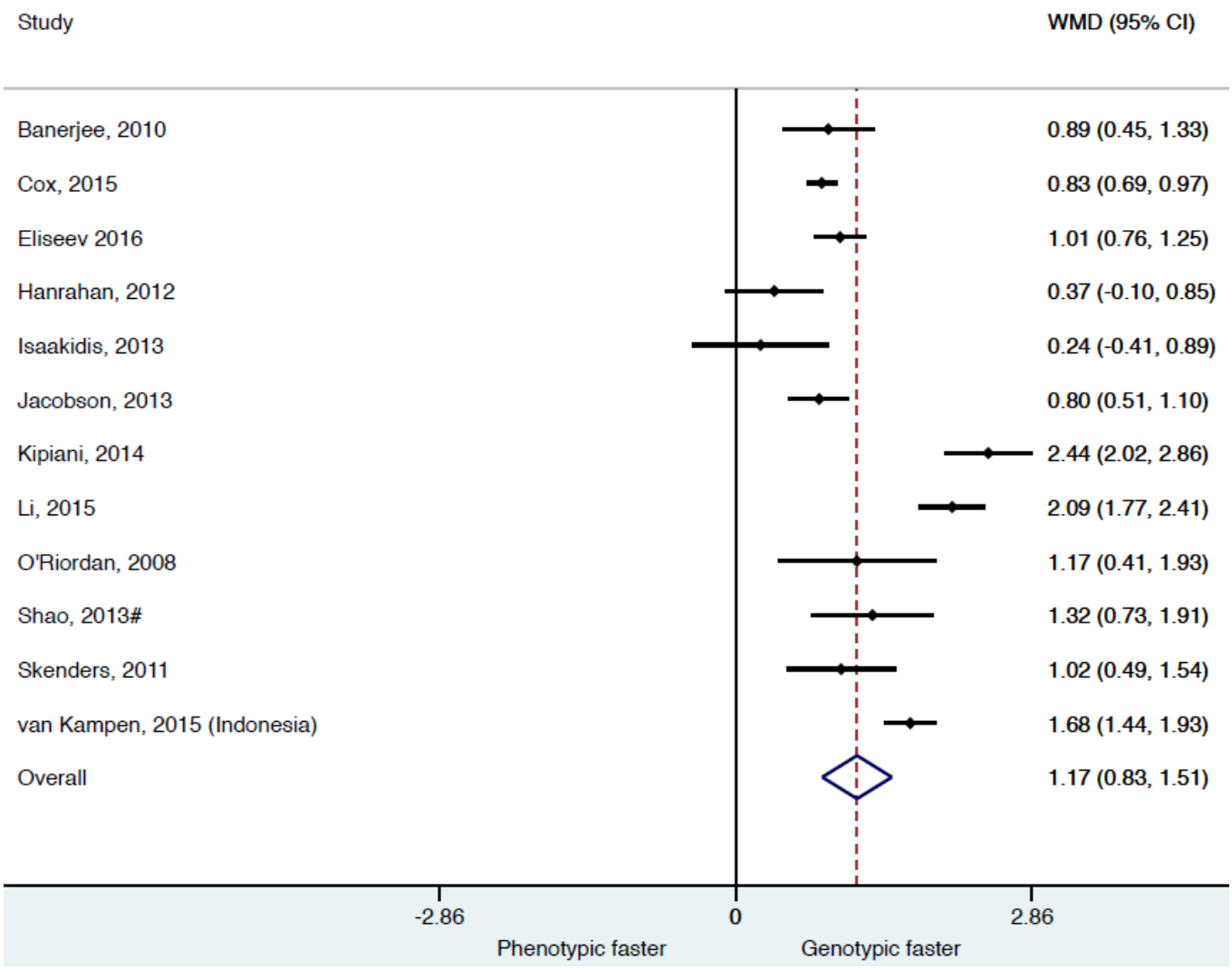


WMD = Weighted Mean Difference

Figure 6.3. Time to treatment initiation by model of treatment provision

Drug susceptibility testing methods

Twelve studies were included in the within-study comparison of DST methods (Figure 6.4). All studies consistently reported a shorter time to treatment with genotypic versus phenotypic DST; the pooled difference across all studies was significantly in favor of genotypic DST (WMD 1.17, 95% CI 0.83-1.51). There were 14 (3,842 patients) cohorts using genotypic DST and 23 (2,460 patients) cohorts with phenotypic DST reporting time to treatment from specimen collection. Mean time to treatment was significantly lower with genotypic DST: 38 days (95% CI 26–49, range 9-94) compared to 108 days (95% CI 98 – 117, range 52-301) for phenotypic DST.



WMD = Weighted Mean Difference

Figure 6.4. Time to treatment initiation by laboratory drug susceptibility testing methods

Time to treatment by year of cohort

Among cohorts with time to treatment measured from specimen collection, the mean time to treatment decreased over time (β- coefficient, - 3.13, 95%CI -5.09 - 1.18, P= 0.002) (Figure 6.5). Figure 6.6 (unpublished) displays mean time to treatment for each cohort over time, graphed by the year each individual cohort began. The weighted mean time to treatment from specimen collection prior to 2010 was 98 days (95% CI 85-111, range 9-301), compared to 39 days (95% CI 28-50, range 12-87) for 2010 or later.

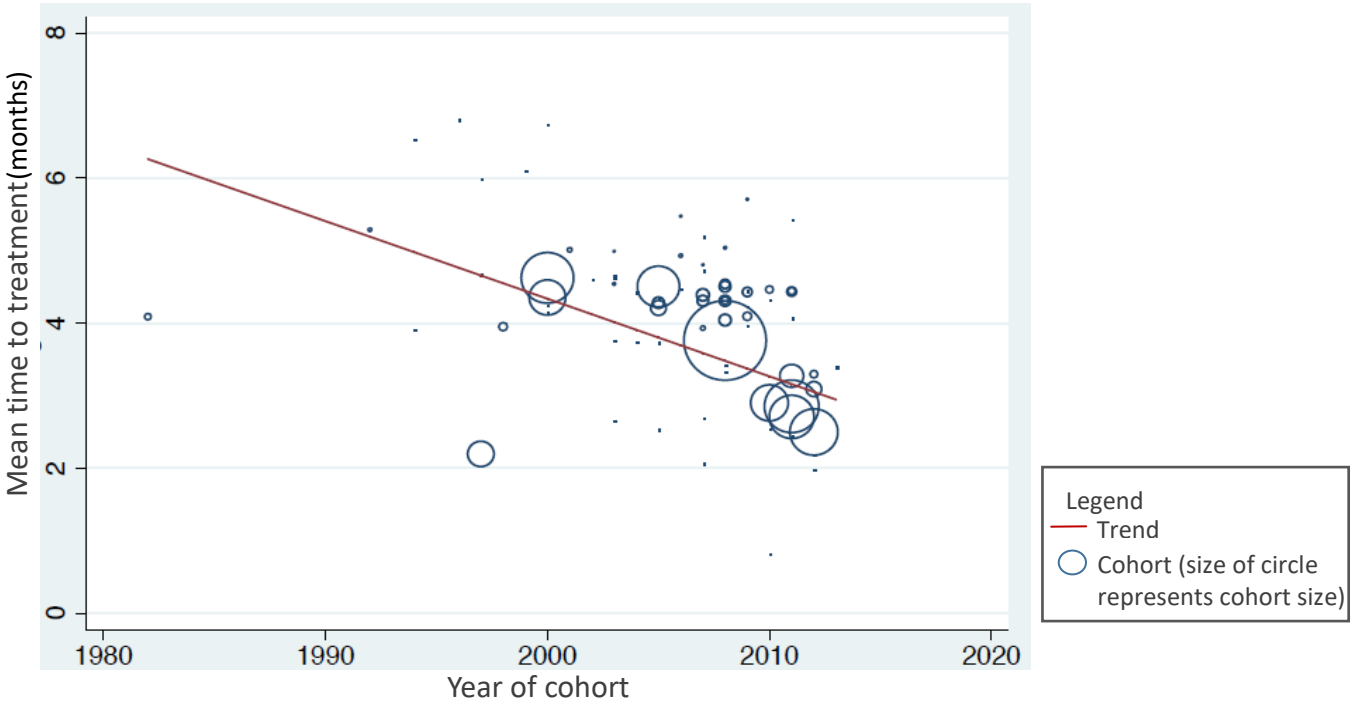


Figure 6.5. Trends in mean time to treatment initiation over time

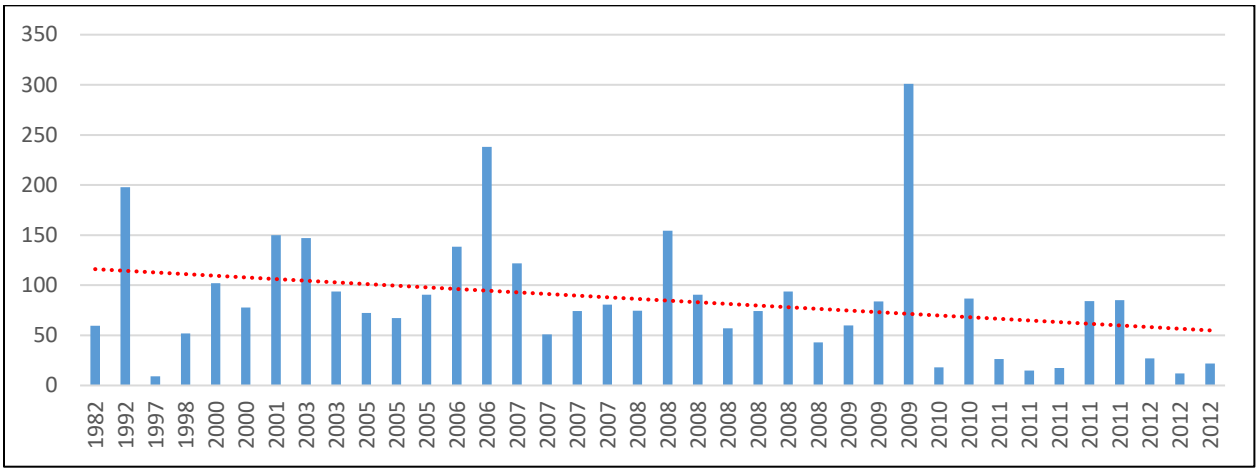
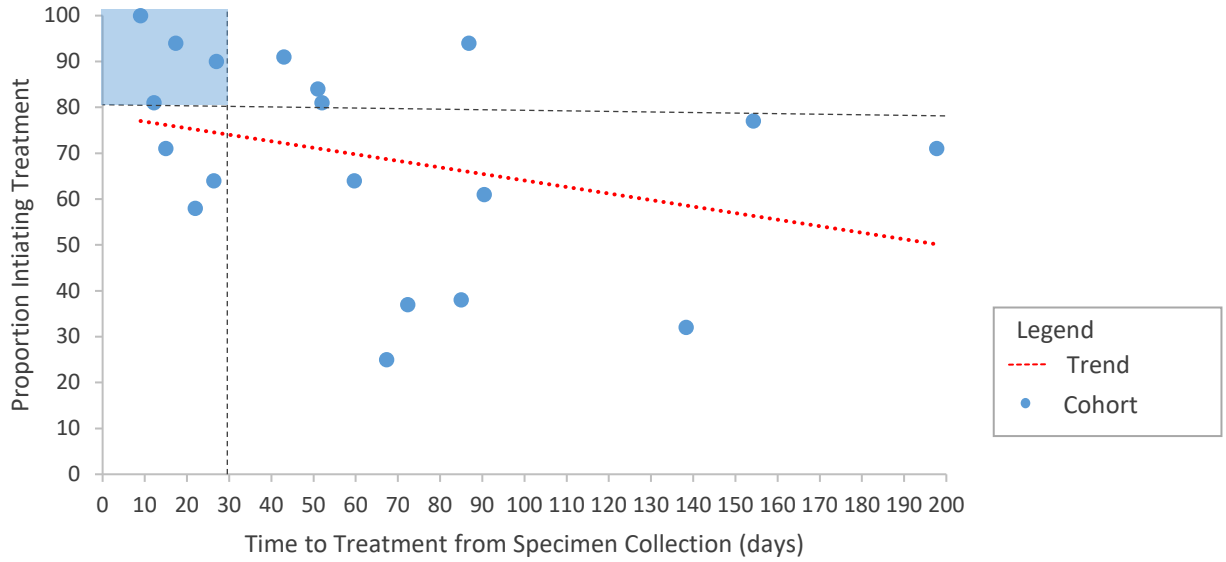


Figure 6.6. Mean time to treatment (days) over time (unpublished)

Time to treatment by proportion initiating treatment

The mean percentage of diagnosed patients initiating treatment (reported for 31/83 cohorts) was 76% (95%CI 70-83%, range 25-100%) (Table 6.1). Figure 6.7 compares mean time to treatment to the proportion initiating treatment for the 19 cohorts reporting time to treatment from specimen collection. The upper-left shaded portion represents cohorts with a mean time to treatment of ≤30 days and at least 80% of diagnosed patients initiating treatment to represent best practice; only four cohorts[37, 39, 40, 172], representing 458/3286 (14%) patients included in the analysis, fell into this category. All four cohorts used genotypic DST; model of treatment provision was ambulatory for two cohorts, hospital based for one and not reported for one.



Dotted lines at 80% and 30 days highlight 4 cohorts with both high proportion initiating treatment and short time to treatment, to represent best practice[37, 40, 171, 172]

Figure 6.7. Time to treatment initiation by proportion initiating treatment

Combination of Interventions (unpublished)

The shortest weighted mean time to treatment from specimen collection was among patients diagnosed using genotypic DST and initiated on treatment under ambulatory models of care (Table 6.2). However, this was not significantly different compared to patients diagnosed using genotypic DST and initiated on treatment under hospital based models of care. Mean time to treatment for both of these combinations using genotypic DST is significantly shorter when compared to the two combinations which include phenotypic DST (Table 6.2).

Interventions	Number of cohorts	Sample size	Weighted mean time to treatment, days (95% CI)
Molecular DST methods used and ambulatory treatment available	4	1520	35 (17-52)
Molecular DST methods used and hospital based treatment required	9	2620	42 (22-61)
Culture based DST methods used and ambulatory treatment available	2	145	87 (73-101)
Culture based DST methods used and hospital based treatment required	18	2353	102 (93-111)

Table 6.2. Combination of interventions and time to treatment initiation

6.7 Discussion

Delays in initiation of second-line treatment can negatively impact clinical and public health outcomes. Even reductions of several weeks or months are likely to significantly impact community transmission[68] and are likely to improve patient outcomes[64, 177]. This systematic review and meta-analysis has shown that time to treatment is extremely variable across studies and often lengthy. Overall, the average time to treatment from specimen collection was 2.5 months, with trend for reduction in delay in more recent years. This is consistent with advances in RR-TB diagnosis and treatment, and potentially reflects greater recognition of the need to initiate treatment sooner to improve patient outcomes and reduce ongoing transmission risk. The use of genotypic DST methods and provision of treatment through ambulatory based models of care both contributed to shorter times to treatment. While significant reductions in time to treatment are seen over time, substantial delays remain in recent years.

Molecular testing methods result in more rapid laboratory turnaround times[64, 203-205] and are therefore likely to reduce time to treatment. This was confirmed in our analysis, with genotypic testing, using LPA or Xpert, resulting in significantly shorter time to treatment compared to phenotypic methods reliant on culture, and our findings are consistent with the results of a randomized trial[206] and a retrospective cohort study published after our search was concluded[42]. Xpert is of particular interest due to the feasibility of testing in peripheral laboratories,[207, 208] potentially reducing reliance on transport and resulting in more rapid communication of results. Studies which have implemented faster, molecular DST show lower mortality and loss to follow-up and therefore a higher proportion of patients starting treatment[41]. Rapid DST has also been shown to reduce treatment failure[194] and result in higher treatment success[177]. However, currently available genotypic methods are restricted by the number of drugs that can be tested, often resulting in continued reliance on phenotypic DST for second-line drugs.

Ambulatory second-line treatment can result in similar treatment outcomes compared to hospital-based treatment,[89] and can lead to higher proportions of patients initiating treatment[37, 39, 180]. Our review complements these positive findings, providing evidence that ambulatory treatment results in shorter time to treatment compared to hospital-based treatment. Patients receiving treatment in hospital-based setting may experience further delays due to the preparation needed to be admitted to the hospital; these may include referral processes, informing family and work, making arrangement for the care of children and other home responsibilities and actually traveling to the hospital.

We identified a wide range in delay across studies, particularly among cohorts with hospital based models of care as well as cohorts with phenotypic DST. The authors of the main studies with lengthy times to treatment, refer to prolonged referral processes[59] and the use of phenotypic DST methods[172]. Although reduced delays are

seen with both genotypic DST and ambulatory treatment provision, several more recent studies show times to treatment greater than 1.5 months.[37, 58, 166] Studies report delays in reporting results to clinics and in contacting patients as potential contributing factors[39, 167]. Programmatic factors such as sample transport and results communication could be improved[209].

Time to initiation of second-line treatment needs to be considered in terms of the proportion of diagnosed patients who actually start treatment. Several studies reported relatively rapid times to treatment (less than 30 days), but still less than 70% of diagnosed patients starting on treatment[38, 41, 188]. These studies highlight the need to assess areas of improvement along the entire diagnosis and treatment cascade for RR-TB; from diagnosis of TB, identification of drug resistance, treatment initiation and finally treatment success.

Our systematic review has identified several limitations in the current evidence base. First, the definitions of time to treatment were not reported clearly or consistently across several studies and were grouped into categories described in Table 6.1 for ease of analysis. Studies reporting time to treatment from specimen collection can provide a clearer picture of delays caused by various elements in health care systems, including specimen transport, diagnostic delays, results reporting, patient notification and referral. However, there are several delays that could have occurred prior to sending a specimen for DST, including patient level delays in seeking treatment and restricted access to DST. Without universal access to DST, patients may first be treated for drug sensitive TB and only offered DST upon failure of treatment. Secondly, neither time to treatment nor the proportion of diagnosed patients initiating treatment were primary outcomes for many of the studies in this analysis. This contributes to unclear definitions and also uncertainty introduced through calculation of means and standard deviations. The inconsistency in reporting the proportion of patients initiating treatment (only reported for <40% cohorts) also may skew the time to treatment data. Third, there may be other factors influencing time to treatment that were not reported by the studies and could not be assessed in our analyses, including decentralized lab services, availability and accessibility of treatment services, and inclusion of migratory populations. Fourth, due to lack of data, authors were not able to stratify analysis by Xpert and LPA. Another important limitation to the conduct of this review is the limited number of databases that were searched. One study in this analysis is a randomized control trial, and we acknowledge that this may introduce bias as additional delays may be caused by the randomization process; it is important to note that this study is not included in the majority of analyses for this review, those that measure time to treatment from sputum collection and therefore, has little impact on the primary findings. Additionally, 77% of the cohorts in this review are from retrospective studies, and we acknowledge risk of misclassification bias with retrospective study design and the implication that the effect may be underestimated. Finally, as with any systematic review, there may be publication bias; we attempted to mitigate this bias by including abstracts.

