Linkage to treatment following RR-TB diagnosis in the Western Cape

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DECLARATION

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Abstract

Background: Patients diagnosed with rifampicin resistant (RR) tuberculosis (TB) in South Africa frequently fail to link to appropriate drug resistant (DR) TB treatment. The aim of this study was to explore barriers and enablers to expedited linkage to treatment following RR-TB diagnosis in the Western Cape Province, within the context of ongoing decentralisation of DR-TB services and the scale-up of Xpert MTB/RIF diagnostics.

Methods: An embedded case study approach, using qualitative research methods, was employed to explore barriers and enablers to expedited treatment linkage following RR-TB diagnosis. The case of investigation in this study was 'treatment linkage following RR-TB diagnosis in the Western Cape Province during the ongoing decentralisation of DR-TB services and scale-up of Xpert diagnostics'. DR-TB is used in this study as an encompassing term to refer to RR, multidrug resistant and extensively drug resistant TB. The embedded units of analysis in this study were patients' linkage outputs, defined as: (1) expedited treatment initiation, (2) delayed treatment initiation and (3) non-initiation of treatment following sputum collection on which RR-TB was diagnosed. Seventeen patient, 8 family member, 49 healthcare worker and 4 key informant open-ended, in-depth interviews were conducted and 59 patient folders were reviewed. Additionally, an extensive literature review was conducted. The tools used for data collection in this study were developed from the literature review and Coker et al.'s (201) conceptual framework for evaluation of a communicable disease intervention. A framework approach using Coker et al.'s conceptual framework was applied for analysis.

Results: This study identified multiple factors that enabled and constrained expedited treatment linkage following RR-TB diagnosis. Enabling factors included: 1) the availability of

clinic level DR-TB counsellors and tracers; 2) living in walking distance of decentralised services and 3) having a strong social support network. Constraining factors included: 1) low usage of Xpert diagnostics, 2) delays in acting on results and missed (or unseen) results, 3) rotation of nurses or the lack of dedicated TB nurses in clinics, 4) limited clinic-level administrative support, 5) information systems challenges and 6) waiting lists for beds and limited access to transport services in rural areas.

In linking to treatment, patients commonly face challenges due to competing subsistence needs and household or employment responsibilities. Additionally, substance addiction, having a history of treatment interruption, hopelessness regarding treatment, as well as not having a stable place to stay or social support may increase patients' risks of linkage failure.

Conclusion: Within the Western Cape Province there is significant opportunity to improve linkage to treatment through strengthening the health systems mechanisms to link patients to treatment following RR-TB diagnosis. Expanding access to psychosocial services (substance abuse rehabilitation and psychosocial evaluations) following RR-TB diagnosis may assist in linking high risk patients to treatment. Additionally, the provision of food support (in addition to social grants) should be evaluated as a tactic to improve treatment linkage and adherence.

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Contributions of the Linkage Study staff and my supervisors to this dissertation research

Task	Performed by
Development of the protocol	Catherine Tomlinson with input from Veloshnee Govender, Helen Cox and Lindy-Dickson Hall
Organisation of NHLS and EDR data for patient sampling	Matthys Kroon and Jessica Workman
Development of interview guides	Catherine Tomlinson with input from Christa Oosthuizen, Sheily Busisiwe Ndwayana and Veloshnee Govender
Training of interviewers	Catherine Tomlinson
Conducting interviews	Catherine Tomlinson, Christa Oosthuizen, Sheily Busisiwe Ndwayana, Portia Ngondeka and Riyaad Hendricks
Extraction of data from patients hospital folders	Catherine Tomlinson, Christa Oosthuizen, Sheily Busisiwe Ndwayana, Portia Ngondeka and Riyaad Hendricks
Organising and coding of data	Catherine Tomlinson with input from Veloshnee Govender and Marsha Orgill
Organisation of sample patients' diagnostic data from the NHLS, and review of all types of test performed in the Western Cape	Matthys Kroon and Jessica Workman
Data analysis	Catherine Tomlinson with input from Veloshnee Govender and Marsha Orgill
Write-up of study findings	Catherine Tomlinson with input from Veloshnee Govender and Marsha Orgill

Dissertation contents

Glossary

Tuberculosis (TB): Tuberculosis or TB is an infectious illness that is spread through air-borne bacteria in the respiratory fluids of people with active TB.

Drug susceptible TB (DS-TB): Drug susceptible TB or DS-TB is regular TB that is not resistant to any of the main medicines used to treat TB. DS-TB is treated with a combination of medicines - comprising of rifampicin, isoniazid, ethambutol and pyrazinamide - that are taken daily for a period of 6 months.

Drug resistant TB (DR-TB): For the purposes of this study, drug resistant TB or DR-TB is used as an encompassing term to talk about all types of drug resistance, including rifampicin-mono resistant TB, multi-drug resistant TB and extensively-drug resistant TB.

Rifampicin resistant TB (RR-TB): For this study rifampicin resistant TB or RR-TB is used to indicate that a patient has been diagnosed with rifampicin resistant TB and should be started on a standard MDR-TB regimen while awaiting the results of further resistance testing. Further resistance testing should be performed on patients diagnosed with RR-TB to determine whether the patient has rifampicin-mono resistant TB, MDR-TB or XDR-TB.

Rifampicin-mono resistant TB: Patients that are resistant to rifampicin, while remaining susceptible to isoniazid, are categorised as rifampicin-mono resistant. While these patients are not categorised as multi-drug resistant, they should be treated with standard MDR-TB treatment regimens, in combination with isoniazid.

Multi-drug resistant TB (MDR-TB): Patients that are resistant to both rifampicin and isoniazid are categorised as multi-drug resistant. These patients should be treated with standard MDR-TB regimens. Depending on the time of a patient's culture conversion, this regimen should be taken for 18 months to 2 years.