The proportion of diagnosed RR-TB patients who initiate treatment and the delay to second-line treatment are important indicators of programmatic performance. While the proportion of the estimated global burden of RR-TB that receives treatment is gradually increasing, there is still much room for improvement[156]. The WHO End TB Strategy calls for integrated, patient-centered care and prevention, including universal DST and treatment of all people with RR-TB; bold policies and supportive systems including political commitment and engagement of communities; and intensified research and innovation[210]. Such interventions and commitment should contribute to reducing the diagnostic and treatment gaps, and treatment delays. Routine monitoring and reporting of the proportion of patients initiating treatment and time to treatment, ideally measured from specimen collection to highlight most delays, are needed to identify gaps and areas for intervention.

Chapter 7: Utilization of Xpert MTB/RIF (Xpert) and the impact on time to second-line treatment

7.1 Chapter overview

This chapter will include two sections. The first section will describe all Xpert testing conducted in Botswana in 2013 and 2014. Section 1 will specifically address how patients with RR or RR indeterminate results by Xpert were managed in Botswana. The second section will describe a time to second-line treatment analysis using two cohorts: the Xpert Cohort including RR-TB patients initiating RR-TB treatment based on Xpert diagnosis, and a comparison cohort (the NTRL Cohort) including RR-TB patients initiating RR-TB treatment based on diagnosis from the National Tuberculosis Reference Laboratory (NTRL). The chapter starts with background/policy review and methods relevant to both sections.

7.2 Hypotheses and aim

Hypothesis 1: Xpert improves time to treatment as compared to DST conducted at the centralized laboratory.

Hypothesis 2: There are gaps in confirmatory testing for patients initially tested by Xpert.

Aim: To assess patient management and linkage to care for TB patients with RR detected or RR indeterminate results by Xpert in 2013 to 2014

7.3 Background/Policy review

At the time of this research, there was one laboratory facility in Botswana with the capacity to conduct culture testing and first-line phenotypic DST, the NTRL. The 2011 National TB Program Manual indicated that the following people should have samples submitted to the NTRL for culture and first-line DST[16]:

- HIV positive individuals with presumptive TB with 2 negative sputum smear results
- New TB patients who remain or become smear positive at month 3 of treatment
- All previously treated TB patients regardless of reason (failure, relapse, or loss to follow-up)
- All children with presumptive TB
- Patients who develop TB during or after IPT
- Symptomatic individuals at higher risk of MDR-TB: lab workers, MDR-TB contacts, health care workers

Additionally, according to the 2009 National Guidelines for Management of DR-TB, all patients diagnosed with RR-TB and initiating second-line treatment should have a baseline culture and first-line DST at the NTRL[48]. First-line DST at the NTRL consists of testing for at least isoniazid and rifampicin, and generally includes testing for all

first-line TB drugs: isoniazid, rifampicin, streptomycin, and ethambutol (and sometimes includes testing for pyrazinamide).

Xpert was first introduced in Botswana in 2012 through an operational research study, the Xpert Package Rollout Evaluation Study (XPRES), conducted by the Centers for Disease Control (CDC) Botswana in collaboration with the Botswana Ministry of Health and Wellness. The study aimed to compare the sensitivity of microscopy-based and Xpert-based pulmonary TB diagnostic algorithms in diagnosing sputum culture-positive TB and to evaluate the impact of Xpert and intensified case finding on all-cause, 6-month, adult antiretroviral therapy (ART) mortality[46]. During this time, 13 Xpert devices were placed throughout the country in district laboratories or in TB/HIV clinics (point of care) (Figure 7.1). The study enrolled and followed up all HIV positive persons initiating ART with symptoms of TB seeking treatment at 22 participating TB/HIV clinics from 2012 to 2014. The devices were also used by the government of Botswana for routine testing of patients with presumed TB at the participating clinics. The analysis described in this chapter will include all tests conducted by Xpert in 2013 and 2014, including patients tested for the study and patients tested through routine government testing.

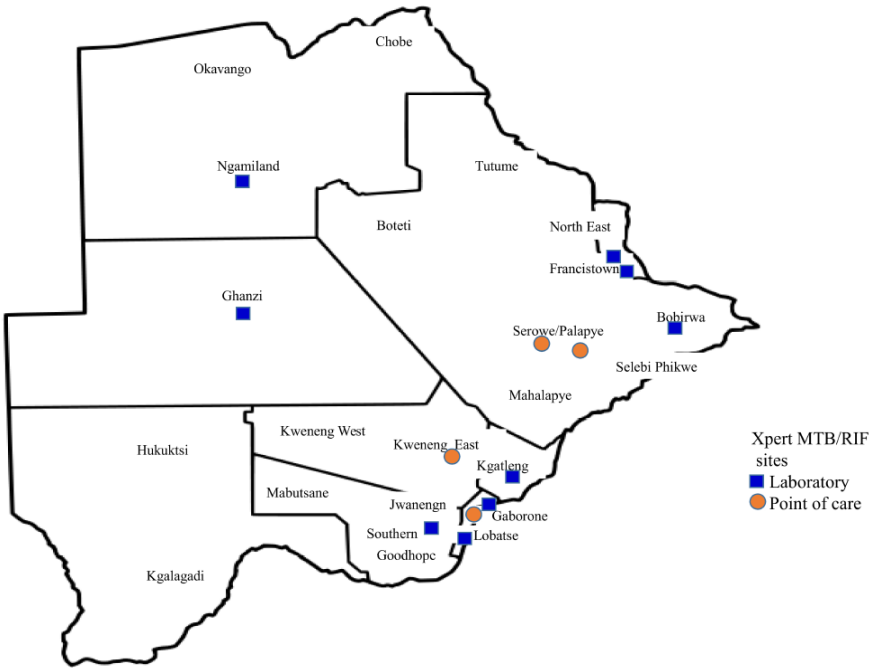


Figure 7.1. Location of Xpert devices in Botswana in 2013-2014[31]

After the XPRES study ended and follow-up was complete (2015), the Xpert devices were donated to the MoHW; the MoHW installed additional devices as well bringing the total Xpert devices in use to 34 by 2015. Xpert was not fully incorporated into the National TB Program in Botswana until 2016, when the diagnostic algorithm including Xpert (Appendix A) was finalized and distributed. While Xpert was used prior to 2016, it was not intended to replace routine practices in the country, described in the first paragraph. Any patient who would

have had a sample sent to the NTRL for testing should still have had a sample sent to the NTRL, regardless of Xpert result. Additionally, the government specifically released guidance to all facilities utilizing Xpert, instructing that any patient with an Xpert test indicating RR should have confirmatory DST conducted at the NTRL and should be initiated on second-line treatment while waiting on results of confirmatory culture and DST. Guidance also indicated that any test with an RR indeterminate result by Xpert should have a repeat Xpert test and follow-up testing at the NTRL if warranted based on the second test or other recommendations for routine testing.

7.4 Methods

The development of the Xpert database used in this analysis was described in Chapter 3.

The analysis in Section 1 includes a description of all Xpert tests conducted, using proportions. This broad analysis includes all tests conducted. Tests run for quality assurance and training were removed, but no deduplication was conducted; there may be more than one test for a single patient included in this overall description of testing results. More specific analyses were conducted among tests for which the results were RR detected or RR indeterminate.

For Xpert test results which were RR detected, tests were manually reviewed (using name and identification number) to identify any duplicate samples per patient. Duplications were removed, and the analysis is presented in terms of patients, rather than tests. Patients with a test result of RR detected were investigated for the following (techniques for deduplication and matching with other datasets were fully described in Chapter 3):

- If treatment was initiated
- Time from Xpert result to treatment initiation. The date of Xpert result is defined as the date the test was conducted.
- If confirmatory DST results were available
    - Confirmatory DST results were included in the analysis if they were available (recorded in the LIS) within 6 months of the Xpert result. This is based on the analysis described in section 2, which shows it is not uncommon for DST results from the NTRL to be available up to 6 months after specimen collection.
- Time from Xpert result to confirmatory DST

Data for patients with RR indeterminate results also underwent the same process of deduplication and matching that were used for the patients with RR detected results. Patients with RR indeterminate results were investigated for the following:

- If a repeat Xpert test was done
- Results of repeat tests
- If any testing was done at the NTRL
- Results of any the NTRL tests

Proportions were used to describe testing, results and treatment among patients with an Xpert result of RR detected or RR indeterminate. Medians and interquartile ranges were used to describe time to treatment or confirmatory testing.

The researcher followed up on patients that had an RR-TB diagnosis by Xpert but were not located in the RR-TB registry as having initiated treatment. Both the district TB coordinator and the RR-TB treatment facility which serves the district in which the patient was diagnosed were contacted (by phone) in 2015. The TB coordinators and the staff at the treatment center were asked if they were aware of the patients and if they knew why they were not initiated on treatment.

The Section 2 analysis describes a comparison of time to treatment between two cohorts. The Xpert cohort includes any RR-TB patients with RR diagnosed by Xpert who initiated treatment. Any patient whose Xpert RR result was only available after treatment initiation was excluded from the time to treatment analysis**.** The NTRL cohort includes any patients diagnosed with RR at the NTRL (centralized location) who initiated treatment. Any patient whose DST result was only available after treatment initiation was excluded from the time to treatment analysis. DST results include results from MGIT testing and LPA testing, though LPA testing was limited during the time of this study.

Time to treatment was measured in various ways for the two cohorts. The specimen collection date was not available for the Xpert cohort; this is not recorded in the gxx. Therefore, the main comparison of time to treatment is defined as time from diagnosis to treatment initiation. Diagnosis is the date the result is recorded in the respective databases. Additional analysis and time points were calculated based on estimates or available data, as described below for each cohort:

Xpert cohort:

- Time to treatment from diagnosis = the date of treatment initiation in the RR-TB register MINUS based on the date of the Xpert result as automatically recorded in the gxx file.

- Time from specimen collection to diagnosis = estimated at 10 days, per standard practice (data unavailable)

NTRL cohort:

- Time to treatment from diagnosis = the treatment initiation date in the RR-TB register MINUS the date the result has been entered and reviewed at the NTRL (defined as 'reviewed date' in the LIS)
- Time from specimen collection to diagnosis = the date the result has been entered and reviewed at the NTRL MINUS the date of specimen collection as recorded in the LIS.
- Time from specimen collection to treatment = the treatment initiation date in the RR-TB register MINUS the date of specimen collection as recorded in the LIS.

Time to treatment was measured using medians and interquartile ranges. A pairwise comparison using nonparametric test was used to describe the difference in medians, with .05 significance and 95% CI levels.

All analyses were conducted using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) or Excel for basic charts and graphs.

7.5 Results (Section 1)

Xpert test results

Figure 7.2 displays the results of all Xpert tests conducted from January 1, 2013 to December 31, 2014. Of 9,086 total tests, 1,147 (13%) had a result of MTB Detected. Of those with MTB detected, 86 (8%) had a result of RR detected, and 48 (4%) had a result of RR indeterminate. There was a total of 966 (11%) failed tests.

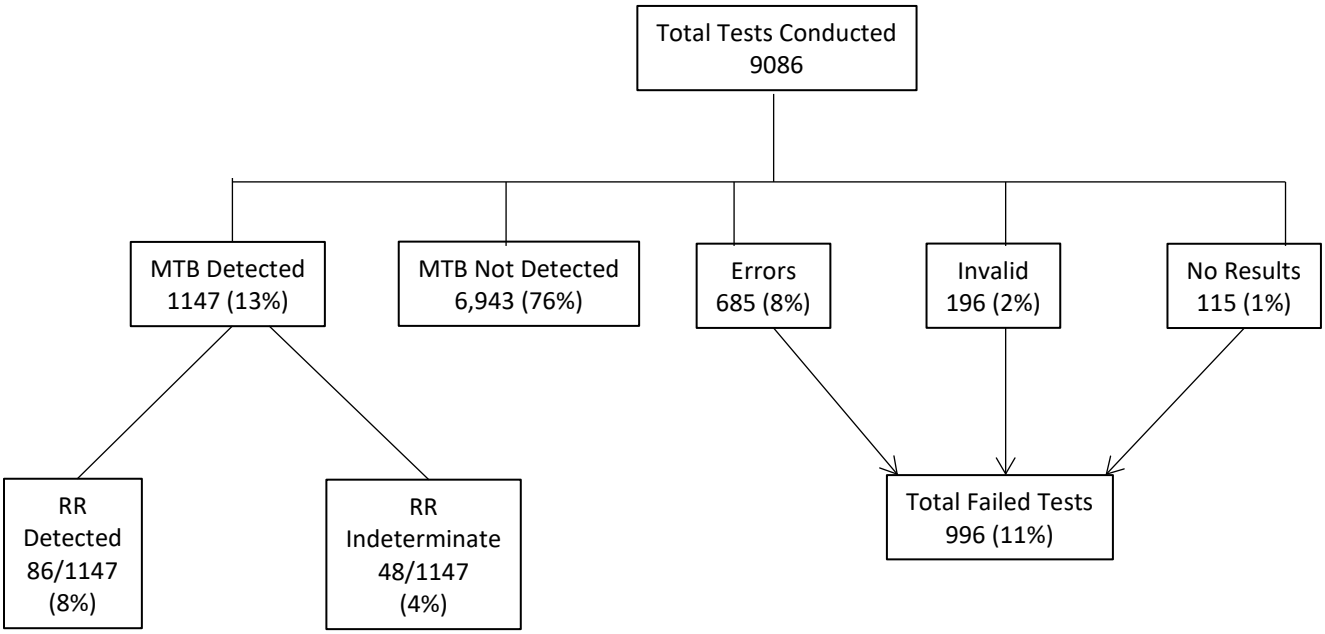
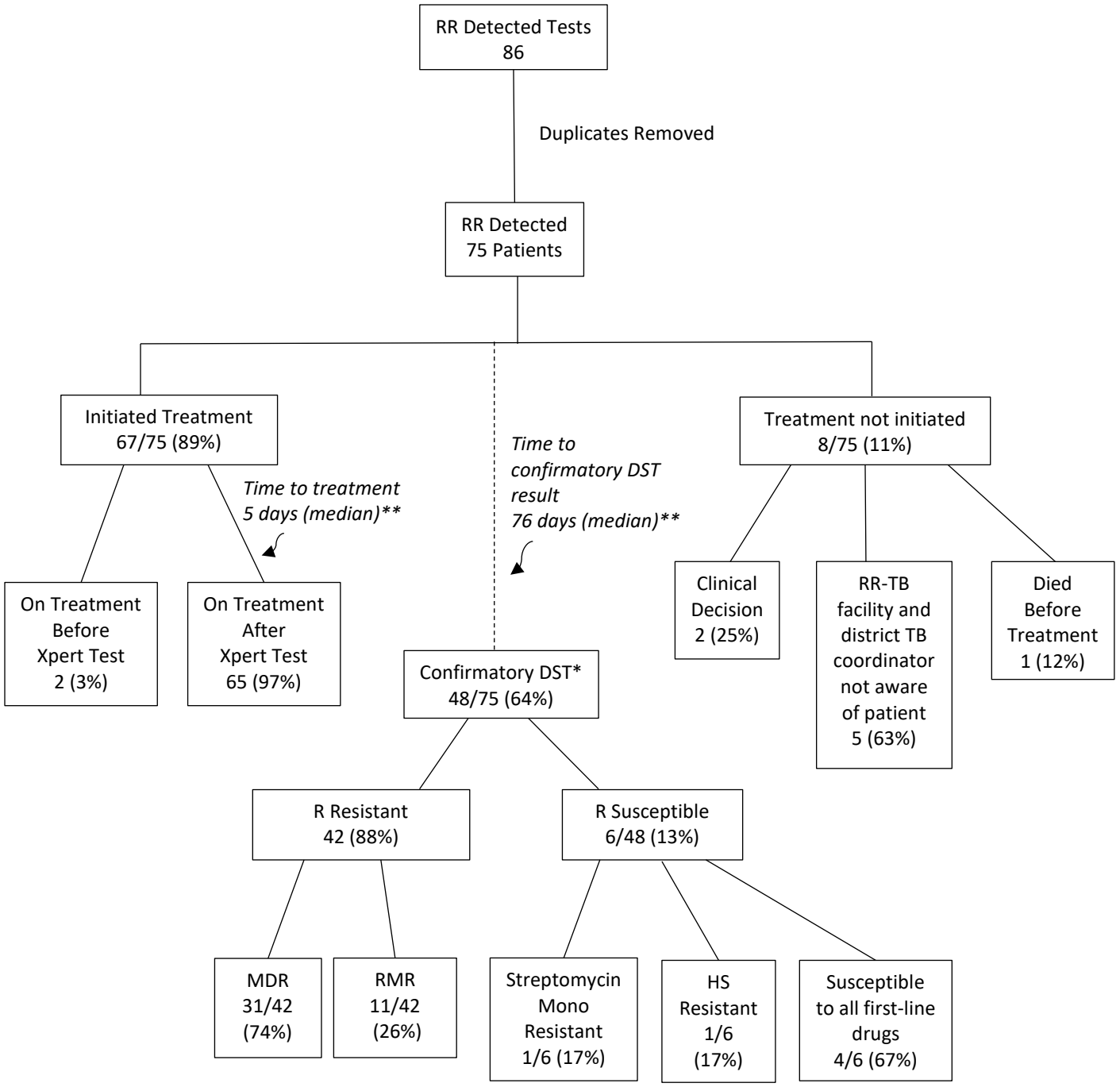


Figure 7.2. Xpert testing results, total tests, 2013-2014 (no deduplication conducted)

Management of patients with RR-TB result by Xpert

Figure 7.3 describes the management of patients with an RR detected result by Xpert. Out of the 86 tests with an RR detected result, this represented 75 patients after removing duplicates (same patient with multiple tests). Of the 75 patients, 8 (11%) did not initiate treatment. Reasons for not initiating treatment were solicited from the district TB coordinators and the RR-TB treatment centers. Based on feedback from the RR-TB treatment centers two did not initiate treatment based on clinical decision, and one died before treatment initiation; for five patients the RR-TB facility nor the district TB coordinator were unaware of the patients, indicating they had not been referred for treatment. No other information was available for these five patients. Of the two that did not initiate treatment based on clinical decision, one had follow-up phenotypic DST and was susceptible to all first-line drugs; the other had no follow-up DST and no additional information about the patient was available. Sixty-seven (89%) patients did initiate second-line treatment; two had initiated treatment before the Xpert result was available. For the 65 who initiated treatment after the Xpert result was available, the median days to treatment was five, and this will be further explored in section 2 of this chapter.

Confirmatory DST was available for only 48 (64%) of the patients with an RR-detected result by Xpert, a median of 76 days (IQR 43-105) after the Xpert result. Confirmatory DST revealed that 42/48 (88%) were confirmed to be RR, with 31/42 (74%) classified as MDR and 11/42 (26%) classified as RMR. Of the 48 patients with confirmatory DST results, 6 (13%) were R susceptible, of which 4 were susceptible to all first-line drugs. Of all confirmatory DST results, 10 were from LPA testing, and 38 were from MGIT testing.



* MGIT or LPA DST Results

** Time to treatment and DST result further described in Table 7.2

Figure 7.3. Management of patients with an RR result by Xpert, 2013-2014 (all data de-duplicated)

Management of patients with RR indeterminate result by Xpert

Figure 7.4 describes the management of patients with an RR indeterminate result. Out of 48 tests with RR indeterminate, this represented 47 patients after removing duplicates. Of all patients with an RR indeterminate result, 20 (43%) received a second Xpert test, and none of the tests revealed RR. Out of 47 patients, 18 (38%) had results at the NTRL, and none revealed RR.