Extensively-drug resistant TB (XDR-TB): Patients that are resistant to rifampicin and isoniazid, plus at least one fluoroquinole (moxifloxacin, levofloxacin, ofloxacin) and one injectable (kanamycin, amikacin, capreomycin) are categorised as extensively-drug resistant. Patients with XDR-TB should be treated with South Africa's standard XDR-TB regimens or, preferably, with individualised regimens that reflect patients' drug susceptibility profiles.

Linkage to treatment/ Treatment linkage: Linkage to treatment and treatment linkage are used interchangeably throughout the dissertation. Linkage to treatment is defined as the initiation of an appropriate DR-TB regimen (according to available resistance results) following diagnosis of RR-TB. Patients are defined as 'linked to treatment' if they initiated drug resistant TB treatment for the episode of DR-TB under investigation, regardless of whether or not treatment was completed.

Non-initiators: Patients that did not initiate DR-TB treatment within six months of sputum collection on which RR-TB was diagnosed are defined as 'non-initiators'. In academic literature, these patients are also defined as initial defaulters.

Expedited initiators: Patients that initiated treatment within one month of the date that sputum collection, on which RR-TB was diagnosed, are defined as 'expedited initiators'.

Delayed initiators: Patients that initiated treatment more than one month and less than six month of the date of sputum collected, on which RR-TB was diagnosed, are defined as 'delayed initiators'.

Lost to follow-up/ Loss to follow-up: Patients that are defined as 'lost to follow-up' are patients that cannot be traced by the health system if 'loss to follow-up' occurs. Loss to follow-up may occur due to health system and patient factors, and the interactions between these factors. This may occur when inadequate information is collected from patients in order to locate and communicate with them further. Loss to follow-up may also occur when health facilities' procedures and systems for tracing patients are inadequate.

Diagnostic delay: Diagnostic delays are defined as delays between the collection of sputum and the processing of results.

Action delay: Action delays are defined as delays between processing diagnostic results and recalling patients.

Missed results: Missed results are defined as results that were never seen by HCWs at diagnosing and/or referral facilities.

Centralised treatment initiation: In this study, centralised treatment is defined as hospital-level treatment initiation.

Decentralised treatment initiation: In this study, decentralised treatment is defined as clinic-level treatment initiation.

Coker et al. domains: In their conceptual framework for comparative analysis of communicable disease interventions, Cocker et al. define key domains for consideration, which include: 1) context, 2) epidemiological problem, 3) intervention, 4) output and 5) outcome.

Context: A key domain of Coker et al.'s framework, context "denotes the political, legislative, social, economic and technical environments within which communicable disease control programmes sit" (Coker et al., 2010, p. i23). Context encompasses the local, regional and international environments in which the programme is operating, which may enable or constrain programmatic success.

Epidemiological problem: A key domain of Coker et al.'s framework, epidemiological problem "refers to infection levels and various diseases characteristics" (Coker et al. 2010, p. i23) that the health programme seeks to respond to. For this study, the epidemiological problem refers to large burden of DR-TB, coupled with high rates of HIV co-infection. The epidemiological problem also encompasses the low rate of treatment linkage, which drives onward transmission of DR-TB.

Intervention: A key domain of Coker et al.'s framework, intervention refers to "the intervention intended to serve public health" which are generally "recommended through clinical and policy guidelines and are evidence-based, thus lending themselves to scrutiny against gold standards" (p. i23). The interventions of focus in this study are the Xpert rollout and the decentralisation of DR-TB services.

Mechanisms: A key domain of Coker et al.'s framework, mechanisms refer to the "mechanism(s) by which interventions are delivered", as such it encompasses the "mechanisms within a programme, required to function effectively" (Coker et al., 2010, p. i23). Coker et al. link mechanisms to the health system functions - representing the functions of the health system necessary to implement the intervention.

Output: A key domain of Coker et al.'s framework, output refers to "public health concepts that can be measured or determined and include equity, acceptability, efficiency and effectiveness of the control programmes as a result of interventions" (p. i23). This study will use outputs of treatment linkage (expedited, delayed and non-initiation of treatment) as selection criteria for patients.

Outcome: A key domain of Coker et al.'s framework, outcome refers to the impact of the intervention and health programme on the epidemiological problem, "such as reduced incidence of disease or decreased mortality" (p. i23).

Patient: In this study, Coker et al.'s framework has been amended to include 'patient' as an additional key domain. This study has drawn from Shippee et al.'s (2012) model of patient complexity to define the patient domain. In this study, the *patient* domain encompasses factors arising from patients' workloads and capacity as defined by Shippee et al.

Patient workloads: Adopting Shippee et al.'s definition, patient workloads "encompasses all the demands in patients' lives, including everyday responsibilities alongside the demands of patient-hood… includ[ing] job, family, travel/transportation, childcare, scheduling and attending clinical appointments" (p. 1042).

Patient capacity: Adopting Shippee et al.'s definition, patient capacity "denotes the resources and limitations affecting patients' ability or readiness to do [patient-related] work, such as mental/physical functioning, unpleasant symptoms… pain, stress, or fatigue… Capacity also encompasses socioeconomic and psychological resources, literacy, language, and social support..., [as well as patients'] attitudes and beliefs about health care" (p. 1043).

Dimensions of access: In their conceptual framework for measuring access, McIntyre et al. (2009) define 3 dimensions of access: availability, affordability and acceptability.

Availability: Adopting McIntyre et al.'s (2009) definition, "availability is concerned with whether the appropriate health care providers or services are supplied in [the right manner] to meet the prevailing needs of the population" (p. 184)

Affordability: Adopting McIntyre et al.'s (2009) definition, "affordability is concerned with the 'degree of fit' between the full costs to the individual of using the service and the individual's ability to pay" (p. 186)

Acceptability: Adopting McIntyre et el.'s (2009) definition, "acceptability is concerned with the fit between provider and patient attitudes towards and expectations of each other" (p. 187).