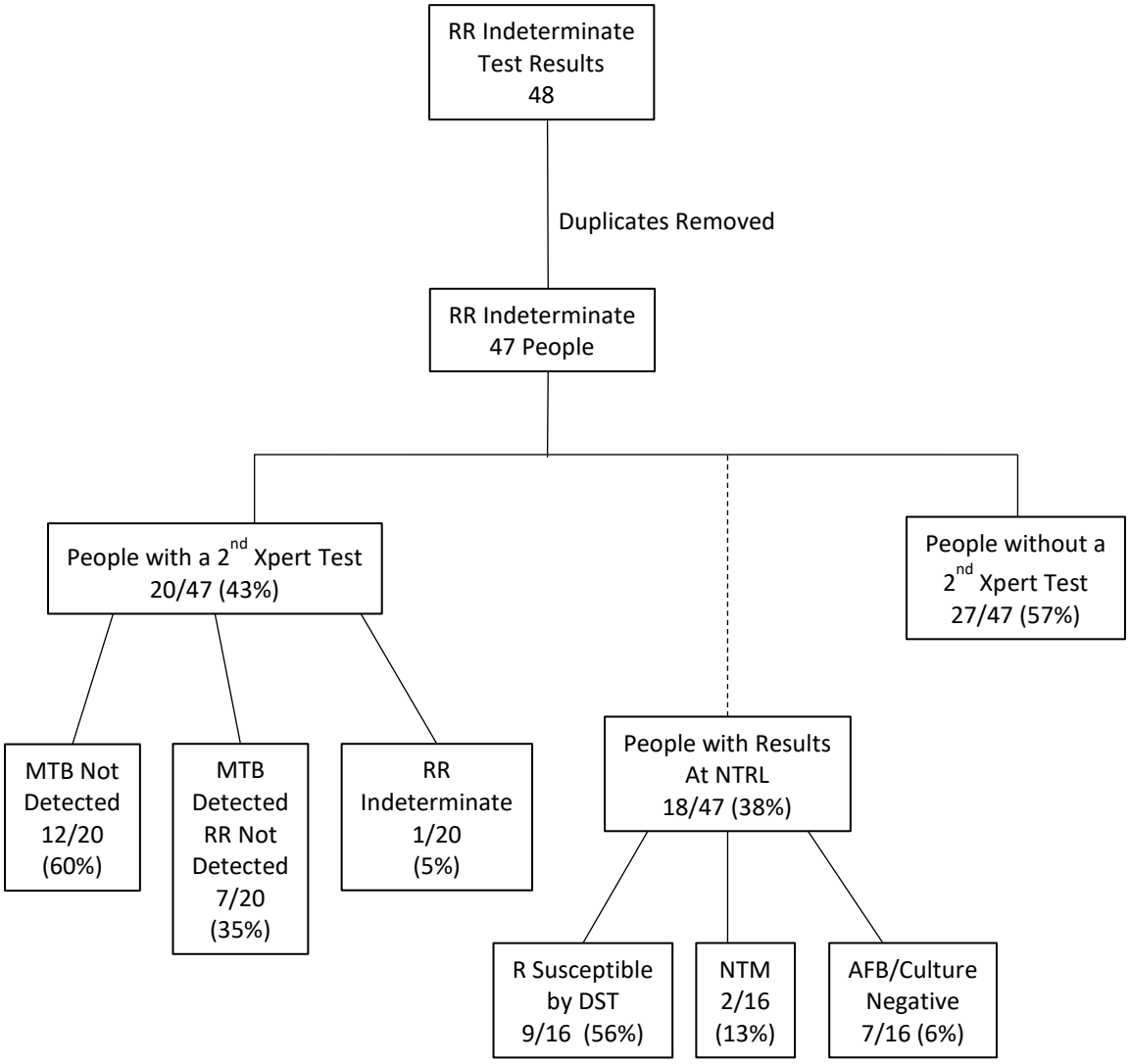


Figure 7.4. Management of patients with an RR indeterminate result by Xpert, 2013-2014 (all data de-duplicated)

7.6 Results (Section 2)

Time to treatment analysis

Of the 245 patients who initiated treatment for RR-TB in 2013-14, 128 (52%) had a diagnosis before initiating treatment; the remainder initiated treatment empirically and were excluded from this analysis (n=117). Sixty-five of the 128 (51%) patients started treatment based on results from Xpert (Xpert Cohort), and sixty-three (49%) patients started treatment based on results from the NTRL (NTRL cohort). Patient characteristics of the NTRL and Xpert Cohorts are displayed in Table 7.1.

Patient characteristics	NTRL Cohort N=63	Xpert Cohort N=65
	n (%)	n (%)
Age, median (IQR)	33 (25-39)	37 (32-42)
Female gender	39 (62%)	28 (43%)
HIV positive	40 (63%)	39 (60%)
Treatment outcomes		
Success	53 (84%)	52 (87%)
Lost to follow-up	2 (3%)	2 (3%)
Death	8 (13%)	6 (10%)

Table 7.1. Patient characteristics of the cohorts

Time from specimen collection to diagnosis

Data on specimen collection was only available for the NTRL cohort where time from specimen collection to diagnosis was a median of 77 days (IQR 63-91, range 25-216) Table 7.2. Date of specimen collection was not reported for the Xpert Cohort. A maximum estimate of 10 days is used for comparison based on anecdotal reports that Xpert testing is done within 10 days of specimen collection.

Time from diagnosis to treatment

The time from diagnosis to treatment was a median of 22 days (IQR 14-36) for the NTRL cohort compared to 5 days (IQR 2-10) for the Xpert cohort (Table 7.2), p-value <0.001 . Figure 7.5 below shows the proportion of patients who had initiated treatment by time (days) after diagnosis. By 15 days after diagnosis, 83% of the Xpert cohort initiated treatment, versus 33% of the NTRL cohort at this same time point. Additionally, the time to reach 95% of patients initiating treatment was 40 days for the Xpert cohort and 100 days for the NTRL cohort.

Time from specimen collection to treatment

The time from specimen collection to treatment was a median of 105 days (IQR 85-126) for the NTRL cohort (Table 7.2). This can be compared to approximately 15 days for the Xpert cohort, based on adding the maximum

time of 10 days for specimen collection to diagnosis to the 5 days from diagnosis to treatment initiation. Figure 7.6 displays the proportion of patients who had initiated treatment by time (days) after specimen collection. The data for the Xpert line is estimated by using the time from diagnosis to treatment and adding the maximum estimate of 10 days. It is evident that there is a greater difference in time to treatment from specimen collection; compared to time to treatment from diagnosis, with Xpert leading to much shorter time to treatment.

Time from diagnosis to confirmatory DST

The time from diagnosis to confirmatory DST is only relevant for the Xpert cohort. The median time from diagnosis to confirmatory DST for this cohort is 76 days (43-105). But confirmatory testing was only available for 64% of patients with RR detected by Xpert.

	NTRL	Xpert	Median Difference
	median (IQR)	median (IQR)	p-value
Time from specimen collection to diagnosis, days	77 (64-91)	NR*[¥]	
Time from diagnosis to treatment, days	22 (14-36)	5 (2-10)	<0.001
Time from specimen collection to treatment, days	105 (85-126)	NR*	
Time from diagnosis to confirmatory DST, days	NA[**]	76 (43-105)	

* NR = not reported; [¥] Estimated at 10 days; [¥]NA = not applicable

Table 7.2. Time to diagnosis and second-line treatment, 2013-2014

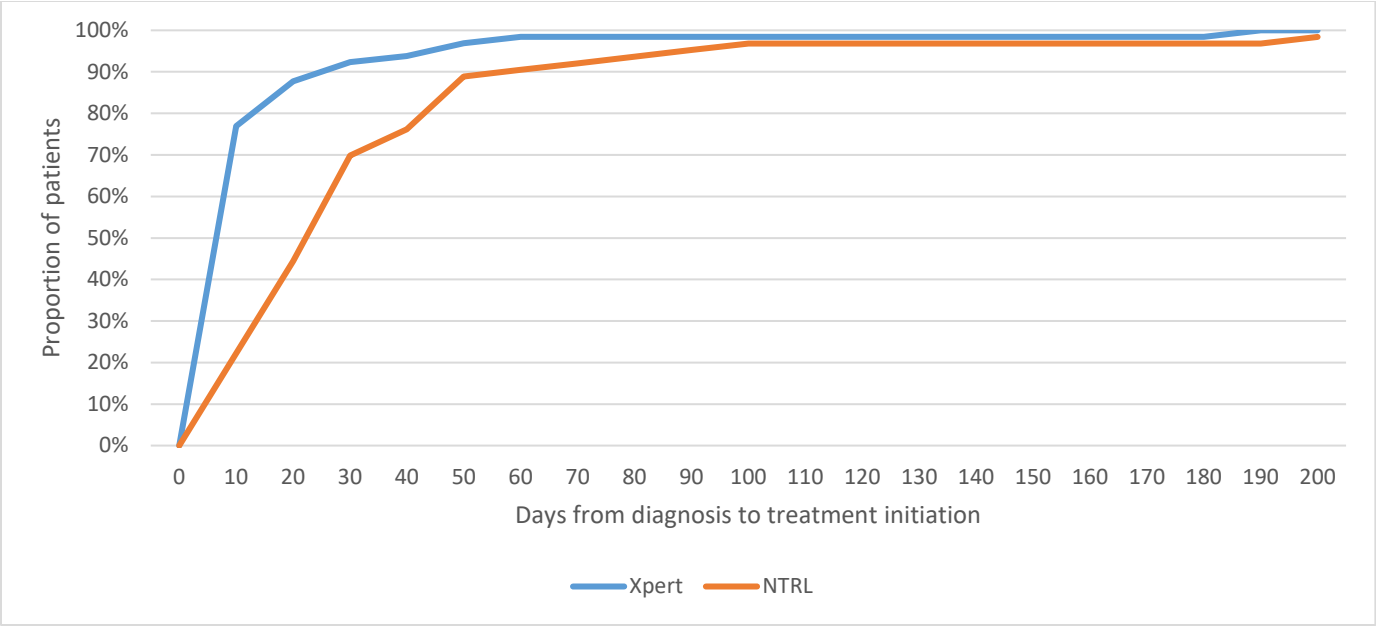


Figure 7.5. Cumulative proportion of patients initiating second-line treatment after RR-TB result available, Xpert and NTRL cohorts, 2013 – 2014 (Xpert cohort N = 65, NTRL cohort N= 63)

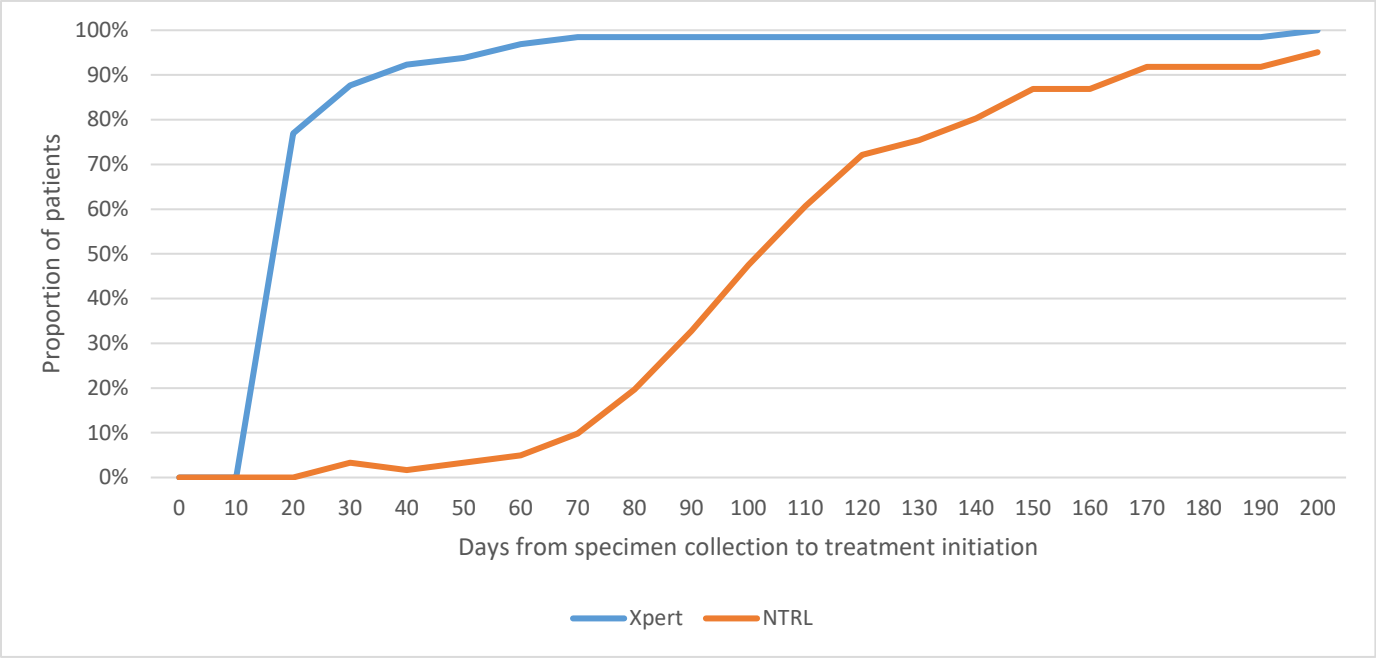


Figure 7.6. Cumulative proportion of patients initiating second-line treatment after RR-TB specimen collection, Xpert and NTRL cohorts, 2013 – 2014 (Xpert cohort N = 65, NTRL cohort N= 63)

7.7 Discussion

During this early phase of Xpert implementation in Botswana, many patients were linked to confirmatory diagnosis and treatment, but gaps were identified. Among patients diagnosed with RR-TB by Xpert, 89% initiated second-line treatment, and 64% received confirmatory DST. Among patients with an Xpert result of RR indeterminate, only 43% had a second Xpert test, and 38% had samples submitted to the NTRL for culture testing. The use of Xpert in decentralized locations did significantly shorten time to treatment initiation for patients diagnosed with RR by Xpert, compared to those diagnosed at the NTRL.

Despite Xpert implementation, many studies are continuing to report a treatment gap (defined as patients with RR-TB that are not making it onto treatment), and have suggested that Xpert alone is not enough to significantly improve this treatment gap[42, 211]. A nationwide analysis in South Africa reported that while Xpert reduced the delay to treatment for RR-TB patients, it did not reduce the treatment gap[42]. A study in Mozambique reported that of all RR-TB patients diagnosed by Xpert in 2012-2015, 53% were initiated on treatment[212]. In Zimbabwe, a study reported that 56% of RR-TB patients diagnosed by Xpert in 2014 initiated treatment[213]. Mnyambwa et al reported that only 32% of RR-TB patients diagnosed by Xpert in 2013-2016 were initiated on treatment[214]. This study further explored this treatment gap through qualitative interviews and identified several potential factors negatively influencing linkage to treatment, including deficiencies in the health system (lack of adherence to guidelines, limited training, poor communication between lab and health facilities) and patient level factors (superstition, stigma, limited knowledge on transmission)[214]. The 89% of RR-TB patients initiating treatment based on Xpert results in Botswana reported in this study is higher than many other settings.

Research has also highlighted low proportions of patients with RR-TB diagnosed by Xpert receiving confirmatory DST (phenotypic or LPA). The current research reported confirmatory DST for 64% of RR-TB patients diagnosed by Xpert in Botswana. A study in South Africa reported that 50% of RR-TB patients diagnosed by Xpert received confirmatory DST[38]. In Mozambique, only 29% of RR-TB patients had confirmatory DST[212]. Another study from South Africa reported that among 1,332 patients diagnosed with RR-TB in South Africa, only 45% had second-line DST; among those with second-line DST, 40% initiated a potentially suboptimal regimen[215] Confirmatory DST after Xpert diagnosis is important to confirm, not only rifampicin resistance, but also to confirm resistance to other drugs to guide appropriate treatment. The World Health Organization (WHO) recommends that patients at high risk of MDR-TB with a diagnosis of RR-TB by Xpert should immediately have follow-up DST for at least isoniazid, fluoroquinolones and second-line injectables[28]. For patients at low risk of MDR-TB with a diagnosis of RR-TB by Xpert, the WHO recommends a second Xpert test; in the event the second test is also positive for RR, the WHO recommends follow-up DST to confirm rifampicin resistance as well as susceptibility testing for isoniazid, fluoroquinolones and second-line injectables[28].

Discordance with rifampicin resistance between Xpert results and confirmatory DST (phenotypic or LPA) results has been reported by other research[38, 216].The current research cannot definitively draw conclusions about concordance since testing with Xpert and with confirmatory DST were not from the same sample, and time between specimens may be up to a few weeks. However, other studies have reported on concordance using similar methods, and can be used as a comparison. In Botswana, this current research reported that 88% of patients with RR-TB by Xpert were confirmed as RR-TB by DST conducted at the NTRL; 74% of these were MDR-TB, while 26% were RMR-TB. Dlamini-Mvelase, et al reported that, of patients with RR-TB by Xpert in South Africa, 91% were RR-TB by confirmatory DST; 85% of these were MDR-TB and 15% were RMR-TB[38]. In Zambia, confirmatory DST revealed confirmed rifampicin resistance for 81% of patients with RR-TB by Xpert. Reasons for discordant results have been addressed by other research and include factors such as mixed infections[216] or a silent mutation on the *rpoB* gene[217-219]. This again highlights the need for confirmatory DST. This current research shows that confirmatory DST revealed RMR-TB among 26% of RR-TB patients in Botswana. These are patients who would have been denied the use of isoniazid in their treatment regimen, if they had not received confirmatory DST for rifampicin and other drugs and were placed on a standardized RR-TB regimen.

As highlighted in the systematic review (Chapter 6), molecular testing methods, such as Xpert, result in more rapid laboratory turnaround times[64, 203-205]. Although the data to calculate time from specimen collection to diagnosis was missing for the Xpert cohort, an estimate can be made that the maximum number of days from specimen collection to diagnosis would be 10 days. Based on local practice in Botswana, all specimens received at a peripheral laboratory must be tested within 10 days or discarded. Comparing this estimate of time from specimen collection to diagnosis of 10 days for the Xpert cohort to the calculated median of 77 days (IQR 64-91) for the NTRL cohort (an estimated median difference of 67 days), it is clear that Xpert has substantially reduced laboratory turnaround time. It should be noted that using the imputed value of 10 days for the Xpert cohort in comparison to recorded times for the NTRL cohort may overestimate the difference; while it would be more convincing to have had recorded values for the Xpert cohort, this data was unavailable and is a acknowledged as a limitation of this result. In addition to faster laboratory turnaround time, time to second-line treatment from diagnosis was faster among the Xpert cohort compared to the NTRL cohort in this current research.

It is also important to note that the observed differences in this analysis were based only on the DST method. However there may have been other factors contributing to the observed differences. One factor that may have contributed to the observed difference is that there was a large research study (XPRES) being conducted during the time of this analysis, using Xpert. Therefore, the additional attention and research staff focused on Xpert results may have influenced these results to be available more quickly than in a purely programmatic setting. However, we expect this affect is small as only 6/65 (9%) of the RR-TB patients included in this analysis were also participants in the XPRES study.

Additional bias may have been introduced in this study by excluding patients who were diagnosed but never initiated treatment. Unfortunately, this data was unavailable for the NTRL cohort and therefore unable to include for comparison. This is noted as a limitation of these findings, and the potential impact is that this analysis may have underestimated time to treatment; time to treatment would likely be longer if the excluded patients were added to the analysis and remained 'at risk' for the event of interest (treatment start).