Acronyms

CCW: Community care workers

HCW: Healthcare worker

DS-TB: Drug susceptible TB

DR-TB: Drug resistant TB

EDR: National electronic DR-TB registry

KI: Key informant

MDR-TB: Multidrug resistant TB

RR-TB: Rifampicin resistant TB

NDoH: National Department of Health

NHLS: National Health Laboratory Services

TB: Tuberculosis

WHO: World Health Organisation

XDR-TB: Extensively drug resistant TB

Xpert: Xpert MTB/RIF diagnostic

Part A:
Protocol

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Introduction

Over the past decade, South Africa has witnessed an increasing burden of drug resistant (DR) tuberculosis (TB). Between 2004 and 2012, the number of laboratory diagnosed cases of multidrug-resistant (MDR) TB rose from 3,219 to 14,161. During this time, the number of extensively drug-resistant (XDR) TB cases rose from 85 to 1,545 (Ndjeka, 2013).

South Africa's efforts to curb DR-TB have historically been plagued by poor case detection and long delays to diagnosis and treatment initiation (Streicher et al., 2012). Seeking to improve case detection and linkage to treatment, the National Department of Health (NDoH) embarked on a national rollout of the Xpert MTB/RIF diagnostic tools during 2011. Since March 2011, the NDoH has placed 284 testing machines in sites around the country and performed more than 2 million tests (NHLS, 2013, p. 3).

However, as DR-TB case detection has improved, treatment rates have failed to keep pace - leading to a widening treatment gap. According to NDoH estimates, less than half of patients diagnosed with MDR-TB initiated treatment during 2012 in the Western Cape and nationally (Ndjeka, 2013).

The study will use a qualitative, embedded case study approach to explore barriers and enablers to expedited treatment linkage following diagnosis of rifampicin resistant TB (RR-TB). RR-TB is a good marker of multi drug resistance as around 90% of patients that are resistant to rifampicin are also resistant to isoniazid and are therefore categorised as MDR. (Coovadia et al., 2013; Dlamini-Mvelase et al., 2014). The case in this study is 'linkage to treatment following RR-TB diagnosis in the Western Cape during the Xpert rollout and ongoing decentralisation of DR-TB services.' The embedded units of analysis are patients' treatment linkage outputs, defined as: expedited initiation of treatment, delayed initiation of

treatment and non-initiation of treatment following sputum collection on which RR-TB was diagnosed.

Thirty six RR-TB patients diagnosed between January and March 2013 in the Western Cape will be purposively sampled as data sources for the embedded units. Although, additional patients may be sampled to achieve data saturation. Patients that initiated treatment within one month of sputum collection on which RR-TB was diagnosed will be categorised as expedited initiators. Patients that initiated treatment more than one month and less than six months after sputum collection on which RR-TB was diagnosed will be categorised as delayed initiators. Finally, patients that did not start treatment within 6 months of sputum collection on which RR-TB was diagnosed will be categorised as non-initiators.

Each sample patient's journey will be investigated through a combination of patient record review and multiple perspective interviews. Multiple perspective interviews will be conducted with patients, their family members and healthcare workers. Additional key informants may also be identified and interviewed during the research period. A framework approach, using Coker et al.'s (2010) conceptual framework for evaluation of communicable disease interventions in the health system, will be applied to analyse data.

Purpose of the study

The aim of this study is to investigate why patients diagnosed with DR-TB in the Western Cape frequently fail to link to timely treatment. Seeking to understand this phenomenon, the study will explore barriers and enablers to expedited treatment linkage following RR-TB diagnosis in the Western Cape. The study will explore how health system, contextual and patient

factors, and the interactions between these factors, contribute to: 1) expedited initiation of treatment, 2) delayed initiation of treatment and 3) non-initiation of treatment.

Background

Xpert rollout

Historically, South Africa's efforts to curb and treat DR-TB have been hampered by poor case detection (MSF, 2011), as well as delayed diagnosis and initiation onto treatment (NDoH, 2011b). Recent studies in KwaZulu-Natal revealed delays ranging between 72 and 93 days between the collection of sputum and initiation of MDR-TB treatment (Loveday et al., 2013; Narasimooloo & Ross, 2012). Troublingly, two studies in South Africa found that over a third of MDR-TB patients died prior to receiving their test results (Gandhi et al., 2010; Heller et al., 2010).

During 2011, the NDoH embarked on a national rollout of Xpert MTB/RIF diagnostic tools in an effort to improve DR-TB case detection and reduce diagnostic turn-around times (NDoH, 2011a). The Xpert MTB/RIF is an automated diagnostic tool that achieves more sensitive and accurate diagnosis of TB than traditional smear microscopy, particularly amongst patients co-infected with HIV (Menzies et al., 2012). The Xpert is also able to detect rifampicin resistance in less than two hours (Menzies et al., 2012), allowing for early treatment initiation. Patients that are resistant to both rifampicin and isoniazid are categorised as multidrug resistant (MDR-TB). Patients that are resistant to rifampicin, isoniazid, any fluoroquinolone and at least one injectable second-line TB drug are categorised as extensively drug resistant (XDR-TB) (WHO, 2008).

Following the Xpert rollout, a large increase in the number of patients diagnosed with MDR-TB (Ndjeka, 2013) and a reduction in diagnostic turn-around time has been observed

(Claassens et al., 2013; Naidoo et al., 2013; Niekerk et al., 2013). According to NDoH figures, a 48% increase in the number of laboratory confirmed MDR-TB cases was observed between 2010 and 2012. However, during the same period, the percentage of laboratory diagnosed MDR-TB patients that are reported to have not started treatment increased from 28% to 54% (Ndjeka, 2013).

While these figures may be subject to some error due to problems with the NDoH monitoring and evaluation systems (Rose et al., 2013), they highlight a widening gap between the number of patients diagnosed with DR-TB versus those initiated onto treatment. The health system's failure to link DR-TB patients to timely treatment is not only harmful to the health of patients, but also to the wider community, as delayed treatment significantly contributes to a patients' risks of onward transmission of DR-TB (Cox et al., 2010; Ebonwu et al., 2013).

2011 Decentralisation guidelines

The 2011 national Xpert rollout was not introduced within a static DR-TB programme or health system. Rather, the rollout was coupled with the adoption of national guidelines for the decentralisation of MDR-TB treatment (NDoH, 2011b). The 2011 MDR-TB decentralisation guidelines recommend that sputum smear-negative MDR-TB patients and patients that refuse hospitalisation are initiated onto out-patient treatment - recognising that traditional, centralised hospital sites are increasingly unable to accommodate the rising number of patients with MDR-TB (NDoH, 2011b).To date, there have been few evaluations of the extent to which the decentralisation guidelines have been successfully implemented across the country. However, a recent article described implementation of MDR-TB treatment decentralisation across provinces as 'patchy' (Besada, 2013).

Western Cape context

Incidence of drug susceptible TB in the Western Cape falls amongst the highest in the world (Western Cape Goverment, 2012). The province also faces a high burden of DR-TB. Between 2004 and 2012, 22% of the laboratory confirmed MDR-TB cases detected in South Africa were in the Western Cape (Ndjeka, 2013) - although this is likely due in part to better detection rates than other provinces in the country.

Importantly, within high burden communities, direct transmission, rather than acquired resistance, is becoming the main driver of new DR-TB infections in the Western Cape (Cox et al., 2010). Onward transmission of DR-TB is exacerbated by a combination of poor case detection and late diagnosis and initiation onto treatment (Cox et al., 2010).

Previous research in Khayelitsha, Western Cape has shown that reduced times to treatment can be achieved through decentralising care (MSF, 2011). In line with this evidence, the Western Cape Department of Health has begun to decentralise DR-TB care in the province - although access to decentralised, clinic-level care remains varied across the Western Cape's six districts. Around 80% of patients initiated onto MDR-TB treatment in the urban City of Cape Town during 2013 were initiated at clinics, whereas less than half of patients initiated onto MDR-TB treatment in rural districts were initiated at clinics (Caldwell, 2013; Theron, 2013).

Linkage barriers

Patients commonly face barriers and delays prior to diagnosis and initiating treatment (Jacobson et al., 2013; Naidoo et al., 2013). Previous studies have demonstrated that linkage barriers may occur at many stages along the pathway to care for DR-TB patients.

A 2013 Gauteng cohort study demonstrated that patients' location of diagnosis impacts on linkage to treatment. Patients referred to treatment from clinics were eight times more likely to initiate treatment than patients referred from hospitals. The authors speculated that this may be due to better systems at a clinic level for following up with newly diagnosed patients (Ebonwu et al., 2013).

The initiation of DR-TB treatment at centralised versus decentralised sites further impacts on linkage to treatment. During 2011, Médecins Sans Frontières reported that the decentralisation of MDR-TB care in Khayelitsha improved rates of treatment initiation and reduced time to treatment (MSF, 2011). Similarly, a comparative study in KwaZulu-Natal demonstrated shorter times to treatment amongst patients initiated onto treatment at decentralised sites versus patients that initiated treatment at the centralised hospital (Loveday et al., 2012).

Shortages of beds at centralised sites commonly contribute to linkage delays. According to the NDoH, "waiting lists for patients [who] need to be admitted to centralised units are long, delaying the initiation of treatment in some provinces for three or four months. In addition, several patients die before starting treatment" (NDoH, 2011b, p. 5). Similarly, Jacobson et al. (2013) found that poor clinical infrastructure and a shortage of beds contribute to treatment delays at Brewelskloof Hospital in the Western Cape.

However, while available evidence demonstrates that decentralisation improves linkage to treatment, many areas face challenges in implementing decentralised care. Challenges within Western Cape's rural districts include patients' preferences for in-patient treatment given difficulties in accessing decentralised sites daily and perceptions of better support at hospitals (Theron, 2013).

Surprisingly, given evidence that decentralisation improves linkage, a recent KwaZulu-Natal study did not identify an association between time to treatment and the distance that patients travel between diagnosing and treatment initiating facilities (Smith et al., 2013) - although this may be due to inadequate decentralisation to date. Further research is needed to investigate how costs of, and access to, transport impacts on linkage to treatment.

Shortages of healthcare workers may further encumber linkage to treatment. To address this, the NDoH has identified the need for nurse initiated and managed MDR-TB care (NDoH, 2011b), although this has not been implemented to date. Amongst healthcare workers providing MDR-TB care, inadequate training and confusion regarding DR-TB diagnostic and treatment algorithms further exacerbate treatment delays (Bamford & Taljaard, 2010; Farley et al., 2012).

Along with health facility factors, multiple overlapping patient factors influence linkage to treatment. A recent qualitative study in Cape Town found that patients may miss appointments due to family, financial and employment responsibilities (Niekerk et al., 2013). Similarly, according to the NDoH, patient's household responsibilities may contribute to treatment delays amongst patients referred to centralised services (NDoH, 2011b). For patients that take care of young children in single headed households, initiating in-patient treatment may not be feasible. Importantly, a study in the KwaZulu-Natal found that 70% of MDR-TB patients' households were headed by females (Marra, 2009).

A recent cohort study of MDR-TB patients in Gauteng found that patients that were previously treated for TB or co-infected with HIV face significantly higher risks of linkage failure. The study also found that patients' places of residency significantly influence their risks of linkage failure. Reasons for non-initiation onto treatment identified in the study

included: death (31.2%), loss to follow up (19.8%), refusal (2.6%), or not being traceable (46.4%) (Ebonwu et al., 2013).

Finally, a systematic review of studies examining diagnostic and treatment delays amongst patients with drug susceptible TB found that poor perceptions of public sector care, substance abuse, education, stigma, beliefs and migrancy influence linkage to treatment. Similar factors have been identified as contributing to MDR-TB treatment default in South Africa (Holtz et al., 2006; MRC, 2009) and therefore likely also impact on DR-TB treatment initiation.

Conceptual framework

Given the complex nature of health systems, the Alliance for Health Policy and System Research and the World Health Organization recommend the use of a conceptual framework when undertaking health systems research (Gilson, 2012). The use of a conceptual framework can be employed to navigate and identify the 'complex casual pathways' that influence the outcome of an intervention. The framework can be used to generate hypotheses, organise data and generate explanations for the phenomenon of investigation (Gilson, 2012).