The benefits of Xpert have been well documented. Shortened time to treatment initiation is reported by numerous studies and has been addressed in this current research. Studies also report Xpert increasing case detection[43, 44] and leading to less empiric treatment[45]. Boehme, et al discussed the benefits of providing access to early and accurate diagnosis, leading to reduced diagnostic delay, dropout and mistreatment[29]. Despite these benefits, challenges remain in ensuring all patients are linked to treatment and that they access confirmatory and second-line DST.

Overall, this research highlighted that, during early implementation of Xpert in Botswana, a high proportion of patients were linked to treatment. Additionally Xpert led to faster time to treatment from diagnosis in this research. The successes seen with Xpert implementation in Botswana appear to be a result of faster time to diagnosis with genotypic testing methods, as well as decentralization of lab services away from the NTRL and closer to the point of care for patients seeking treatment.

Chapter 8: When policy and practice do not align: a qualitative study of patient and provider experiences with RR-TB diagnosis and treatment in Botswana.

8.1 Chapter overview

This chapter describes the analysis of qualitative data collected by interviewing RR-TB patients, health care providers, and national level government staff. The background and policies have been fully described in preceding chapters; therefore, the background will describe only any additional context as well as specific changes or policies, which are different for the time frame of this analysis (2017), compared to previous analyses.

8.2 Hypothesis and objective

Hypothesis 1: There are gaps in the diagnosis and treatment process in Botswana that can be identified by patients, providers and government staff.

Objective:

To identify and describe common themes through analysis of individual interviews with patients, health care providers, and national level government staff.

8.3 Context and update

Global recommendations indicate that the current focus for RR-TB management should be on improving patient outcomes and decreasing transmission through key interventions including early diagnosis, effective therapy and active contact tracing. Furthermore, as part of the End TB Strategy, the WHO includes patient centered-care as a core principle, focusing on ensuring universal access to TB services with increased attention to vulnerable and hard to reach populations. Therefore, the interviews conducted for this analysis specifically aimed to get first-hand in depth input from patients and providers regarding their experiences with RR-TB diagnosis, treatment and overall management of the RR-TB program. Furthermore, the interviews aimed to gain some personal insight to help understand findings from the preceding analyses.

In order to provide context into the setting of Botswana and the expected capacity of the RR-TB program, the following describes key economic indicators. Botswana's economy is classified as upper-middle income, in contrast to other neighboring, sub-Saharan African countries, such as Zambia (lower-middle income) and Zimbabwe (low income). In 2017, Botswana's gross domestic product (GDP) was $17.41 billion USD and GDP per

capita was $7,595.60 USD[220]. Current health expenditure (CHE) in Botswana is 6% of the GDP. South Africa, another neighboring country, is also classified as upper-middle income and CHE is 8.2% of the GDP. CHE in all of Africa is 6.2% of GDP[8].

By the time these interviews took place, the TB diagnostic algorithm including Xpert (Appendix A) had been finalized and distributed, along with recommendations for universal testing by Xpert for all patients with signs and symptoms of TB. As of 2015, there were 34 Xpert machines owned and operated by the national TB program, placed in every health district of Botswana, with more than one in high volume districts; no additional Xpert machines have been added since 2015. A sixth RR-TB treatment facility was added in 2015 (in Mahalapye) to further decentralize care. By 2017, Botswana had begun to have limited supplies of the new TB drug, bedaquiline, through a donation program but only for patients who were faring very poorly on the standardized regimen, which still included amikacin at this time.

8.4 Methods

Setting

The study took place in two (out of six total) government RR-TB treatment centers in Botswana, one in the capital city of Gaborone, an urban setting and the other in the rural town of Ghanzi, 670 km from Gaborone. The treatment centers provide both inpatient and outpatient services for patients registered for RR-TB treatment.

Study investigators

Several personnel were involved in the analysis described in this chapter. Rosanna Boyd (RB) is the author of this thesis. RB was responsible for the development of the data collection tool (questionnaire), setting up and leading the interviews, overseeing the transcription, and leading the data analysis. Jennifer Furin (JF) is a medical anthropologist, experienced in qualitative research and analysis. JF provided guidance on development of the analysis plan and served as a second data analyst for the study. Helen Cox (HC) provided guidance on the development of the research plan and data collection tool as well as in the interpretation of the findings. Lucas Payton (LP) served as a second interviewer in all interviews. Unami Mathebula (UM) is an experienced TB study nurse in Botswana, is fluent in Setswana, and served as an interpreter for the study.

Participants

Participants in this study included 8 patients (4 hospitalized and 4 ambulatory), 3 direct health care providers and 2 individuals involved in managing the RR-TB programme at the national level as part of the National TB Program. Patients were selected based on convenience; ie. they were physically present at the health facility and willing to participate on the days that the interviewers went to the facility. Patients were classified as

ambulatory or hospitalized based on current status at the time of interview. Providers included direct health care providers at treatment facilities as well as providers/consultants from the national level; all were classified as health care providers. Results are presented in terms of patients and providers.

Data collection

Data were collected between May and September 2017. Participants were informed by the interviewers of the purpose of the study and were asked to consent to the interview and to the use of recording devices during the interview. Written informed consent was obtained from all participants prior to the interview process. In-depth, standardized interviews were conducted by two researchers. The same two interviewers (RB and LP) were present at each interview. In Gaborone, a study coordinator (UM) provided translation into Setswana where required; in Ghanzi, the RR-TB nurse performed the translation into Setswana or Sesarwa as needed. Five of the eight interviews with patients required translation; all other interviews were conducted in English. Interviews were recorded, and all results were translated, transcribed, and saved in Word documents. For one interview, the patient did not consent to being recorded; this interview was conducted in English and, in this case, notes were taken and fully written up as a transcript immediately following the interview.

Definitions

Interviews included questions to describe experiences with diagnostic delays and delays with linkage to care. Diagnostic delays refers to any delay from the time a patient is first ill to receiving a diagnosis of RR-TB, including patient related delays in seeking care, as well as health system and laboratory related delays of reaching a diagnosis. Linkage to care delays refers to the time between a diagnosis and a patient being referred for treatment initiation.

Data analysis

To analyze the data in the study a thematic analysis was performed, as described in Vaismoradi, et al[221]. Two researchers (RB and JF) independently performed the analysis; results were compared, combined and any discrepancies were resolved via discussion and re-review. Interview transcripts were read through to identify patient and provider experiences with RR-TB treatment, themes were uncovered and transcribed on to note cards which included specific quotes, participant ID numbers and thematic codes. Additional review of transcripts was conducted to refine the themes and to identify and code subthemes. Using ArcGIS, a map was created to describe where patients lived in relation to treatment centers, both for ambulatory and hospitalized patients. The distance between village of residence and treatment centers was calculated using Google maps.

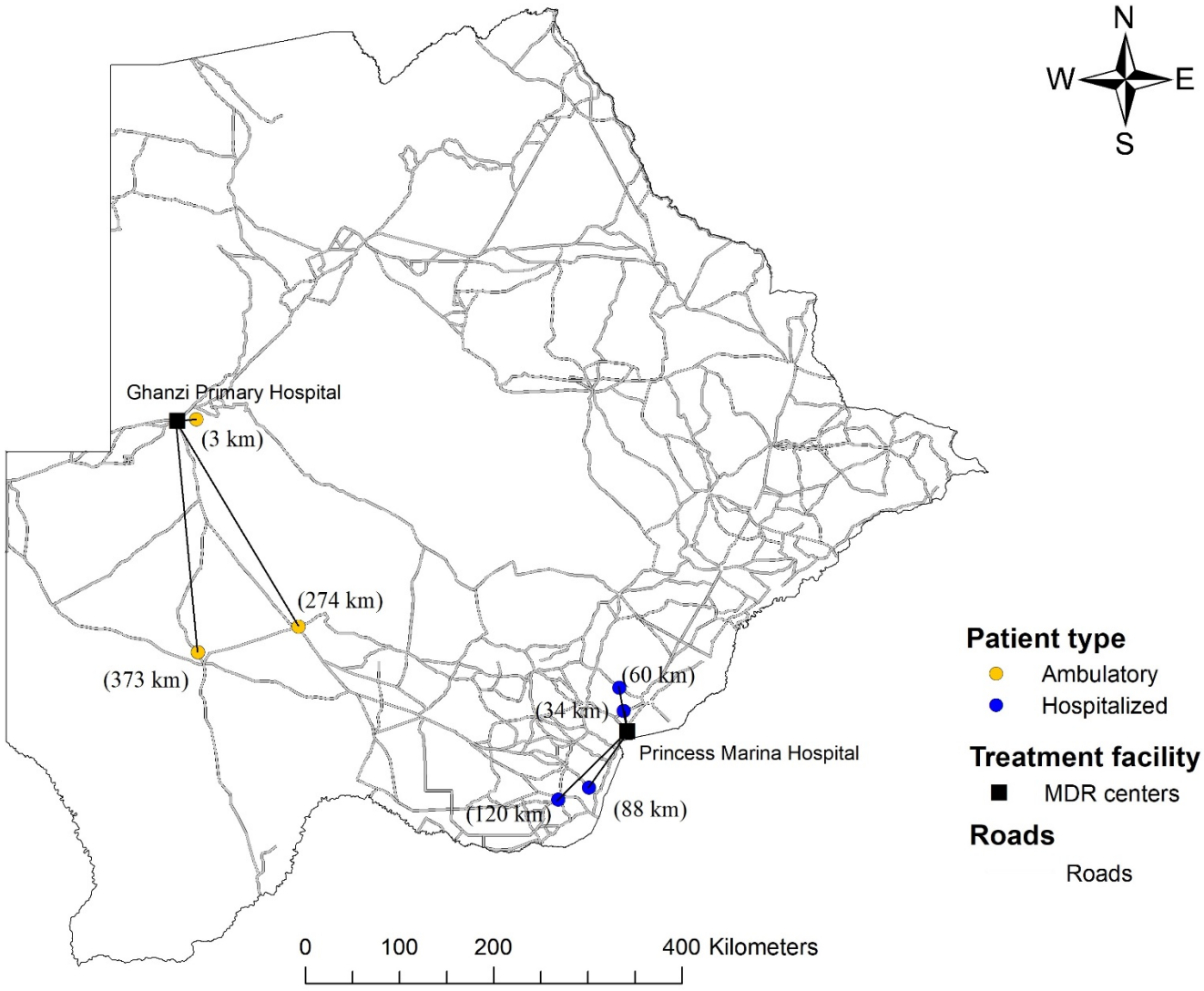
8.5 Results

Patient characteristics

Table 8.1 describes the characteristics of the interviewed patients. Of the eight patients, four were male and four were female, and ages ranged from 31 to 50 (median 38). One patient was married; three others reported cohabitating with a partner. The median number of people per household was 6.5 (range 2-13). Highest education levels reported for patients were primary school (1), trade school (1), secondary school (5) and college (1). All patients were of Motswana nationality. The distance to treatment facility from village of residence ranged from three to 373 kilometers (median 104). Figure 8.1 indicates the location of the home village for each patient in relation to the treatment facility. Providers included one doctor, one nurse, one ward supervisor and, at the national level, a laboratory manager from the National TB Reference Laboratory (NTRL) and the lead RR-TB consultant/physician.

Gender	Age	Marital Status	# in household	Education level	Occupation	Nationality	Patient status	MDR facility	Distance to MDR facility (km)
Male	33	cohabitating	5	secondary	unemployed	Motswana	outpatient	Ghanzi	3
Male	37	single, never married	8	other, brigade trade school/junior secondary	unemployed	Motswana	outpatient	Ghanzi	373
Male	50	married	2	Advanced /college	teacher	Motswana	outpatient	Ghanzi	373
Female	45	single, never married	8	secondary	unemployed	Motswana	outpatient	Ghanzi	274
Male	45	cohabitating	5	primary	driver	Motswana	inpatient	Gaborone	33.7
Female	33	cohabitating	13	secondary	security guard	Motswana	inpatient	Gaborone	88.2
Female	39	single, never married	13	secondary	unemployed	Motswana	inpatient	Gaborone	59.5
Female	31	single, never married	5	secondary	unemployed	Motswana	inpatient	Gaborone	120

Table 8.1. Characteristics of interviewed patients



* Two patients receiving treatment in Ghanzi live in the same village, represented by one yellow circle, 373 kilometers from Ghanzi

Figure 8.1. Map of patient home villages in relation to RR-TB treatment facilities

Thematic areas

Six main themes relating to RR-TB treatment emerged from the data: 1) stigma and discrimination, 2) disclosure and contact tracing, 3) diagnostic delays, 4) overall experience with care, 5) barriers to care, and 6) RR-TB knowledge and education.

Stigma and discrimination

Stigma and discrimination from friends, family, employers and health care workers

Among patients, there was concern about discrimination. While some reported that they were given support because of their place in the family, most patients (6) reported having been discriminated against, with some people (family, friends and health care providers) even refusing to greet or speak with them. According to many patients, this discrimination appeared to be based on fear:

> *"They call it the strong TB in Setswana, they think when you have got MDR it's a death sentence." "Some of them (friends and family) wouldn't even greet me when they came here to visit, they will just stand there but I understood it's only that they don't have information"* 33 YEAR OLD MALE (AMBULATORY PATIENT)

> *"When I converted I transferred to the clinic next to my house, but the nurses themselves were afraid and they will even say I must wait outside."* 33 YEAR OLD MALE (AMBULATORY PATIENT)

> *"When you have not started treatment people are afraid of coming closer to you. They stay away from you and they deprive you of food"* 37 YEAR OLD MALE (AMBULATORY PATIENT)

Some patients did also report fear of job loss because of their illness and having to be away from work.

> *"that is one issue that is still troubling me big time. At work they were given a letter and they accepted it but now they have stopped giving me the salary. I don't know (if they will take me back) but all I know is that when I leave this place I am going back to them"* 45 YEAR OLD MALE (HOSPITALIZED PATIENT)

Providers were not asked specifically about stigma and discrimination in the standardized interview, but one provider did mention this, expressing the perception that patients are affected by discrimination/stigma and that this affects their health seeking behavior:

> *"Yes, for people the stigma of HIV still stands. It's still there. People are not aware of the signs and symptoms of TB very well. In such a way, they think that if you get sick, you are infected with HIV. Now for them to go consult a medical officer they'll think that they will be exposed. So people they shun going*

to a health center for screening for TB because they think their sickness is due to HIV" HEALTH CARE PROVIDER (GABORONE)

Isolation as a form of discrimination

Some patients expressed that they feel they are 'made' to stay in the hospital to receive treatment and see this as a form of discrimination. The patients who were currently hospitalized reported being in the hospital for two to three months at the time of interview. All of the ambulatory patients reported being hospitalized in the past for three to four months, except for the one patient with extrapulmonary RR-TB who was never hospitalized. One currently hospitalized patient had been previously hospitalized the year before and was now readmitted for what appeared to be failure of the treatment:

"they told me that another tablet is not working, and at that time I was receiving injections in my treatment and that's when they brought me back here for readmission." 33 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

Patients' perceptions of why they were hospitalized were to avoid infecting others with TB, especially children , which perhaps reflects what patients are told about the need to be hospitalized. The following quotes from patients reflect their dissatisfaction with being hospitalized, as well as their perception about the reasons for isolation:

"The discrimination I see is the isolation that is being done, by bringing us here and taking us away from the community…… I was just told to come here, as this is the place where people are kept .I was not given any option to choose any place, and when I got here I was asked who I stay with at home, and they told me that the problem is small kids, since small kids are vulnerable to infections…. it is an inconvenience but the problem is that I am sick, and there is nothing I can do about it."…. "I feel it's ok because it helps me not to spread the disease to my children"…. "here, it will be all MDR patients and there will be no one to spread the disease to." 45 YEAR OLD MALE (HOSPITALIZED PATIENT)

"When it's MDR they don't allow you to be isolated from home at all especially if there is no spare room but even if there is a spare room at home they don't allow because at home kids can't be controlled; they will always come to you" 39 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

In order to address the idea of hospitalization as a perceived discrimination, we further explored what providers understand in relation to when and why patients are hospitalized. Providers expressed that the main reason for isolation is to avoid infecting others. One provider explained in detail the national policy describing the criteria that is to be used to determine whether or not a patient should be hospitalized for treatment initiation and their perception about how this policy is being implemented:

"So, we counsel you and then find out the infection control at home. One thing we want to know is do you have under 5s at home, where do you sleep in the house, so if they live in one room like this then automatically we would admit. But we give an option. For example, if they live in Gaborone, we say, what about your home village? Do you have a compound where you can go? And then in those situations where they have one room but they say they can go to their home village, then we make a decision and say ok you can go there and isolate yourself. And sometimes after counseling the patients even if they do have their own room, they opt to be admitted. Usually it's for the first 2 months. But even those patients maybe who currently live in one room and they don't want to go to their home village we would admit them. But throughout treatment if they get tired of the hospital and want to go their home village, then we make a decision and send them. XDR-TB – we admit. There is no criteria. So it's all based on the discussion with the patient. So those patients if there is under 5s and they live in a one room we then let them know the reason why we have to admit. And pre-warn them that it is going to take a long time. Because marina [MDR ward] – we actually do say, maybe you should go see our site. It's not like princess marina [general hospital wards] they get their own rooms at our site (unlike general hospital wards). So that's why. And sometimes the patient may not want to be admitted but the family member wants them to be because they don't want them to be at home so we often admit them because this family member will convince them. They say ' you need to be admitted' and then they go ahead. But it's a collective decision made" HEALTH CARE PROVIDER (GABORONE)

However, there were conflicting reports about how this policy was being implemented. Three of the providers indicated that all or most patients are hospitalized until they 'convert' (become culture negative). One reported that most patients are not hospitalized.

The reports from the providers that describe the purpose of hospitalization as a way to decrease risk of transmission matches up with the perceptions of the patients about why they are hospitalized. There is a widespread notion that patients with RR-TB need to be isolated when they initiate treatment and that this will protect the community. There appears to be little understanding that transmission will most likely have already occurred before the patient was diagnosed and treatment initiated. While the perception that hospitalization for treatment initiation will protect the community is inaccurate, it does reflect the rationale for hospitalization given in the national policy.

Of the eight patients interviewed, all except the one patient with extrapulmonary RR-TB were hospitalized for treatment initiation.

Gender based discrimination

All patients reported that they do not see gender-based discrimination in seeking care for TB, including the four women who were interviewed. Most patients reported that partners should allow one another to seek care and to support one another in seeking care.

> *"And yes they have to inform their partner and I also have to accept because when one is not well, they are not well. Yes it's important, you just have to tell your partner that you are going to the hospital."* 37 YEAR OLD MALE (AMBULATORY PATIENT)

> *"Why should you ask for a permission? As for me I think if somebody feels that he is not feeling well with the disease it's his/her own choice to seek medical service, it's just my belief"* 50 YEAR OLD MALE (AMBULATORY PATIENT)

Disclosure and contact tracing

Although patients did report discrimination and reported being worried about telling others of their RR-TB diagnosis, all patients did report disclosing to at least some family members and friends; in some cases this was possibly connected to screening of close contacts. Patients did report that some of their close contacts were screened, often limited to household contacts. However, some patients reported that they were concerned that children over five were not being screened:

> *"isn't it 9 years and downwards were not checked since they said 5 years upwards have to cough out sputum but it's difficult for a 6 year old child to cough out sputum…. That is what is worrying me is that why did they not give the test to the others who are 9 years downwards since it could help them."* 39 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

Providers' perceptions of screening practices varied. While some report that they routinely screen all close contacts, others say they do not believe that screening of contacts is done consistently. Interviews did not address the reasons why this is not being done consistently.