This study will draw on a conceptual framework developed by Coker et al. (2010) in order to allow for comparative analyses of the health systems' effectiveness in implementing interventions to combat communicable diseases. Coker et al. employed the framework in undertaking a cross-country analysis of integration of HIV and TB programmes. The framework has since been adapted to undertake a country analysis of HIV and TB integration in South Africa (Loveday & Zweigenthal, 2011).

Coker et al.'s framework allows for investigation into a complex array of overlapping factors that influence a patient's journey through the health system and whether or not the

patient is linked to the appropriate treatment. The five critical domains for analysis identified within the framework include: context, epidemiological problem, intervention, mechanisms (for implementation of the intervention), output and outcome. For the purposes of this study, the framework has been amended to investigate critical factors that may impede or facilitate DR-TB patients' pathways to treatment.

Table 1. Amended Coker et al. (2010) framework

Domain	**Health system and patient related factors**
Context	Urban versus rural location
	Economic and socio-demographic context
	Community knowledge, attitudes and beliefs
	Patient's household and employment responsibilities
	Leadership – national, provincial, district, facility
	Location and provincial support
	Staff motivation and attitudes
Epidemiological problem	Incidence of MDR and XDR-TB
	MDR and DR-TB related morbidity and mortality
Intervention	National Xpert rollout – access to Xpert testing tools
	Decentralisation of MDR-TB sites and treatment – access to decentralised versus centralised treatment
	Rapid initiation of rifampicin resistant patients onto treatment
Mechanisms	Diagnostic tools
	Medicines
	Information systems
	Infrastructure – availability of beds
	Transportation
	Human resources
	Staff training
	Patient education
Output	Accessibility of care
	Quality and acceptability of care
Outcome	Expedited initiation of treatment
	Delayed initiation of treatment
	Non-initiation of treatment

Study hypothesis

It is anticipated that numerous, overlapping health system factors contributing to linkage barriers will be identified in this study – as seen in previous linkage literature. However, with the recent adoption of decentralisation guidelines in South Africa, it is hypothesised that: 1) level of decentralisation, 2) location of care, 3) availability of transport, and 4) living in an urban versus rural area will emerge as important factors influencing patients' linkage to treatment outputs.

Methodology

Study design

The study will use a qualitative, embedded case study approach in order to explore how health system, contextual and patients factors, and the interactions between these factors, impact on linkage to treatment. The case in this study is 'linkage to treatment following RR-TB diagnosis in the Western Cape during the Xpert rollout and decentralisation of DR-TB services'. Embedded units of analysis are patients linkage to treatment outputs, defined as: expedited treatment initiation, delayed treatment initiation and non-initiation of treatment. Thirty six patients will be purposively sampled to explore as data sources for the embedded units. Additional patients in each embedded unit may be sampled to achieve data saturation.

Each purposively sampled patient's journey will be mapped out through reviewing their medical records and conducting multiple perspective interviews with the patient, a family member of the patient and a healthcare worker that provided care to the patient between RR-TB diagnosis and treatment initiation. Interviews with additional key informants may also be conducted in order to achieve data saturation. Comparative analysis of embedded units will be performed in order to draw out explanations regarding why many RR-

TB patients fail to initiate treatment or experience delays in linking to treatment following diagnosis.

Characteristics of the study population

Patient selection criteria

Thirty six patients will be purposively sampled whose experiences following diagnosis will be examined in-depth. Sample patients will be selected from a larger cohort of patients identified in the national 'Linkage to care for drug resistant TB following Xpert implementation in South Africa' study (hereafter referred to as 'the National Linkage Study').

The cohort from the National Linkage Study includes all of the patients that were diagnosed with RR-TB in the Western Cape between January and March 2013. As part of the National Linkage Study, each of these patients will be defined as expedited initiators, delayed initiators or non-initiators. The 36 sample patients selected for this study will include, 12 'expedited initiators', 12 'delayed initiators' and 12 'non-initiators'.

It is anticipated that some patients in the National Linkage Study cohort may have subsequently died. Patients that have died will not be excluded from being sampled, as their journeys may provide important insight regarding the barriers that patients face in linking to treatment. In the event that sample patients have subsequently died, their journeys will be investigated using record review and interviews with family members and healthcare workers.

Amongst expedited and delayed initiators, it is also anticipated that some of these patients will have defaulted from treatment, given the high rates of DR-TB treatment default in the country (Holtz et al., 2006). Both treatment defaulters and patients retained in care will be eligible to be sampled. However, for sample patients that are retained in care, effort will

be made to select patients that are retained in care within one of the study districts and facilities to allow for in-person interviews. This will be done through reviewing their recent NHLS records to determine where their most recent tests were performed. This data is available for the National Linkage Study cohort.

A similar proportion of male and female patients will be selected in order to explore how gender impacts on linkage to treatment. Within each gender group, effort will also be made to select patients with a wide age range - representative of the age range seen in the National Linkage Study cohort - in order to explore how age influences linkage to treatment. Patients under 18 will be excluded given the complexity involved in securing their informed consent to participate in the study.

District and facility selection criteria

Figure 1: Western Cape districts

With the decentralisation of DR-TB treatment to a primary care level, districts play an increasingly important role in linking patients to treatment (NDoH, 2011b). Sample patients for this study will be selected from 3 districts – the Cape Town metro, the Cape Winelands and the West Coast. Each of these districts has been selected as a 'study district' due to characteristics of interest.

The Cape Town metro has been selected as the only urban district within the Western Cape (Western Cape Goverment, 2012b). The district has spearheaded decentralised DR-TB care in the province, initiating approximately 80% of MDR-TB patients onto treatment at a primary level during 2013 (Caldwell, 2013).

The Cape Winelands district has been selected as a rural district with low rates of decentralised care. Similarly to the Eden and Central Karoo districts, only around 5% of MDR-TB patients diagnosed in Cape Winelands East initiated treatment at a primary care level during 2013 (Theron, 2013). Finally, the West Coast district has been selected given its relative success in implementing decentralised care in comparison to the other rural districts in the province. Within the West Coast district, approximately 40 – 50% of MDR patients are initiated onto treatment at a primary level (Theron, 2013).

Table 2: Sampling strategy by district and treatment linkage outputs

	Cape Town metro	Cape Winelands	West Coast	Total
Expedited initiators	4	4	4	12
Delayed initiators	4	4	4	12
Non-initiators	4	4	4	12
Total	12	12	12	36

Finally, patients may be sampled due to convenience. In other words, a few sample patients may be chosen from a single facility in order to avoid the need to visit a different facility for each sample patient and to ensure that the study is feasible within available time and resources. Sample patients will be selected from a maximum of seven facilities within each district.

These seven 'study facilities' per district may be primary level clinics, community health centres or hospitals. These facilities should include the facilities where sample patients were

diagnosed, as well as the facilities where patients were initiated onto treatment (when relevant). Additional selection criteria may be clarified once the data from the National Linkage Cohort is reviewed. Additional selection criteria to be reviewed include:

- Initiation of treatment at a clinic versus a hospital
- Distance between the diagnosing and treatment initiating site.

Inclusion criteria

- Part of the National Linkage Study cohort
- Diagnosed and/or initiated onto treatment in the Cape Town metro, Cape Winelands or West Coast district
- Diagnosed and/or initiated onto treatment within one of five facilities per district
- Male or female
- Over 18 years old

Exclusion criteria

- Under 18 years old

Research procedures and data collection methods

Patient record review

Following the identification of sample patients in each district, the facilities that diagnosed each sample patient and/or initiated treatment (if relevant) will be visited in order to review each patient's medical records. It is anticipated that reviewing the records of sample patients will provide important insight regarding why patients did or did not initiate treatment and/or experience a delay in initiating treatment following diagnosis.

A recent study in KwaZulu-Natal demonstrated the richness of data that may be extracted from the medical records of patients with DR-TB. Loveday et al. (2013) identified

numerous barriers that patients face in accessing DR-TB treatment through reviewing clinical notes in medical records – including descriptions of missed appointments due to lack of transport, health facility strikes and medicine stock-outs. A limitation of this method is that the availability of clinical notes in medical records will likely be inconsistent. In reviewing 1549 patient records in KwaZulu-Natal, Loveday et al. found that clinical notes were missing from approximately 15% of records.

Multiple perspective interviews

Data on sample patients' journeys following RR-TB diagnosis will also be collected through undertaking open-ended interviews with patients, their family members and healthcare workers. This approach, known as multiple perspective interviews, involves the triangulation of data from multiple sources regarding one patient's journey. The use of multiple perspective interviews allows for a deeper exploration of the factors that influence linkage to treatment than individual perspective interviews (Kendall et al., 2009).

Multiple perspective interviews are recommended in researching childhood illnesses and palliative care (Kendall et al., 2009). In the case of DR-TB, multiple perspective interviews are particularly valuable for exploring patients' journeys following diagnosis, as some sample patients may have died, or may no longer be traceable.

For sample patients that can be traced, interviews will be requested with the patient and a family member (or alternate carer) nominated by the patient. Interviews will also be requested with the healthcare worker (or healthcare workers) responsible for the patient's care.

For sample patients that have died or cannot be traced, interviews will be requested with the healthcare worker (or healthcare workers) responsible for the patient's care. An

interview will also be requested with the patient's emergency contact and/or an alternate family member nominated by the emergency contact. This method of enquiry is similar to conducting 'verbal autopsies', which are recommended by the World Health Organization when investigating the cause of death in patients where mortality records are unavailable (WHO, 2012). However, in this study the tactic will investigate patients' experiences leading up to death, rather than cause of death.

Finally, patients and family members that consent to be interviewed will be given the opportunity to be interviewed together or separately. Sakellariou et al.(2013) and Kendall et al. (2009) recommend that patients and their family members decide whether or not to be interviewed together, and highlight that joint interviews can provide richer data than individual interviews, as participants may build on each other's explanations to provide a more detailed narrative. Similarly, in the case that more than one healthcare worker provided care to a sample patient in the diagnosing or treatment initiating facility, then the healthcare workers will be given the opportunity to be interviewed jointly or individually.

Key informant interviews

Within each district, additional interviews may be conducted with key informants that are able to provide additional insight regarding the factors that impede or enable linkage to treatment in each district. A flexible approach will be used to identify and recruit key informants during the research process, with the aim of achieving data saturation. Key informants may include district heads of DR-TB services or alternate individuals responsible for over-seeing or providing care.

Interview procedures

The date, time and location of interviews will be arranged over the phone (see recruitment procedures below). For the most part all of the interviews will be conducted with two interviewers present – the principle researcher, as well as an Afrikaans and Xhosa speaking interviewer. Each interview will be conducted in the interviewee's language of preference.

Semi-structured, open-ended interview guides will be used to guide the interviews. Open-ended questions will be used to draw out interviewees perceptions regarding why sample patients did or did not initiate treatment and/or experience a delay. However, as the study is exploratory, the interviewers will not be limited to questions in the guides. The interviewers will be trained to ask probing questions to gain more detail regarding interviewees' responses and to ask reflexive questions in response to new issues that emerge.

All of the interviews will last approximately 30 minutes and will be recorded and transcribed. Field notes will also be recorded after each interview in order to recall observations made during the interviews.

Recruitment, enrolment and data collection strategy

A phased, multi-step approach will be used in order to identify and recruit healthcare workers, patients and their family members to the study. While the multi-step approach adds complexity to the study design it has been selected in order to minimise harm to sample patients and their families.

Step 1: Visit diagnosing and treatment initiating facilities to review patient records

Following the identification of sample patients from the National Linkage Study cohort, the facilities that diagnosed and initiated treatment (when relevant) for each sample patient will be visited. The sequencing of facility visits will be arranged for convenience.