> *"On paper yes. It's partially done. The only ones that are – that you find the TB focal persons take consideration – is when you see more than one family member showing up with MDR-TB. There was an active screening group for XDR-TB, the TB program would do that themselves, but now it's not being done. Contacts won't be screened. Or they may do the first screening but not follow-ups. Unless it's the family themselves that go and demand to be screened."* 33 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

Diagnostic and linkage delays

Patient perceptions of diagnostic delay

Patients expressed frustration with diagnostic delays. In particular, patients noted challenges when first seeking care at the primary care clinic and district levels. Some patients reported having to request TB tests for themselves or seek care elsewhere because their illness was not being diagnosed. The following quotes comes from patients who felt turned away by the local clinics:

> *"I sought treatment at the clinic for about one month because I had a cough, night sweats and a headache. The clinic said you're coming too much. And I said I'm not well"* 31 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

> *"I started not feeling well for about 3 weeks, it was so strong and I kept coming to the clinic and they asked me to give out sputum, I told them I am not coughing. But I am feeling pains and the issue is I wanted them to take me for an x-ray so that at least I can clear my conscious because I had taken care of people who had TB. I had taken care of people with TB, and even my mother was diagnosed through X-ray and after her death the hospital said we must be screened for TB at home and the clinic refused saying my mother was diagnosed through X-ray so she was not coughing and that TB is not transmittable."* 39 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

Diagnostic delays were often long, according to patients. The one patient with extra-pulmonay RR-TB reported being sick and seeking care for seven months at the district hospital. After going to a private hospital in the capital city (at his own expense), he received the correct diagnosis and began RR-TB treatment. Another patient who reported his girlfriend had RR-TB, expressed concern about how long it took to diagnose him when he sought care:

> *"I was sick for 5-6 months. They could not catch it; they did the screening, I brought the sputum but it took long. I was concerned because I knew that my girlfriend (had RR-TB) we were staying together in one house."* 33 YEAR OLD MALE (AMBULATORY PATIENT)

Several patients reported taking one or more courses of first-line treatment before being diagnosed and starting second-line treatment. This was expressed as a source of frustration, particularly by one patient who was on first-line treatment for more than one year before being diagnosed with RR-TB:

> *"I delayed because of mistreatments. I will start treatment and be told I am not healed and be started on another lap of treatment." "from 2014 to September 2016. I started the first lap of 6 months and I*

was told I am not cured, then I was started again on another 6 months lap which was extended to 9 months and that's when I was told I had MDR" 33 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

Provider perceptions of diagnostic delay

Providers reported that patients often delay seeking treatment thinking it's another illness such as flu. Most patients reported being ill for about one month before seeking treatment. If this is the case, the diagnostic delays are much greater than the health care seeking delays from the patients.

Providers also expressed concern about diagnostic delays. Their perception is that delays (after the patient presents for care) are caused by various factors, including laboratory closures, inconsistent availability of reagents, lengthy laboratory processes for culture results, and having only one culture facility for the entire country. Although the updated TB diagnostic algorithm recommending universal DST by Xpert had reportedly been implemented in 2016, providers confirmed that many patients are treated with first-line medication before testing for drug resistance. Some providers expressed frustration that health care workers at the primary care clinics do not follow the guidelines and ensure that at least high risk patients (such as previously treated patients) receive culture and DST at treatment initiation. The providers do acknowledge that health care workers likely need more training on this. The quote below describes that for a sample to be sent for culture, a health care worker must specifically request the test on the lab request form

"Well the health care worker would have to request for culture. If they don't the district lab won't transfer them. If culture has been requested, they (the district lab) just package and ship them through the lab network to NTRL."

(Interviewer: If they don't request culture does the district lab do smear testing?)

"Yes and discard the specimen. So it's up to the health care worker seeing the patient" HEALTH CARE PROVIDER (GHANZI)

There was concern expressed by providers that the diagnostic delays / inadequacies may contribute to mortality.

"the lab has not been fully functioning so maybe we are missing cases and they are dying with MDR-TB" HEALTH CARE PROVIDER (GABORONE)

Impact of Xpert on diagnosis

All providers reported that the introduction of Gene Xpert in district labs throughout the country has helped with diagnostic delay; they feel more comfortable having early results and starting treatment for a patient with

confirmed RR, rather than starting empiric treatment while waiting for DST results. The providers expressed that starting people on RR-TB treatment empirically used to occur much more before the introduction of Xpert. Providers also reported that they believe they are diagnosing cases of RR-TB that would have been missed in the past.

On the other hand, providers reported many challenges with Xpert that do contribute to diagnostic delay, including frequent stock-outs of cartridges, modules not working and not being repaired, and machines not being calibrated. Furthermore, providers report that after the introduction of Xpert, providers throughout the country no longer routinely send samples for confirmatory testing at the NTRL; only the RR-TB treatment centers routinely send samples to the NTRL. The laboratory manager describes his perception of this issue:

> *"Gene Xpert has taken our job. Our sample receiving has drastically reduced by more than 75%. The samples that we were receiving in a month are the ones that we are receiving in a year. So, we don't know what's happening but I think it's because of Gene Xpert people are no longer forwarding samples for culture. Though the algorithm says despite the Xpert result they should send the sample for TB culture. I think it's not well understood*" HEALTH CARE PROVIDER (GABORONE)

Another provider confirms that samples are not being routinely sent to the NTRL for confirmatory testing:

> *"The ones I have a good idea about are those ones sent from the MDR-TB sites, those patients are on treatment. Those they will send each time they have an encounter (with the patient). But how frequently from the other sites/facilities, I don't know. It used to be better but it's dropped. I think because of Xpert. I think there is just a lack of knowledge. People are just no longer sending. The lab is actually complaining because they are getting less samples. It's a matter of us just training the health care workers."* HEALTH CARE PROVIDER (GABORONE)

<u>Linkage to care</u>

Overall delays to linkage to care were not reported. Both patients and providers reported that once a RR-TB diagnostic result is received, treatment is initiated very quickly (same day or within a few days). Providers felt that, in this instance, health care workers at the primary care level are helpful:

> *"And I think what actually helps is that health care workers don't necessarily want to develop MDR-TB so if there is a case, they want to send (the patient for treatment) as soon as possible"* HEALTH CARE PROVIDER (GABORONE)

Overall experience with care

Care in the hospital versus the outpatient clinic setting

In general, patients expressed satisfaction with their providers, the waiting times and the clinic hours of operation (although participant 33 YEAR OLD MALE (AMBULATORY PATIENT) was an exception). Although some patients had expressed that being hospitalized was a form of discrimination and that they didn't enjoy being in the hospital (a perception confirmed by interviewed providers), most patients did express a belief that the care received while in the hospital was better than care received from a local clinic. Patients explained that they believed the hospital staff were more available and the quality of care was better.

> *"Here [in the hospital] it's much better because the nurses are always available, and they also monitor your health and any side effects that comes with the medication"* 33 YEAR OLD FEMALE (HOSPITALIZED PATIENT)
> *In the hospital "it will be all MDR patients and there will be no one to spread the disease to. And also when we feel pain we are attended to immediately"* 45 YEAR OLD MALE (HOSPITALIZED PATIENT)

> *"I recognize the nurses of the hospital much more better than the clinic ones. All the assistance I needed I got it at the right time and they are also patient."* 45 YEAR OLD FEMALE (AMBULATORY PATIENT)

Drug stock-outs

All patients noted major problems with drug stock-outs and interruptions in treatment. One patient dealt with this by procuring his own medications. Patients expressed stress and frustration about this issue:

> *"The day I arrived here I was started on treatment and took it for 7 days and then the medications got finished, and I stayed for the whole month of April with no medication"* 39 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

> *"Here it is a stressful experience, the whole of April we did not have medications. We did not have the drip and the injection. There was nothing we were taking at all because…. You can't take the pills without the drip since they go hand in hand. The meds only came last week and there are some hearsay that by Sunday it might finish and that's a problem"* 33 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

Some patients indicated that they had been told the stock-out were caused by lack of funding and lack of prioritization given there are few RR-TB patients in Botswana.

"I don't know what can be done because as for us we do try to speak out, but as we speak out they tell us that they do check at the pharmacies, and the government does not have money and also that MDR patients in Botswana are not so many and again we don't get the same treatment. At times maybe it's the suppliers who dodge around with medications looking at the fact that medications are very expensive but with few people taking them. For example when I got here the injection I was given is not the one I am getting now. Because it was out of stock for a long time. I kept talking to them till they switched me to this one." 39 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

Providers confirmed that drug stock-outs have been a major problem and source of concern for them as well. They also confirm that treatment disruption has occurred. They indicate that stock-outs are more common now than in the past and that they are having to be more creative and proactive to try to manage stock-outs (sharing drugs between facilities). Although the patient perception was that the government does not have funding to buy the medications, the providers did not completely confirm this. Rather, they explain the cause as logistical issues of the supplier, Central Medical Stores (CMS), and how the funding is allocated and utilized. A 'vote' is an account at CMS into which the government puts funding. The vote specifies what the funding should be used for.

"CMS (Central Medical Stores) say they used to have a vote (account) for MDR-TB drugs. Now since last year they didn't, so they were just batching up with all the other drugs they were buying. In the vote they had for every other drug. So that proved to be a huge challenge. We had so much stock-outs, something we never used to be able to see. And now I think we were treating more patients than what we are now."

Interviewer: Will this be addressed in the next financial year?

"I don't know" HEALTH CARE PROVIDER (GABORONE)

"Just because I heard the information from the CMS. It's the issue of funds and the changing of suppliers and signing of contracts that delay the supply of these drugs" HEALTH CARE PROVIDER (GHANZI)

One provider explains their efforts to avoid stock-outs when possible.

"For instance when we didn't have augmentin, we got augmentin from Mahalapye. So we will call the sites. Francistown will call us and say we don't have moxifloxacin and so we will find out does Gaborone have enough moxifloxacin. Can they share? And they will call around all the MDR-TB sites. And if they have enough, they will share." HEALTH CARE PROVIDER (GABORONE)

Some providers at the treatment center expressed frustration but seemed unsure of the cause of stock-outs:

"Yes we (currently) have drugs available to treat MDR-TB. The facility has experienced shortages of MDR-TB drugs in the past for 1 to 2 months. The stock-out came from CMS (Central Medical Stores). I don't know why. We order the drugs but they don't show up here." HEALTH CARE PROVIDER (GHANZI)

Adverse events

All patients reported concerns about adverse events and side effects including high blood pressure, mobility problems, nausea/vomiting, loss of appetite and dizziness. The largest concern for patients was hearing loss, and one patient who was approached for interview could not participate because they had hearing loss due to use of the second-line injectable drug. The following quote describes the patients' frustration and fears about hearing loss:

"You are told (by providers), it all depends on luck, that there is a possibility of you losing your hearing and all those discussions you have. And when you tell them (providers) that to lose hearing is very painful if you have ever heard before they will tell you is it not better to be crippled and be alive than death. And the painful thing is that if you lose your hearing it is not treatable or give you hearing aid to help you or when you tell them that you feel you are losing your hearing, I don't know if there is any action that they take or they reduce the treatment dosage to avoid hearing lose, but most of us we lose our hearing because of this treatment…… The only thing is that they should be serious about these drugs because there are too strong and also the issue of injections because that is what makes me so worried above all things. Because to hear and then later lose your hearing it's a problem, you can't do anything for yourself let alone to walk alone and again I don't think the government will give us jobs because we lost our hearing while on treatment, it will be our own problem." 39 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

Providers also reported that patients are particularly worried about hearing loss and report that they are working to get access to better tolerated medications.

"What they (patients) do remember is the side effects, the hearing loss. They will tell you before they start that they don't want the injection" HEALTH CARE PROVIDER (GABORONE)

"One, bedaquiline, one of the new drugs, USAID is offering it as a compassionate drug. So countries are requested to apply for that. They've paid for that through the WHO but there's certain requirements you have to meet before you do that and then you have to estimate the amount you need in a year. So ministry of health were in the process of doing that and submitting those documents to USAID. Once that's done the bedaquiline is available." HEALTH CARE PROVIDER (GABORONE)

Barriers to care

Transport

In general, transportation was reported as a concern and barrier to care by both patients and providers. However, it was noted by all participants that the government provided transportation and this was appreciated. Overall, transportation is free and is provided; the concerns are with consistency and timeliness.

> *"They provide transport, it's only that they come late so that's why I normally walk"* 33 YEAR OLD MALE (AMBULATORY PATIENT)

> *"We have one day allocated each month for MDR-TB patients. If for some reason a patient is unable to come we call the clinic and re-book. They usually miss because of transport"* HEALTH CARE PROVIDER (GABORONE)

> *"I guess the issue may be transport. If the facility doesn't have transport to bring them to the clinic (monthly check up) then they have to change it. But at least the facility will call and say we don't have transport today, can we change it to another day?"* HEALTH CARE PROVIDER (GABORONE)

Access to Food

Participants also discussed that access to food was a problem and should be provided to mitigate adverse events. Even when hospitalized and food was provided, many complain about the quality and quantity of food.

> *"The challenge here (hospitalized) is that we don't eat properly. Sometimes there is only bread in the morning and again in the evening. Sometimes there is not enough soup to go with the rice we are given. It is less than what we can get at home"* 31 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

> *"what we (ambulatory patients) always emphasize is that we should be provided with lunch like now we don't have money where are we going to get food now. So that at least if you take these tablets without eating obviously you are going to vomit they should always provide lunch for us."* 50 YEAR OLD MALE (AMBULATORY PATIENT)

Providers agree that access to food is a problem and a concern for patients. They do report that they advocate for food baskets for patients but that this is not always successful; the decision for this food support is made by social workers who are available at each treatment facility. One provider did indicate that the 2017 updated national guidelines for management of drug-resistant TB (still in draft, 2019) include a policy to provide food baskets for all RR-TB patients, but these updated guidelines are not yet finalized, approved and distributed.

These new policies will require additional funding support from the national level and are waiting for approval from the Ministry of Health and Wellness.

> *"And mainly the main thing that they tend to want is food. It's very difficult but we do refer them. Some will get food, some won't. So this is something we are trying to advocate for from the ministry of health that can this be something that all of them can get now that they're MDR can they just get it."* HEALTH CARE PROVIDER (GABORONE)

> *"Then the other thing is trying to help those patients to cope with taking those treatment trying to involve the social workers so that they give them food baskets because most of our patient here are not working so they need that support. Now have a big problem because when we refer them to the social workers they will just tell them no, you are not eligible for those food basket, but it was an issue that was discussed so that the social workers can be informed that automatically whenever a patient is diagnosed with MDR should be given food basket until the end of their treatment. For now I will think it's not the issue of money it's the problem of communications between the ministry and the social work department."* HEALTH CARE PROVIDER (GABORONE)

<u>Directly observed therapy</u>

For ambulatory patients, a majority of patients reported receiving a supply of medications as opposed to taking them daily at the clinic (although one went to the clinic and took them daily). They report that receiving the supply is based on trust the providers have in them. People also reported that they preferred to take medications at home because they wanted to take them with food. Treatment support, for taking medications at home, was usually provided by females in the lives of the participants (mother, sister or wife). Hospitalized patients noted as a positive that nurses remind them to take medications at the right times and that they do receive food with medication (even though there are some complaints about food).

<u>Funding</u>

Providers reported concerns about decreased lab capacity for a variety of reasons, including stock-outs of laboratory reagents and Xpert cartridges and closures of the NTRL, making it difficult not only to diagnose patients but also to manage them properly. Providers do report that funding support is not adequate and leads to these problems.

> *"From 2010 until now that we stopped (conducting second-line DST). I think it had to do with money. So there was a gap of no second-line DST. And then they trained and then the lab closed (2014). So that's how many years, 6-7 years, with no second-line DST. It is a big deal especially when our doctors in 2008*

showed we have high new infections so there is high transmission." HEALTH CARE PROVIDER (GABORONE)

"We (NTRL) run out of reagents which will disrupt the testing of the patients, diagnosis of the patients, monitoring of the patients so we don't know exactly if we are where we are supposed to be there…. We are (currently) using the solid method but the quickest and the best way is to use the liquid method. But we don't have the reagents for the liquid method now but we are using the solid method. It's slower, cumbersome… Whoever has the say about the financial support of the lab thinks treating the patient will be cheaper than buying the reagents which is not the way. They think it is better to have the infection spreading then we will treat the patient which is not the way. So I think it is a matter of prioritizing the funding itself" HEALTH CARE PROVIDER (GABORONE)

"The program has a very good plan and strategies for MDR treatment but unfortunately I think it's to do with financial support. The program does not have enough funds for the support for the proposals they have raised. We always have strategies that are put in place but they do not take over because of financial constraints." HEALTH CARE PROVIDER (GABORONE)

Missing cases

Providers felt that, as a consequence of decreased lab capacity and decreased utilization of lab services, patients with RR-TB are being missed/undiagnosed.

"At the moment I think we should be seeing more MDR cases. If we truly used Xpert I think we should be picking up more cases. But since 2011 our MDR-TB cases have dropped because of the lab support." HEALTH CARE PROVIDER (GABORONE)

"We usually diagnose about 1 or 2 cases of MDR-TB per month. This past year, we have only diagnosed 1 patients. There have been no cartridges for Xpert so maybe our diagnosis is down" HEALTH CARE PROVIDER (GHANZI)

Knowledge and education

This theme explores TB knowledge and beliefs among patients and, for providers, examines access to and adequacy of training and guidance.

Patient knowledge and education

Providers and patients both report that education about RR-TB is provided to patients, and accompanying family members, at the time of treatment initiation. This education includes information about the medications, the

side effects and infection control. Prior to initiation of RR-TB treatment, most patients had heard of TB but not RR-TB or MDR-TB, and reported receiving health information from a mix of health providers, friends/family, community events and television. Those that had previously heard of RR-TB, had limited information:

> *"I had heard that there is a big TB which is stubborn"* 37 YEAR OLD MALE (AMBULATORY PATIENT)

It appears that the education provided at treatment initiation is not sufficient for all patients. It is possible that the information provided is sufficient but that it is not retained or completely comprehended. While some patients appeared to have good knowledge about RR-TB during the interview, others expressed limited knowledge, and some expressed an interest in finding out more about TB:

> *"Can I ask you something, this word 'culture' what does it look like?"* 33 YEAR OLD FEMALE (HOSPITALIZED PATIENT)
>
> Regarding side effects: *"this hearing thing when it changes, what are the signs?"* 39 YEAR OLD FEMALE (HOSPITALIZED PATIENT)

When asked how they think they got RR-TB, one patient reported that his girlfriend had MDR-TB; others speculated reasons such as working a dusty environment or that it may have been transmitted sexually, and some did not know:

> *"I don't know how I got it, I just found myself sick"* 45 YEAR OLD FEMALE (AMBULATORY PATIENT)

<u>Provider access to training</u>

Overall, interviewed providers reported being satisfied with their training. Three of the providers received training provided by the International Union Against Tuberculosis and Lung Disease (IUATLD); these providers then provide training for others in the program. The interviewed nurse from Ghanzi, for example, reported receiving hands on training at the Gaborone treatment facility (the doctors and specialists at this treatment facility have received IUATLD training). Providers did indicate that there is a lack of training for staff at primary care levels and that this influences many aspects of RR-TB management. Only one interviewed provider (the laboratory manager) reported their training as being inadequate:

> *"The training will never be enough. There are always new things coming up and we can't say it's enough. We don't know how far we can reach and we cannot give ourselves boundaries"* HEALTH CARE PROVIDER (GABORONE)

Provider access to guidance and expert consultation

Providers reported good access to experts for consultation. All providers reported that they frequently consult with the lead RR-TB physician and that she is readily available. This lead physician also has access to a TB expert at the Union and reports that he is "always happy to consult".