Upon visiting the diagnosing and treatment initiating facilities, each sample patient's records will be reviewed. Clinical notes relevant to why the patient did or did not initiate treatment and/or experience a delay will be extracted by manually copying the clinical notes into the data extraction form. Extracted clinical notes will be stored under a unique patient identifier code.

Step 2: Identify healthcare workers responsible for sample patients' care and request interviews

During initial facility visits, the primary healthcare worker (doctor or nurse) responsible for providing care to the sample patient will be identified through reviewing the patient's records and discussing the patient case with the TB-room/unit manager.

- In the event that the patient never initiated treatment, then the healthcare worker identified as responsible for the patient's care at the diagnosing facility will be requested to consent to be interviewed. (1 interview to be conducted)
- In the event that the patient was diagnosed and initiated treatment at the same facility, an interview will be requested with the healthcare workers identified as responsible for the patient's care. (1 interview to be conducted)
- In the event that the patient was diagnosed in one facility and initiated treatment in another, then an interview will be requested with the healthcare workers identified as responsible for the patient's care at both the diagnosing and treatment initiating facilities. (2 interviews to be conducted).

While the study researchers will seek to identify and interview the primary doctor or nurse responsible for the patient's care at each facility, additional interviews may be conducted if it becomes apparent that additional healthcare workers are able to provide further insight regarding the sample patient (I.e. assistant nurses, counsellors, community health workers).

Additional interviews may be conducted to achieve 'data saturation', which is a central goal of qualitative research. Data saturation is concerned with collecting adequate data in order to generate theory that is balanced and without gaps regarding the phenomenon of investigation (Given & Saumure, 2008).

Step 3: Categorising sample patients for follow up

After reviewing data from the National Linkage Study cohort data, reviewing patients' records and conducting interviews with healthcare workers, sample patients will be categorised as:

- 'Known to be alive'
- 'Known to be dead'
- 'Circumstances unknown'

Patients that are known to be alive will be further defined as 'Retained in care', 'Defaulted care', or 'Never initiated care'.

Step 4: Locating potential participants and requesting their consent to be contacted and participation in the study

The approach to requesting consent from sample patients – or their emergency contacts in the event that sample patients have died or cannot be traced – will be guided by the category in which each patient falls.

<u>Locating patients that are 'known to be alive' and 'retained in care' and requesting their consent to be contacted</u>

Given the study selection criteria, patients retained in care should be receiving treatment from one of the seven 'study facilities' per district. Under these circumstances, the doctor or nurse currently overseeing the patient's care will be identified at the facility and asked to request consent from the patient to be contacted by study researchers.

If sample patients are currently receiving treatment at a facility outside of the 'study facilities', the doctor or nurse that initiated the patient onto treatment will be asked to contact the patient via telephone to request their consent to be contacted via by the study researchers. The feasibility of conducting in-person interviews with these patients will be judged on a case by case basis, taking into account the location of where they are currently receiving treatment.

Locating patient that are 'known to be alive', yet not retained in care and requesting their consent to be contacted

Healthcare workers will also be asked to attempt to contact patients that are defined as 'known to be alive', yet never initiated or defaulted treatment, as well as patients defined as 'circumstances unknown'. The healthcare worker responsible for the patient's care at the diagnosing facility will be asked to contact the sample patient to request their consent to be contacted by study researchers.

In the event that a patient cannot be located, then the healthcare workers will be asked to contact the sample patient's emergency contact to request updated contact information for the patient. If the emergency contact is able to provide updated contact information, then a second attempt should be made to contact patients to request their consent to be contacted by study researchers.

If the emergency contact is unable to provide updated information for the patient, then the healthcare worker should request consent from the emergency contact to be contacted by study researchers.

Contacting patients that provide consent to be contacted and identifying relevant family members

Patients that provide consent to be contacted by the study researchers will be contacted via telephone. Effort will be made to contact patients in their first language, as identified by the

health facility. Upon contacting patients, a standard script will be used by study researchers to request their participation in the study.

Patients that agree to participate in the study will be asked to nominate a family member (or alternate carer) whose participation in the study may be requested. Patients that nominate a family member will be asked to contact the nominated family member to discuss their participation in the study. A follow up call will be arranged to clarify whether the family members is willing to participate in the study and to obtain his/her contact details.

Locating family members of patients that cannot be traced or have died

In the event that a patient cannot be traced or has died, then the responsible healthcare worker at the diagnosing facility will be asked to contact the patient's emergency contact to request their consent to be contacted by study researchers.

Emergency contacts that provide consent to be contacted will be contacted via telephone by the study researchers. A standard script will be used to explain the purpose of the study and effort will be made to contact emergency contacts in their first language. The emergency contact will be asked to consent to be interviewed or to nominate another family member that may be contacted to participate in the study.

In the case that patients have died or cannot be traced, the emergency contact or nominated family member may choose to be interviewed on his/her own or together with another family member that is able to provide additional insight.

Data safety and monitoring

A study database will be developed and housed by the University of Cape Town's Department of Medical Microbiology. Data for this study will be catalogued as a sub-study housed within the secure database developed for the national 'Linkage to care for drug resistant TB following

Xpert implementation in South Africa' study. The National Linkage Study has hired a data manager in order to oversee issues of data security. The database will be securely password protected and only authorised staff members will have access to it.

Audio recordings and transcriptions of interviews will be stored in the study database. Interview recordings will be uploaded to the study database as soon as possible after the interview and deleted from the audio recording device. In the case that access to the study data is requested by researchers outside of the study, access to audio recordings will not be granted. Access to interview transcripts may be granted to other researchers solely for research purposes. All names and other identifiable information will be extracted from the transcripts, which will be stored under unique identifier codes.

The database will also store data collected from medical records. This data will be extracted manually from medical records into data extraction forms. Each form will be given a unique identifier code and no names or other identifiable information will be extracted from records or recorded on the data extraction forms. Data collected using extraction forms will be uploaded to the study database as soon as possible following facility visits and the forms will be destroyed.