One area in which providers expressed some dissatisfaction was the availability of updated RR-TB management guidelines. All providers reported that guidelines were available in the facilities but that they are not up to date; all reported having access to the version from 2009. Providers reported that a newer version has been in development but that there is a delay:

> *"Well, the guidelines they have changed but they're still not in the facility. The last guidelines that were in the facility were in 2009. A lot has changed since 2009. They've been revised since last year but they waited for endorsement from the Permanent Secretary because it requires budget changes. Like the new drugs and they've also put in this part of MDR-TB patients getting food baskets so she needs to approve it before it goes out."* HEALTH CARE PROVIDER (GABORONE)

Understanding of TB transmission among providers and patients

Although patients reported receiving education about RR-TB and providers report overall satisfaction with training, there does appear to be some misconceptions among both patients and providers about TB transmission. None of the patients mentioned airborne transmission when asked how they think they acquired TB, and others mentioned different modes of transmission (sex, environment). Furthermore, the idea of hospitalization because of transmission risk was mentioned by both patients and providers, and reflects and misunderstanding about the low risk of transmission once on treatment. No one mentioned that most transmission would have occurred prior to treatment initiation, therefore negating this as a reason for hospitalization.

8.6 Discussion

This is the first qualitative study of a cohort of RR-TB patients and providers in Botswana. This study provides a wide variety of insights about the successes and challenges of RR-TB management in Botswana based on patient and provider experiences.

There are several areas in which the program appears to be succeeding. The interviewed providers involved directly in RR-TB patient care (those at RR treatment facilities and those that provide support from national level) showed compassion and support for patients; patients reported being satisfied with the care they received in the RR-TB treatment centers. This research indicated that patients do not experience gender based discrimination in Botswana. Although delays in diagnosis were reported, linkage to care once patients were diagnosed was reported to be rapid. Providers felt they have adequate training and good access to experts for consultation as needed, though some of the challenges and misunderstandings identified in this research call into question whether or not the training available is actually adequate.

Overall, Botswana has good policies in place that are in line with global recommendations; however, these are not implemented consistently, and this creates many challenges in the program. One major area of misunderstanding is with the policy for hospitalization. Providers view hospitalization as one of the main ways to reduce transmission and a great deal of effort is placed on ensuring patients are hospitalized and on managing patients in the hospital. While it is a common perception that isolating patients is needed to reduce transmission[86, 222], it is not in line with current the WHO recommendations. Research has shown that with effective treatment, RR-TB patients quickly become noninfectious[223]. The focus on isolating patients can also create a false sense of security whereby health care workers and communities believe that they are not at risk when 'infectious' patients are removed from the community; but this fails to take into account the numerous patients who are undiagnosed and are still in the community with the possibility of transmission[69]. Furthermore, even settings which recommend hospital based care for RR-TB patients recognize the limitations. Oladimeji et al. reports the usefulness of hospitalization in Nigeria but also notes that less than 5% of estimated cases initiated treatment, and surmises that with the expected scale-up of RR-TB care, the hospitalized model would be hard to sustain[86]. Additionally, systematic reviews suggest that hospitalization is not associated with better outcomes than ambulatory treatment[89, 90]. In the current research, one provider in Botswana reported that, in line with national policy, most patients are not hospitalized for treatment initiation. However, other providers reported that most patients are hospitalized until culture conversion and all patients interviewed, with the exception of one extrapulmonary RR-TB patient, reported being hospitalized for several months. This indicates a misunderstanding of the policy and of the main factors contributing to transmission. While so much effort is placed on hospitalization, other important factors are ignored.

Early diagnosis of drug resistance is one of the most important factors to reduce transmission, and Botswana did implement an updated TB diagnostic algorithm including universal DST in 2016. However, the diagnostic algorithm is not consistently adhered to leading to lengthy delays in diagnosis, in turn contributing to increased transmission. Several factors contribute to non-adherence to the algorithm. There appears to be misunderstanding and a lack of training at the primary care level where patients are first seen; health care workers at this level often request only smear testing, and even when Xpert testing is requested, a follow-up confirmatory DST is often not requested. As a result, diagnosis of drug resistance is delayed. Once samples arrive at the NTRL, a process including reflex testing is followed whereby any culture positive test automatically triggers first-line DST. However this same concept of reflex testing is not followed at the peripheral labs. Peripheral labs will not automatically forward specimens to the NTRL unless they are accompanied by a form which specifically requests culture and/or DST. Additionally, challenges with maintenance of Xpert instruments and stock-outs of testing reagents, both Xpert cartridges at the district level and laboratory reagents at the national level, lead to inability to adhere to the diagnostic algorithm as well. Other settings have reported similar challenges. Sikhondze et al reported that in the Xpert rollout in Swaziland, the lack of government budget to support maintenance, calibration, and module replacement contributed to the number of unsuccessful tests[33]. A study in Nepal also reported barriers to successful implementation of Xpert including timely supply of cartridges, replacement of damaged modules and machine maintenance[34]. The study recommends the following to improve Xpert implementation: evaluation of workload and provision of adequate human resources, comprehensive training to staff of Xpert testing locations, and co-operation between Xpert users and suppliers to minimize delay of supply and maintenance[34]. A key element that is relevant in Botswana, and likely other settings, is the importance of adequate funding and logistics to support the supply of cartridges/maintenance.

A systematic review[224] showed that contact investigation for drug-resistant tuberculosis patients is a high-yield intervention for detection of drug-resistant tuberculosis. While Botswana national policy indicates that contact tracing should be conducted for all close contacts of RR-TB patients, there were conflicting reports from providers about this being done consistently. Additionally, some patients reported concern that not all of their contacts were screened, and one patient reported having to request screening even after his girlfriend had been diagnosed and treated for RR-TB. As has been shown in previous chapters describing the RR-TB cohort in Botswana, the number of children diagnosed is low; children are often detected through screening[225] and may be missed due to inconsistent screening practices in Botswana. Inconsistent screening practices also contribute to diagnostic delay.

The delays in diagnosis can lead to ineffective treatment and continued transmission. Most patients report receiving first-line treatment before being diagnosed with RR-TB, with some patients receiving multiple courses of first-line treatment before diagnosis of drug resistance. Studies report that treatment failure can be

determined early and that among those whose treatment has failed, multi-drug resistance is common and therefore important to monitor; Pachas et al reported that smear positivity at 2 months of first-line treatment was strongly associated with failure of treatment, and approximately 75% of those with DST had MDR-TB[226].

Additionally influencing the ability of the program to provide effective treatment are drug stock-outs, which was an area of concern for both patients and providers reporting frequent and lengthy treatment interruption. This same challenge is seen in other settings. A qualitative study in South Africa reported challenges with access to important medicines caused by inefficiencies at the central level including delays in awarding pharmaceutical tenders, absence of contracts for certain medicines and suppliers' inability to provide medications due to stock-outs at multiple levels[227]. Bam et al. conducted a comprehensive evaluation of supply chain issues for second-line TB drugs in South Africa and has produced guidelines to cost-effectively reduce stock-outs by implementing supply chain policies which and take into account lead times from drug suppliers, as well as include maintaining safety stock of medications at a central distributor[228].

At the time of this research, Botswana was using a standardized long course regimen including amikacin. National policy does state that individualized regimens are provided based on DST results, but it is not clear how consistently this is done[48]. As shown in other chapters, many patients in Botswana initiate treatment empirically on the standardized regimen and some patients never receive DST to guide treatment regimens; they remain classified as presumptive RR-TB throughout treatment. The WHO recommends use of treatment regimens in which drugs are likely to effective based on DST, and research has also shown the importance of basing treatment regimens on known drug resistance profiles[13]. The Preserving Effective Tuberculosis Treatment Study (PETTS) showed that patients who received six potentially effective drugs (based on DST) had a 36% greater likelihood of culture conversion than patients who received less than six potentially effective drugs[229].

National policy had not officially addressed shorter treatment regimens and the use of medications with less side effects; however, plans to incorporate these into policy had begun according to interviewed providers. Given the strong concerns and complaints about side effects with the current treatment reported by both patients and providers, it is important to incorporate alternative treatment options. Chapter 5 confirmed that concern regarding hearing loss was warranted, given that 44% of the patients in the studied cohort reported hearing loss, and a publication from another cohort in Botswana reported hearing loss in more than 60% of the patients receiving treatment[110]. As a follow-up to determine if there have been any changes in treatment regimen since the time of this research, the Botswana National TB Program Manager was contacted by the researcher. This follow-up communication (December 2018) revealed that the program has mostly switched from amikacin to capreomycin or bedaquiline containing regimens[11]. Bedaquiline is being provided by USAID as

part of a donation program. Amikacin is still available for individual regimens. The program is still using the long treatment duration as of 2018.

There were several other challenges identified in this analysis, all of which should be considered in this recommended shift of priorities and attention to ensuring policies are adequately implemented. These include challenges with transport being provided consistently, inadequate food support for patients, and a need for opportunity for continued counselling and education of patients throughout treatment. The cost of these supportive interventions is low in contrast to the cost of second-line medications; the WHO reported the median cost of RR-TB treatment per patient was over $7000 USD in 2017[13].

While it has been determined that Botswana policies are in line with global recommendations in many important areas, adherence to the policies is problematic. National program manuals and guidelines are not updated regularly and contribute to this non-adherence. The most recent TB program manual was developed in 2011, and the most recent guidelines for management of drug-resistant TB was developed in 2009. This is a major challenge, given the rapidly changing WHO guidance on RR-TB management. Furthermore, important updates have been made and implemented in Botswana, such as the updated diagnostic algorithm including universal DST through Xpert; however, this update has not been incorporated into the relevant national program manual or guidelines. Botswana produced an updated draft of the guidelines for management of drug-resistant TB in 2017[92]; however, this has remained in draft form waiting for approval at the national level. One interviewed provider did report that the approval and distribution of these guidelines is delayed because the update calls for increased commitment from the government (in the form of new drugs, food support for patients, etc.), so this is pending approval from the Minister of Health. Recent communication (December 2018) with the program revealed that these guidelines have still not been approved and distributed[104], indicating lack of support at the high levels of the Ministry of Health and Wellness.

There are limitations of the study. There were few patients interviewed, but the interviews were very lengthy and in depth. Additionally, there were few providers interviewed and this was limited to providers at the national level and at two of the six RR-TB treatment facilities; this analysis did not include providers from the primary care level. The same translator was not used at each site; due to limited funding, the translator could not travel to Ghanzi, and the RR-TB nurse provided the translation in Ghanzi. The nurse was educated to translate the interviewers' words verbatim, and the transcriptions, which were all performed by the same person, confirmed this was done.

These findings highlight the need to focus attention away from less crucial and more expensive TB control practices such as hospitalization and prioritize case finding and safe, effective treatment without interruption. While the providers interviewed demonstrated strong work ethic and dedication to the successful management

of RR-TB, there is a larger system level problem. Stock-outs of testing reagents and medications, non-adherence to the diagnostic algorithm, inconsistent contact tracing and treatment regimens with serious side effects are evidence of larger system issues. Botswana is an upper-middle income country and should be able to support an effective RR-TB control program including adequate laboratory capacity; however, this is not the case evidenced by the many gaps that have been identified in this analysis. National level support is needed to shift priorities, provide adequate funding, improve communication and training to reverse misunderstandings and to integrate services across all levels of care.

Chapter 9: Conclusions

9.1 Chapter overview

This chapter will summarize the key findings and implications of this research, as well as overall recommendations.

9.2 Key findings and implications

Inadequate RR-TB case detection

There is considerable variation in RR-TB patient numbers diagnosed per year in Botswana suggesting inconsistent case detection. Based on current WHO estimates, it would be expected that 266 (13%) of the 2053 previoulsy treated TB patients notified in 2013 and 2014 would have RR-TB; however the monitoring efforts described in this analysis only identified 36 patients. It is possible that some of these 'missed' patients might have been identified later in their treatment, but this is a missed opportunity for early detection of drug resistance. To explore factors that may contribute to poor case detection and under-diagnosis, this research assessed monitoring for drug resistance among previously treated TB patients, a group at risk of RR-TB, notified in 2013 and 2014. Overall, there was a low rate of monitoring for drug resistance among previously treated TB patients in Botswana; only 42% of patients had samples submitted for culture and fewer still (19%) had DST conducted. Notably, only 43% of patients who had previous first-line TB treatment which failed had samples submitted for testing, and these patients may have been initiating a second round of ineffective treatment. Factors which were associated with lower monitoring for drug resistance included not having a smear test at the diagnosing facility, living in a rural area and having a treatment category of previous treatment success. A wide variation in sample submission rates was seen among health districts. However, spatial and district analysis unfortunately did not provide clarity into this variation among districts, and it appears that this is mainly affected by poor compliance with guidelines. Although the focus of this analysis was on previously treated patients, the implications for failed case detection very likely expand to other at risk patients as well.

While WHO recommends universal DST for all patients with signs and symptoms of TB, this is not implemented consistently in Botswana. The program has reported that they do now recommend universal DST with Xpert. However, the policy remains unclear and based on the most recent reports from WHO this is not yet being accomplished. The most recent 2017 TB country profile for Botswana indicated that only 5% of previously treated patients were monitored for RR-TB. Furthermore, many patients (interviewed in 2017) reported receiving one or more courses of first-line treatment before receiving any TB diagnostic tests including for drug

resistance, indicating this high-risk group (previously treated patients) are still not being screened early for drug resistance.

There were frequent laboratory closures during the time of this analysis, and the qualitative interviews revealed this is an ongoing problem. Although the laboratory reopened in 2016, interviewed providers reported continuing challenges with reagent availability. Xpert capacity was also highlighted as a major challenge. Interviewed providers reported frequent stock-outs of testing cartridges and machines, which have not been calibrated.

As a result of inadequate monitoring, TB patients with drug resistance are likely to remain undiagnosed. These patients may be detected with TB drug resistance during subsequent TB treatment episodes, but in the meantime they are likely to develop more severe disease, and remain infectious for longer[117] possibly transmitting drug-resistant tuberculosis in the community and at the health centers where they are seeking care. However, many patients, particularly those with HIV infection are likely to die during TB treatment if their TB drug resistance remains undiagnosed.

Poor confirmation of first- and second-line drug resistance patterns among patients initiating RR-TB treatment

It is clear that Botswana is missing many patients due to inadequate monitoring. For the patients who are identified, it is crucial to confirm the drug resistance profile to ensure effective treatment. This research assessed confirmation of drug resistance among the cohort of RR-TB patients registered between 2006 and 2014. For patients initiating RR-TB treatment, the first-line drug resistance profile was confirmed for 85%, and this has remained consistent over time. There were 120 patients who received second-line treatment with no information about resistance available at any point during treatment. Second-line DST was available for few patients (24%) and has been impacted by changing practices (not sending samples to South Africa for testing) and no in-country laboratory capacity. Among those who were eventually diagnosed by laboratory tests to have Pre-XDR or XDR- TB, these confirmatory results were available a median of 118 days after treatment initiation, with a delay of more than one year for some patients.

These findings further highlighted the effect of interrupted laboratory services and the inconsistencies in the national guidance about testing recommendations. The qualitative interviews identified concerns among providers that the introduction of Xpert had actually created an even larger gap in patients receiving culture testing and confirmatory DST. They reported that many fewer samples were now being sent to the NTRL for testing and that it appeared that the primary health care facilities were relying solely on Xpert and not seeking confirmatory testing as recommended.

As a result of inadequate monitoring among patients initiating second-line treatment in Botswana, many patients may have received ineffective second-line treatment, and patients with Pre-XDR or XDR-TB may have not been identified. For the patients who were identified with Pre-XDR or XDR-TB, the delay in diagnosis is concerning. Furthermore, because the specimen collection date was not available in the RR-TB registry, it is difficult to discern whether second-line resistance was present at treatment start or developed during treatment.

Mortality during RR-TB treatment

This research explored risk factors for mortality among patients on RR-TB treatment. Botswana has high treatment success but also has consistently high mortality during treatment. The analysis among patients initiating treatment between 2006 and 2014 in Botswana revealed independent factors associated with mortality, including older age, HIV positivity and not on ART at treatment initiation, unknown HIV status, smear positivity at treatment initiation, baseline radiology not recorded, registration category not recorded, unknown drug resistance profile (presumptive RR-TB), Pre-XDR or XDR-TB, treatment at Princess Marina Hospital or Sekgoma Memorial Hospital, and treatment between 2009-2011. The analysis of the 3 year subset (2012-2014) for which chart reviews were conducted also revealed associations with disease severity and risk of mortality.

The results of the mortality analysis are related to the earlier findings about inadequate monitoring. Of all patients initiating second-line treatment described in the mortality analysis, 83% were reported as having had a result of treatment failure from previous first-line TB treatment. Many of these patients likely belonged to one of the high-risk groups (such as previously treated TB patients) and should have had monitoring for drug resistance sooner (before failing first-line treatment). Patients on RR-TB treatment with an unknown drug resistance profile (presumptive RR-TB) were shown to have a higher risk of mortality. They are likely to have been diagnosed and started on second-line treatment after first-line treatment failure, indicating late diagnosis and possibly more severe disease; others may have been diagnosed as contacts of other RR-TB patients. Regardless, these are patients who did not have DST results available to guide treatment and may have received ineffective treatment. Additional factors associated with mortality pointed to potential poor clinical care, including missing clinical information (radiology, smear, etc.).

Reducing delays to treatment initiation and treatment gap with decentralized testing using Xpert

A systematic review and meta-analysis of time to treatment for RR-TB was conducted. This analysis showed that molecular testing methods (Xpert and LPA) led to faster time to treatment. Furthermore, ambulatory care has been shown to be effective and leads to similar treatment outcomes as compared to hospital-based treatment; this analysis reported shorter time to treatment among cohorts with ambulatory treatment, compared to

hospital-based treatment. The studies included in this systematic review did reveal that treatment delay is common, particularly among cohorts with hospital-based models of care as well as cohorts with phenotypic DST. While initiating treatment quickly is important, it is also important to ensure all diagnosed patients actually do make it on to treatment. In this analysis, several studies reported relatively rapid times to treatment (less than 30 days), but still less than 70% of diagnosed patients starting treatment, a large treatment gap.

Building upon this systematic review, this research also described Xpert use in Botswana in 2013-2014 and examined the impact of Xpert use on time to treatment. In regards to the treatment gap described in the systematic review, this analysis indicated that among patients diagnosed with RR-TB by Xpert in Botswana, 89% initiated second-line treatment. Xpert did reduce the time from diagnosis to treatment (median 5 days, IQR 2-10), when compared to the NTRL cohort (patients initiating treatment based on testing conducted at the centralized laboratory, which was mainly using phenotypic DST) (median 22 days, IQR 14-36). Although the time from diagnosis to treatment is shorter for the Xpert cohort, neither cohort had extremely long delays in linkage to care once a diagnosis was available. This finding was confirmed in the qualitative interviews in which patients reported starting treatment quickly once they were diagnosed with RR-TB. The time from specimen collection to treatment was substantially shorter for the Xpert cohort (median ~15 days) compared to the NTRL cohort (median 105 days, IQR 85-126), using estimated times for the Xpert cohort as the specimen collection dates were not available. In regards to follow-up testing of RR-TB patients diagnosed by Xpert, 64% received confirmatory DST, which revealed that 26% of these patients with DST had RMR-TB. Confirmatory DST after Xpert diagnosis is important to confirm, not only rifampicin resistance, but also to confirm resistance to other drugs to guide appropriate treatment. Patients with RMR-TB are denied the use of isoniazid in their treatment regimen if they are placed on a standardized regimen.

It is concerning that providers reported in the qualitative interviews that confirmatory testing has been decreasing in the country, attributed to sole reliance on Xpert. It is also disappointing that the successes shown in this research appear to not be maintained in subsequent years, given the most recent WHO report that few TB patients are being tested for rifampicin resistance. The qualitative interviews also revealed challenges with inconsistent Xpert capacity due to cartridge stock-outs and lack of calibration/maintenance for machines.

Patient and provider experiences with RR-TB diagnosis and treatment

It is unfortunately rare that patients are asked about their experiences with the care they receive, despite the recommendations to provide patient centered care. Patient perceptions and experiences should be an integral part of how programs operate. Both patients and providers were interviewed as part of this research to gain further insight into their personal experiences and in an attempt to understand some of the other findings in this research. This analysis highlighted some successes of the RR-TB program in Botswana. The providers interviewed

all showed compassion and care for the patients, and the patients confirmed this in their responses about their satisfaction with the care they received. There were no reports of gender-based discrimination. National policies are generally in line with global recommendations, and providers reported being satisfied with the support and training they receive.

Despite these successes, many challenges were revealed. Although National policies are in line with global recommendations, there are issues with adherence to National guidelines. Furthermore, guidelines were not up to date and did not incorporate important new recommendations related to RR-TB care. A key finding of this analysis is that many patients are being hospitalized in Botswana for treatment initiation, up to three or four months; there appear to be misconceptions about transmission and need for hospitalization among both providers and patients. This analysis also confirmed delays to diagnosis, which had been highlighted or speculated about in other chapters. Some patients reported more than one course of first-line treatment failing before being tested for drug resistance. Patients reported seeking care multiple times and at multiple locations before being tested, and there were concerns from patients that contact tracing was not done consistently. The analysis also highlighted misunderstandings and likely lack of training at the primary care level, with health care workers not requesting appropriate diagnostic tests for patients. This analysis revealed a very concerning finding that drug stock-outs had been common; all patients and providers reported interrupted treatment for weeks due to drug stock-outs. Patients were also very concerned about side effects of medications, particularly hearing loss, and the results about side effects reported along with the mortality analysis (44% of patients with hearing loss) confirm this is a valid concern. Many challenges were identified, and patients and providers indicated that they think many of these challenges are due to lack of funding.

The findings from this analysis highlight the need to focus attention away from less crucial and more expensive TB control practices such as hospitalization and prioritize case finding and safe, effective treatment without interruption. It is also crucial that guidelines are updated to reflect changing recommendations. It is a concern that the national guidelines are not up to date, and this potentially represents a lack of support from the leadership at the MoHW; updated guidelines for the management of drug-resistant tuberculosis have been drafted since 2017, but these have not yet been released because they have not yet been approved by MoHW leadership. The program is currently operating with guidelines produced in 2009, which do not include important updated global recommendations.

<u>Summary of key findings:</u>

- The impact of interrupted laboratory capacity is clearly highlighted in these analyses, affecting case detection and confirmation of drug resistance pattern.

- Factors contributing to mortality point to poor clinical care and/or misclassification of disease / exposure from missing information.
- One particular problem in Botswana is high empiric second-line TB treatment and then a gap in those who received confirmatory drug resistance testing. This is peculiar to this setting, and this data shows a deviation from national guidelines. Of concern is that those without confirmed drug resistance profile appear to be at a higher risk of mortality.
- A systematic review of factors influencing time to treatment provided a detailed overview of literature to date on the topic, providing new and complementary evidence that molecular diagnostic methods and ambulatory treatment/care models lead to faster time to treatment.
- Inconsistent adherence to guidelines is highlighted in multiple analyses, impacting case detection, diagnostic confirmation and rapid linkage to care.
- Xpert has been shown to reduce time to treatment in Botswana, as in other settings. Challenges of effective Xpert implementation were clearly reflected in the qualitative findings (funding constraints, supply chain issues, lack of adherence to guidelines).
- Qualitative findings further highlighted important and modifiable barriers to effective RR-TB diagnosis and treatment: drug stock outs, inconsistent adherence to guidelines, unnecessary hospitalizations due to misperceptions among health care workers, and health system factors contributing to treatment delay (including patients with multiple first line treatment failures before being tested for drug resistance).

9.3 Recommendations

Before providing recommendations, it is important to recognize the successes of this program. Among RR-TB patients who initiate treatment in Botswana, the success rate is very high (78%), especially for a country with a high HIV burden. Furthermore, the lost to follow-up and treatment failure rates are impressively low (2% each) compared to other countries. The program has compassionate health care providers and national level staff who are very dedicated to the program and the RR-TB patients.

It is a global priority to accelerate efforts to reach the goals set forth in WHO's End TB Strategy, and a key area for action is multisectoral accountability. Important elements of multisectoral accountability include: 1) attention to TB at the level of Heads of State, at global and national levels; 2) engagement from ministers across government and beyond the Ministry of Health; 3) strong process for review and feedback on progress of a program; 4) engagement of civil society and media; 5) strengthened legislative framework; and 6) TB service delivery focused on the "three As": affordability, availability and accessibility[230]. In this context, it's extremely important to consider Botswana's potential, the areas for needed improvement and what the country should be

accountable for. Given the country's high economic standing as an upper middle-income country, Botswana should be able to address some of the challenges identified in this research. To accomplish this, it will be important to focus on all of the aforementioned elements, particularly the attention to TB at higher levels of government and across government, which appears to be lacking in Botswana currently.

Many of the challenges revealed in this research were caused by lack of adherence to recommended guidelines. The research also highlighted inconsistencies in available guidelines, which were drastically out of date. It would be advisable for the program to develop more effective procedures for revising and endorsing guidelines. Global recommendations are currently updated much more frequently than they have been in the past, and Botswana should be able to quickly respond to innovation. Two examples of this are with the introduction of Xpert and with the use of new drugs. Xpert was first used in Botswana in 2012 through a pilot implementation study, and was also used for routine testing starting in 2012; however, the updated algorithm to include Xpert was not finalized and distributed until 2016. The use of Xpert has still not been incorporated into the available national guidelines (the 2011 TB Program Manual and the 2009 National Guidelines for Management of DR-TB). There have also been a number of new drugs and treatment recommendations since these national guidelines were developed. The country has actually moved away from routine use of amikacin, and most patents now receive capreomycin or bedaquiline instead of amikacin, but this is not reflected in current guidelines. Amikacin is still available for use in individualized regimens. It is important to not only respond to change quickly but also to translate that change into guidance to ensure this is implemented effectively in practice. The frequent updates will also require routine and repeated training to ensure adherence to guidelines.

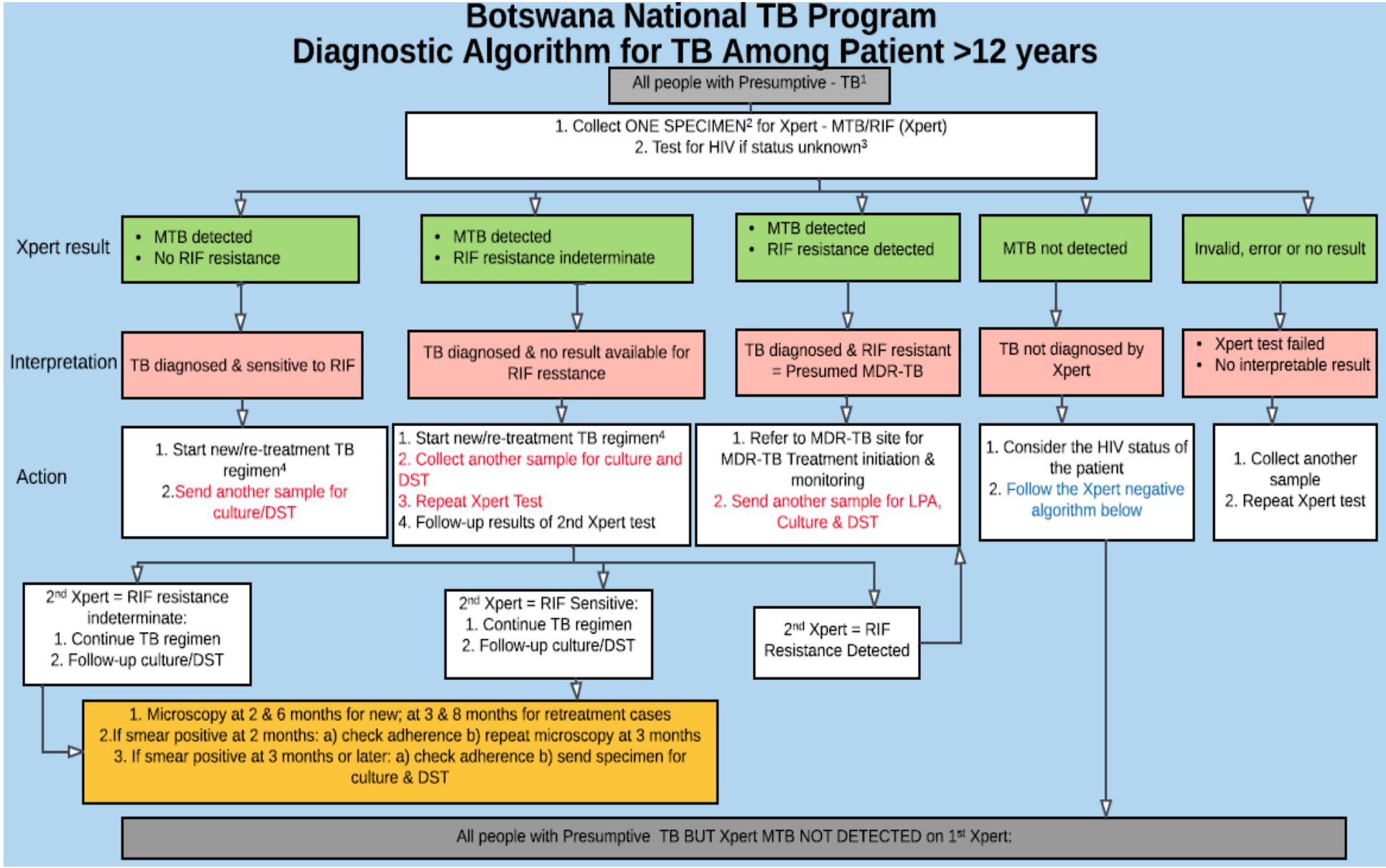
Another major challenge in this research is the frequent interruption in laboratory capacity. Not only have there been frequent closures at the central laboratory for renovations and stock-outs of reagents, Xpert use has also been interrupted due to stock-outs of cartridges and machines which are not calibrated or maintained. The successes of Xpert implementation highlighted in this research (reduced delays to treatment and a high proportion of diagnosed patients initiating treatment) do not seem to be maintained as of more recently. Given the most recent WHO report that only 5% of previously treated patients received testing for rifampicin resistance, it is unfortunately clear that Xpert is not being implemented effectively in Botswana.

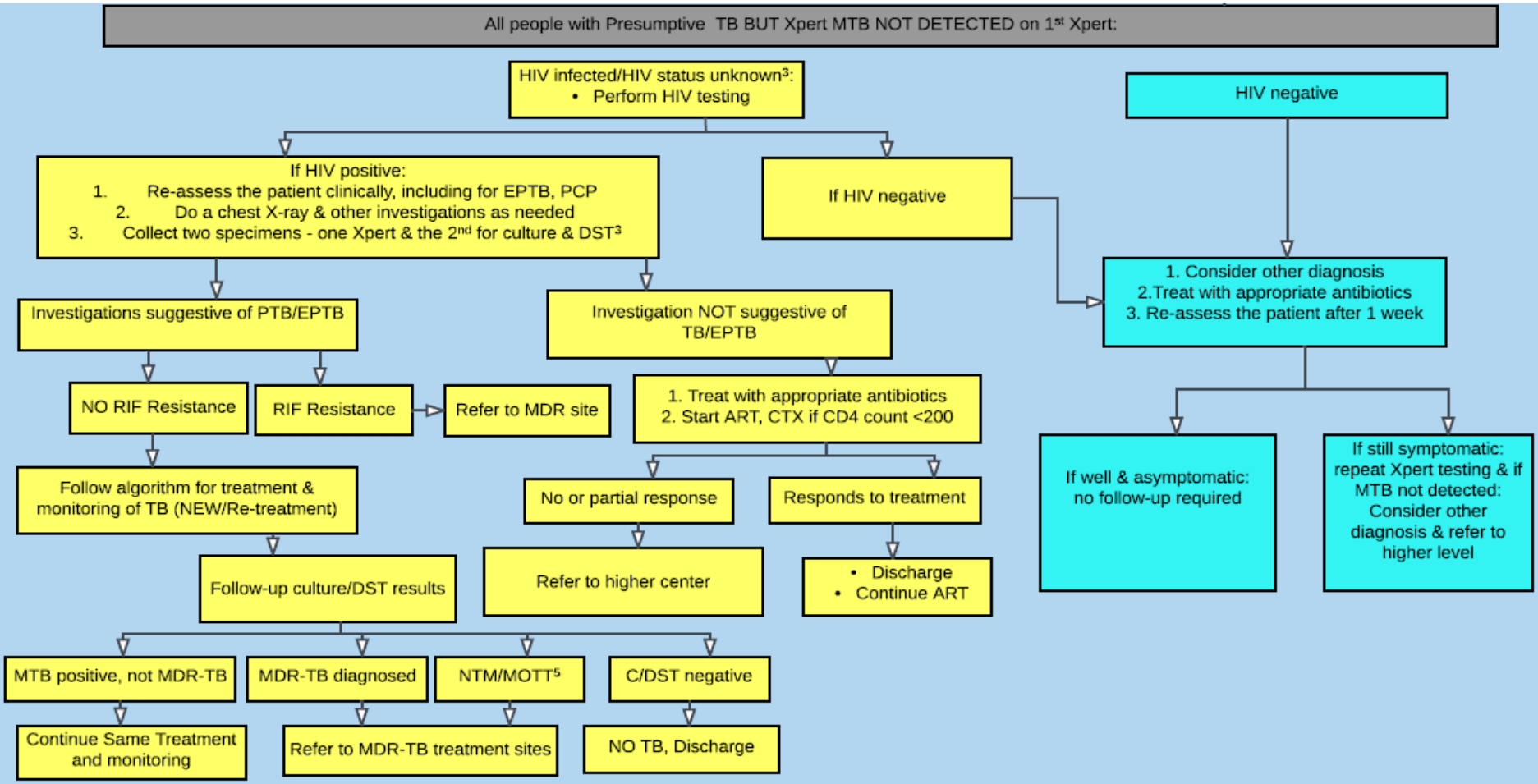
Challenges highlighted in this research include inadequate monitoring for drug resistance, low case detection, high mortality rates, delays to diagnosis and treatment and continued practices that are not patient centered such as hospitalization. Additional challenges included issues with missing important information about patients on treatment. Limitations in this research included missing important information needed for the analyses such as specimen collection dates. And more importantly, there was missing clinical information in the RR-TB register (radiology results, smear results, and information about monthly monitoring of patients on treatment). The

missing information may be a marker of poor clinical care. While the qualitative interviews did report that providers do have compassion and care for patients, they may be inadvertently providing poor clinical care by not adhering to recommended guidelines (of which they may not be aware since national guidelines are not updated).

It is clear from this research that RR-TB case detection is low, and many patients do not make it onto treatment or suffer long delays before initiating treatment. The full scale of the problem is hard to estimate because there has not been a recent drug resistance survey in the country; the last survey is from 2008. It is advisable that the program conduct more frequent surveys to better understand the situation of RR-TB in the country, or this could be accomplished through universal DST, in turn providing ongoing resistance surveillance. Recommendations for the program include increased access to new TB drugs, earlier diagnosis, improvements in data reporting, universal DST for all TB patients, and routine monitoring for treatment failure and resistance acquisition during treatment. All of these recommendations will require disseminating updated guidance, clear education and routine monitoring and support to health facilities at all levels (from hospitals to mobile posts). None of this will be possible without increased national level support to shift priorities, to provide adequate funding, to improve communication and training to reverse misunderstandings and to integrate services across all levels of care. The time has come for Botswana to have a TB program commensurate with its positive standing in the global economic community.

Appendix A: BNTP Diagnositic Algorithm (2016)





NOTES TO ADULT & ADOLESCENT TB DIAGNOSTIC ALGORITHM

1. Presumptive TB criteria: a) If HIV infected /unknown – any one of the symptoms of cough, fever, night sweat and weight loss of **any duration;** b) If HIV uninfected: cough, fever night sweat and weight loss for at least **2 weeks**
2. XpertMTB/RIF can be performed on spontaneous or induced sputum, gastric lavage, pus and cerebrospinal fluid (CSF) only but NOT on lymph node fine needle aspirate and pleural biopsy which are currently not validated in Botswana. All other specimens including but not limited to, lymph node fine needle aspiration, tissue biopsy, bloody sputum, pleural, pericardial and peritoneal fluids should be sent for culture and DST, not for Xpert. If the sputum is bloody, please repeat the sample.
3. In addition to sending a sample for Xpert and/or culture and DST, immediately perform at point of care the Urine Lateral Flow Lipoarabinomannan (LF-LAM) Assay for.
   a. All HIV infected presumptive TB cases; with CD4 counts ≤100 and
   b. Inpatients and outpatients with HIV who are seriously ill regardless of CD4 count.
4. New TB treatment regimen remains the same (2 months HREZ initial phase and 4 months HRE continuation phase), but the retreatment TB regimen no longer contains streptomycin; 3 months HREZ (initial phase) and 5 months HRE (continuation phase).
5. Before consulting with MDR-TB site, contact NTRL and request for speciation of MOTT; collect another sample for TB culture and request for CXR
6. ***All HIV positive patients should be initiated on ART and CTX prophylaxis should be given to all those diagnosed with TB***

Appendix B: Qualitative Questionnaires and Consents

Questionnaire – MDR-TB Patients

Date of interview	DD		MM		YY	
Interview location						
Interviewer name						
Participant ID number						

Informed Consent – MDR-TB Patients (Flesch Kincaid Grade Level = 5.7)

Hello. My name is _____, and I am working on a study to learn about and improve health care for MDR-TB patients. Would you prefer conducting this interview in English or Setswana?

Why is this study being done?

We are doing this study to learn more about how people in Botswana find out if they have MDR-TB. We also want to learn more about how people get the care they need when they have MDR-TB. This study has been approved by research ethics committees at the Botswana Ministry of Health, the University of Cape Town in South Africa and the Centers for Disease Control (CDC). All of these groups are involved in the study.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you are a patient. You have important information about how you found out that you have MDR-TB and how your care has been. This information will help us learn about the health care issues for patients in Botswana.

How many people will take part in this study?

We will talk to 10-20 patients and will also talk to doctors and government workers.

What will happen if you decide to take part in this study?

We will ask you some questions about being a patient. This will take about 30-45 minutes. You do not have to answer every question. If there are any questions that you do not want to answer, that is ok. After we finish this survey, your participation will be finished. We will not contact you again to answer more questions for this study.

What are the risks of taking part in this study?

You may find some of the questions hard to answer. If any of the questions upset you, we will give you the names and phone numbers of people that you can talk to about this. Also, it is possible that someone outside the study could see this data, but we will be very careful not to let this happen. Your name will not be kept in the same place with this data, and all documents will be kept in locked areas at all times.

Who will see the information that you provide during the study?

First of all, we will not put your name on the survey so no one will know that you are the person giving these answers. Also, only the people involved in the study will be able to see your answers. These study staff have been trained to make sure the information is kept confidential. We will keep this survey in a locked office and in a locked cabinet. The consent form with your signature will not be kept with the survey so that no one can link you to your answers.

Are there any benefits for being in the study?

There are no direct benefits from participating in this study. The main benefit of participating is this study is that we will use what we learn to improve health care for people in Botswana. So this may benefit you and would also benefit other patients in the future.

What other choices do you have?

If you do not want to be in the study, that is ok. Participating in the study is voluntary. You can say no, and we will not ask you again. Your choice will have no effect on the care that you receive. If you say no, you will receive the same care.

Who do you speak to (or contact) if you have questions or concerns about the study?

This study is being done by people at the University of Cape Town in South Africa, the Botswana Ministry of Health and the Centers for Disease Control Botswana (CDC Botswana).

You can contact any of the following people for questions about the study or to discuss withdrawing from the study:

1. Helen Cox, PhD
   Lead Researcher

   University of Cape Town

   +27(0)21 650 1860

2. Rosanna Boyd
   Local Researcher
   CDC Botswana
   367-2432

You can contact the following people for questions about your rights as a participant in this study:

3. Health Research Development Committee (HRDC)
   Botswana Ministry of Health

   363-2000

4. Health Research Ethics Committee (HREC)
   University of Cape Town

   +27 (0) 21 406 6338

What are the next steps?

Please take your time to think about this and ask any questions you have. You can ask as many questions as you like.

The information that we get from this survey will be very important and useful. We would like to tape record your answers to make sure that we do not miss anything that you say. We will keep your responses confidential by (1) not sharing this information with anyone not involved in the study (e.g., the media) and (2) not having your name mentioned on the recording (e.g. using a Participant ID Number). If you do not want for this to be recorded, we can do the interview without recording, it will just take more time so that no information is missed.

Do you agree to participate in this survey? ____Yes _____No

Do you agree to have this interview recorded? ____Yes _____No

Signature of participant: _____ (Please note this page with your signature will not be kept in the same place with your answers to the questions).

Patient Information:

1. Gender: _____ Male _____Female
2. Age: _____
3. Marital Status:

   _____Single never married

   _____Single divorced

   _____Married

   _____Cohabitating

   _____Other: _____
4. Number of people you live with: _____
5. Education level:

   _____ Advanced/college

   _____Primary

   _____Secondary

   _____No formal education

   _____Other: _____
6. Occupation:_____
7. Village: _____
8. Nationality: _____
9. Patient status:

   _____ Inpatient

   _____Outpatient

Patient Knowledge/Attitude:

10. How do you think you got MDR-TB?
    Probes: Before you got sick, did you know anyone else who had been sick or had TB?

11. Are people with MDR-TB discriminated against in the community?
    Probes: Should people tell others? Are certain people discriminated against more (i.e. men vs women)?
    b) Does anything worry you about having MDR-TB?
    Probes: Fear of job loss? Is your job waiting for you afterwards?

12. How did you feel when you found out you had MDR-TB?
    Probes: Did you inform friends/family? Any relationships change?
    Do you have children? Were children or other family / friends screened for TB? Outcome?
    For inpatients: Do any of your family or friends visit you here?
13. Women: Do you need permission from husband, boyfriend or family to access health services? Men: Do women in the community need permission from husband, boyfriend or family to access health services?

Access to MDR-TB Diagnosis and Treatment:

14. a) Do you have any challenges accessing / coming to this health facility?
    Probes: Distance, Transport availability and cost?, Easy to get an appointment?
    b) Do you ever use a different facility for getting treatment or care? Experience? Challenges?
    Probes: Distance, Transport availability and cost?, Easy to get an appointment?
15. a) Have you ever been hospitalized for MDR-TB? For how long?
    b) How do you compare receiving care in the hospital versus in the community/local clinic?
    Probes: Why? Any challenges?

16. Please describe the process for your receiving and taking MDR-TB medication. What was the difference between taking your medication during hospitalization and when you come to the clinic?
    Probes: Where do you receive medication? Meds always available? If no, explain. Who helps you remember to take meds? Any challenges?

Health Seeking Behavior:

17. Have you had TB before?
    Probes: If yes, when? List all TB episodes. Please describe treatment (any problems, were you able to complete treatment?).
18. How long were you sick this time before seeking treatment?
    Probes: What symptoms did you have? If there was delay: Why?

Estimation of delays:

19. How long (weeks or months) after seeking treatment did you hear that you have MDR-TB? Where (facility) did you hear you had MDR-TB? After hearing you had MDR-TB, how long (weeks or months) did it take to start treatment? How could these delays be reduced, in your opinion?

Sources of information:

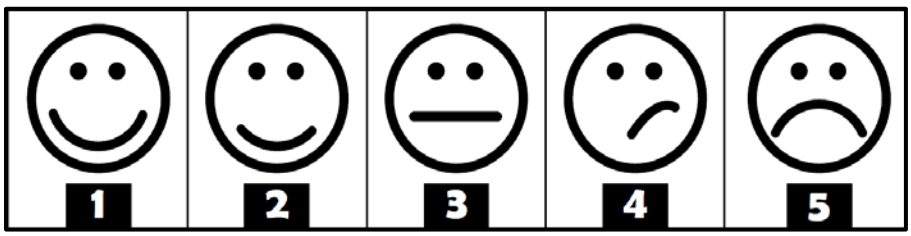
20. Where do you receive most of your health information? Do you receive any health information from family/friends?
    Probe: Had you heard about MDR-TB before you were diagnosed? If yes, where/how

Patient Satisfaction/Feedback on Providers:

21. Please use the provided scale to answer the following questions:

(Likert scale below to be provided on a separate card to patients)

a	Are the health care providers at the hospital supportive and respectful of people who have MDR-TB?	**1 2 3 4 5**
b	If not, in your opinion, why not?	
c	Are the health care providers at your local clinic supportive and respectful of people who have MDR-TB?	**1 2 3 4 5**
d	If not, in your opinion, why not?	
e	Before coming for diagnosis/ treatment, did you expect that the providers would be supportive and respectful of people who have MDR-TB?	**1 2 3 4 5**
f	Have health care workers at this facility answered all of your questions concerning MDR-TB?	**1 2 3 4 5**
g 1)	Are you satisfied with the schedule at the hospital?	**1 2 3 4 5**
g 2)	Are you satisfied with the schedule at your local clinic?	**1 2 3 4 5**
h 1)	Are you satisfied with the waiting time at the hospital?	**1 2 3 4 5**
h 2)	Are you satisfied with the waiting time at your local clinic?	**1 2 3 4 5**
i 1)	Are you satisfied with the availability of drugs at the hospital?	**1 2 3 4 5**
i 2)	Are you satisfied with the availability of drugs at your local clinic?	**1 2 3 4 5**
j 1)	Are you satisfied with your treatment partner/ DOTS supporter at the hospital?	**1 2 3 4 5**
j 2)	Are you satisfied with your treatment partner/ DOTS supporter at your local clinic?	**1 2 3 4 5**



Questionnaire – Health Clinic Staff (Health Care Providers)

Date of interview	DD		MM		YY	
Interview location						
Job Title/ Position						
ID no.						

Informed Consent – Health Clinic Staff (Health Care Providers) (Flesch-Kincaid Grade Level = 5.7)

Hello. My name is _____, and I am working on a study to learn about and improve health care for MDR-TB patients.

Why is this study being done?

We are doing this study to learn more about how people in Botswana find out if they have MDR-TB. We also want to learn more about how people get the care they need when they have MDR-TB. This study has been approved by research ethics committees at the Botswana Ministry of Health, the University of Cape Town in South Africa and the Centers for Disease Control (CDC). All of these groups are involved in the study.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you are a health care provider. You have important information about how people find out they have MDR-TB and about the linkage to health care. This information will help us learn about the MDR-TB health care system in Botswana.

How many people will take part in this study?

We will talk to 5-10 health care providers and will also talk to patients and government workers.

What will happen if you decide to take part in this study?

We will ask you some questions about being a health care provider. This will take about 30-45 minutes. You do not have to answer every question. If there are any questions that you do not want to answer, that is ok. After we finish this survey, your participation will be finished. We will not contact you again to answer more questions for this study.

What are the risks of taking part in this study?

You may find some of the questions hard to answer. If any of the questions upset you, we will give you the names and phone numbers of people that you can talk to about this. Also, it is possible that someone outside the study could see this data, but we will be very careful not to let this happen. Your name will not be kept in the same place with this data, and all documents will be kept in locked areas at all times.

Who will see the information that you provide during the study?

First of all, we will not put your name on the survey so no one will know that you are the person giving these answers. Also, only the people involved in the study will be able to see your answers. These study staff have been trained to make sure the information is kept confidential. We will keep this survey in a locked office and in a locked cabinet. The consent form with your signature will not be kept with the survey so that no one can link you to your answers.

Are there any benefits for being in the study?

There are no direct benefits from participating in this study. The main benefit of participating is this study is that we will share what we learn with the Ministry of Health. So this may benefit you by increasing understanding of the issues and improving health care services.

What other choices do you have?

If you do not want to be in the study, that is ok. Participating in the study is voluntary. You can say no, and we will not ask you again. Your choice will have no effect on your job. Your employer will not know if you have participated or not.

Who do you speak to (or contact) if you have questions or concerns about the study?

This study is being done by people at the University of Cape Town in South Africa, the Botswana Ministry of Health and the Centers for Disease Control Botswana (CDC Botswana).

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You can contact the following people for questions about your rights as a participant in this study:

3. Health Research Development Committee (HRDC)
   Botswana Ministry of Health

   363-2000

4. Health Research Ethics Committee (HREC)
   University of Cape Town

   +27 (0) 21 406 6338

What are the next steps?

Please take your time to think about this and ask any questions you have. You can ask as many questions as you like.

The information that we get from this survey will be very important and useful. We would like to tape record your answers to make sure that we do not miss anything that you say. We will keep your responses confidential by (1) not sharing this information with anyone not involved in the study (e.g., the media) and (2) not having your name mentioned on the recording (e.g. using a Participant ID Number). If you do not want for this to be recorded, we can do the interview without recording, it will just take more time so that no information is missed.

Do you agree to participate in this survey? ____Yes _____No

Do you agree to have this interview recorded? ____Yes _____No

Signature of participant: _____ (Please note this page with your signature will not be kept in the same place with your answers to the questions).

Health Clinic – General

1. What is the average distance that people travel to come to this facility?
   Probes: What is the furthest distance people travel? How do people travel?

2. What days of the week is the clinic open and seeing confirmed or presumptive TB/MDR-TB patients?

3. How many cases of MDR-TB are diagnosed per month at the clinic? How many are currently on treatment at the clinic? (Hospital vs Ambulatory)

4. Do you think that people in this district have good access to MDR-TB services? Do you think overall in the country that people have good access to MDR-TB services. Please explain.

Capacity Building

5. Do you treat patients with MDR-TB?
   Probe: If yes, did you receive any training on MDR-TB? If yes, how often? Adequate?

6. Do you have guidelines on the management of MDR-TB available in the facility?
   Probe: If you have questions about a case, who do you call?

7. Do you have a TB focal person in the facility?

Diagnosis and Treatment (Access, Delays)

8. Is this facility a reference center for MDR-TB suspects? If yes, from where do you receive referrals?

9. On average, how long are MDR-TB patients symptomatic before they present to the clinic to be screened? (days, weeks, months)

10. On average, how long does it take to diagnose a symptomatic patient with MDR-TB in this facility? (days, weeks, months)
    Probe: Where are samples sent? How do you receive the results?

    a) How long does it take to have AFB culture results?

    b) How long does it take to have DST results?

    c) How long does it take to have Gene Xpert results (if applicable)
11. Do you think there are overall delays for MDR patients to start treatment? Is it common for patients to experience delays? What do you think are the main reasons for delay?

12. How often are samples sent from the health facility to the NTRL for testing?
    Probes: are specimen refrigerated if collection takes more than 24 hours? Any challenges?

13. When was Xpert installed in the district? How is it going? Any interruption in use of the machine? What is done when you receive a RR+ from Xpert?

14. What do you think are the effects of using Xpert in the districts?
    Probes: Numbers of people diagnosed, time to diagnosis, time to treatment? Any concerns? Reagent availability?

15. In your opinion, are lab services in the districts adequate? What is needed?

16. What is the average time taken from getting MDR-TB diagnostic results to starting patient on treatment? (days, weeks, months).
    Probe: How are patients notified of results?

17. When is empiric treatment given? How often? Who makes that decision?

18. Do you have second line drugs available to treat MDR-TB?
    Probe: Has the facility/district experienced any shortages of MDR-TB drugs in the past year? If yes, for how long? Why? Did it result in treatment interruption?

19. Where do most patients receive MDR-TB treatment throughout course of treatment (hospital vs. home)? Any challenges?

20. Do you ever receive results for patients that are diagnosed with MDR-TB and then they do not start treatments? How often (per month)? What are the reasons for that? (able to contact, refusal)

21. Who do you think is most vulnerable for MDR-TB? Are vulnerable groups for MDR-TB being identified? Probe: Are the groups being actively approached for TB/MDR-TB screening? Describe.

22. Is active case finding conducted for MDR-TB diagnosis? In which circumstances is active case finding conducted? Please describe. Are family members of diagnosed patients routinely screened? Describe this process? Is it done consistently per recommendations?

23. In general, what are the major challenges in diagnosing and treating TB?

Patient education and support

24. Does this facility offer education and counseling for MDR-TB patients?

    Probe: If yes, please describe. What topics are covered? Who provides these services?

25. When most MDR-TB patients first come to the facility, do they have knowledge about MDR-TB?
    Probe: Is the knowledge complete/correct?

26. Are there support groups for MDR-TB patients? If yes, please describe.

27. Are MDR-TB services free of charge for all patients?
    Do MDR-TB patients receive food/nutrition support?
    Do MDR-TB patients receive transportation or financial support for transportation?

28. Overall, do you think that there is anything that can be done to improve MDR-TB diagnosis and treatment in Botswana? Explain.

Appendix C: Systematic Review Protocol and Study Screening Form

Protocol: Systematic review and meta-analysis, time to treatment for RR-TB patients

Primary objective:

- To assess and summarize studies that report on time to treatment for patients diagnosed with rifampicin-resistant tuberculosis in resource limited settings between 2000 – 2015.

Potential secondary objectives:

- To describe common factors influencing time to treatment
- To describe different diagnostic methods' effect on time to treatment (culture, Xpert, etc)

Types of studies:

All study types will be considered; case reports of less than 10 patients will be excluded. Study design will be recorded for sub-analysis.

Inclusion criteria:

- Any studies that report time from diagnosis (however defined) to treatment initiation

Exclusion criteria:

- Case reports
- Studies whose quality of data is deemed unacceptable (see quality assessment section)
- Studies with small sample size (less than 10 persons)

Search strategy:

A standardized search strategy will be designed to generate a comprehensive list of relevant literature from PUBMED. The search will include a combination of key words:

1. Tuberculosis
2. drug-resistant
3. multidrug-resistant
4. rifampicin-resistance
5. rifampin-resistance
6. MDR-TB
7. treatment
8. time
9. delay
10. outcomes

Search strings:

- (((((("tuberculosis" OR "TB"))) AND (("MDR" OR "drug-resistant" OR "multidrug-resistant" OR "resistant" OR "rifampicin resistant" OR "rifampin resistant"))) AND treatment) AND time
- (((((("tuberculosis" OR "TB"))) AND (("MDR" OR "drug-resistant" OR "multidrug-resistant" OR "resistant" OR "rifampicin resistant" OR "rifampin resistant"))) AND treatment) AND delay
- ((((("tuberculosis" OR "TB"))) AND (("MDR" OR "drug-resistant" OR "multidrug-resistant" OR "resistant" OR "rifampicin resistant" OR "rifampin resistant"))) AND treatment) AND outcomes

Secondary references from selected studies will be reviewed to identify publications not captured by the electronic search. Additionally, authors of selected publications may be contacted for clarification or to further stratify already reported data.

Two independent searches will be conducted by two reviewers, each evaluating titles, abstracts and full text articles. Both reviewers will review all titles and abstracts, using the study selection form (Appendix A). The full text articles will be reviewed for all potentially eligible articles based on the initial review of titles and abstracts. The reviewers will divide the full text articles, each reviewing 60% for 10% overlap.

Data extraction:
Data abstraction forms will be used during the initial review of titles and abstracts for eligibility. For the full text review, a database will be developed to capture all relevant variables. Each reviewer will complete the data abstraction forms and database individually and then comparisons will be made and data will be combined for final analysis.
Quality Assessment:
Study quality will be assessed by reviewing the study methodology, availability of adequate data for inclusion and primary outcome of the study.
Data analysis:
Data will be combined, cleaned and analyzed using Microsoft Excel and SAS, STATA and/or SPSS. The objectives will each be analyzed separately.
Variables:
List of potential variables to be captured:

- Title
- Author
- Publication Year
- Study Year(s)
- Country
- Study Design
    - Prospective or retrospective or both
    - Routine setting or research setting
    - Cohort , Case series, Case control, Randomized control studies…
- Sampling method
- Sample size
- Study population / Patient Characteristics
    - Age
    - Gender
    - HIV status
    - MDR classification (for example if they are only looking at previously treated cases, etc. – probably unlikely)
    - DR profile
    - Special population (prisoners, etc.)
- Diagnostic testing method (s)
- Patient outcomes
    - Time to culture conversion
    - Treatment success
    - Death rate
- How the study calculated time to treatment (from first patient visit, from date of sputum collection, from date of result received)
- MDR rate/burden in the study setting
- Model of care for DR-TB treatment in setting (ie. centralized, specialist hospital vs ambulatory, decentralized)
- Laboratory setting (TB/MDR diagnosis centralized or decentralized)
- Eligible study (Yes or No)
- Time from diagnosis (however defined) to treatment start (median, mean, range, IQR)
- Treatment regimen (standardized or individualized)

Study Screening Form

First Author's last name _____
Journal _____
Publication Year _____ Volume_____ Issue_____ Pages_____
Step One:
Determine whether the article meets all of the eligibility criteria. Circle the response.

1. Does the study population include RR-TB patients? YES NO
2. Does the study report on time to treatment initiation? YES NO
3. Is the study population 10 persons or more? YES NO

If the study did not meet all three study criteria (if you answered no to 1 or more questions above) **STOP HERE**.
If the study did meet all three study criteria (if you answered yes to ALL questions above) please proceed to the full text review using the Systematic Review Database Excel form.

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