Data analysis

The transcripts of open-ended interviews and clinical notes extracted from records will be coded and categorised using NVivo software. Initially, deductive coding will be done, using pre-defined codes and categories drawn out of the themes identified in the conceptual framework. New codes and categories will be created for new themes that emerge from the data and fall outside of pre-existing themes in the conceptual framework. Below is a visual

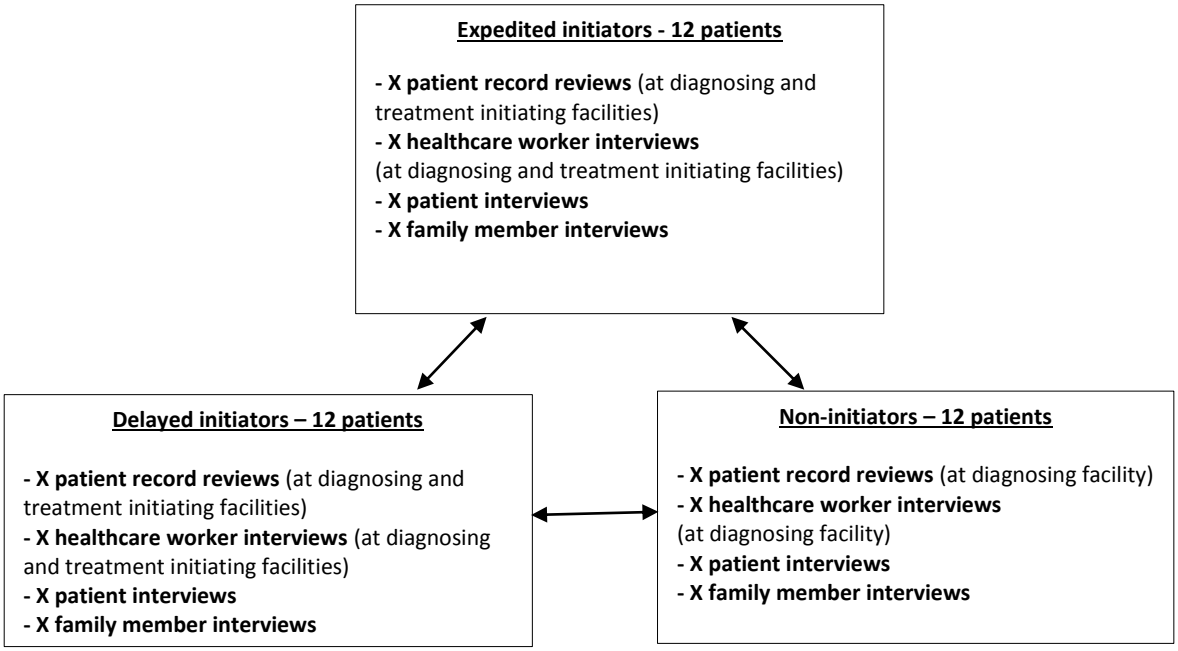
depiction of how data will be summarised following interviews in order to facilitate individual analysis.

	Record review at diagnosing site	**Record review at treatment initiating site**	**Patient interview**	**Family member interview**	**HCW interview at diagnosing site**	**HCW interview at treatment initiating site**
Expedited initiators: Patients 1 – 12						
Patient 1	×	√	√	×	√	√
Details	*Records could not be located*	*Records reviewed*	*Patient interviewed*	*Family member denied consent to be interviewed*	*Nurse interviewed*	*Doctor interviewed*
Patient 2	…	…	…	…	…	…
Patient 3	…	…	…	…	…	…
Delayed initiators: Patients 13 – 24						
Patient 13	√	√	√	√	√	×
Details	*Records reviewed*	*Records reviewed*	*Patient interviewed*	*Grandmother interviewed (jointly with patient)*	*Nurse and counsellor interviewed jointly*	*Healthcare worker no longer working at facility*
Patient 14	…	…	…	…	…	…
Patient 15	…	…	…	…	…	…
Non-initiators: Patients 25 - 36						
Patient 25	√	Not relevant	×	√	√	Not relevant
Details	*Records reviewed*		*Patient died*	*Wife and aunt interviewed jointly*	*Nurse interviewed*	
Patient 26	…	…	…	…	…	…
Total						

Initially, data collected for each sample patient will be analysed in order to develop narrative descriptions of each patient's journeys and to identify why individual patients did or did not initiate treatment and/or experience delays. It is anticipated that both agreements and contradictions will emerge from the multiple perspective interviews. However the aim of this study is not to rank the 'accuracy' or 'importance' of narratives from different sources. Rather it seeks to develop a fuller picture of each patient's experience, as well as illuminate where contradictions and agreements exist.

After the data for each sample patient is analysed individually, comparative analysis of embedded units will be performed in order to draw out explanations and develop theories regarding the main factors that influence linkage to treatment. Sample patients will be grouped and compared across embedded units (i.e. expedited initiators, delayed initiators and non-initiators). Below is a visual summary of how data will be summarised for comparative analysis across embedded units.

Comparative analysis across embedded units



Validity and reliability

In seeking to establish validity in qualitative research, it is necessary to establish the trust-worthiness of the data analysis process and the findings drawn from this process. This is necessary to prevent any subjective biases of the researcher from entering the study's conclusions, as well as to ensure that any causal conclusions drawn from the data are based on logical and replicable processes.

Gilson (2012) and Yin (2014) recommend a number of strategies in order to establish validity when undertaking qualitative research, including using an established framework or theory to guide the data analysis process. In this study, analysis of the study data will be guided by the Coker et al.'s (2010) framework for investigation of health systems interventions for communicable diseases. Along with the use of theory, triangulation of data, peer review and field notes will be used during data analysis in order to strengthen the validity of the study's findings.

Triangulation of data involves using more than one source of data in order to increase the trustworthiness of the study's findings. Data collected from patient records and multiple perspective interviews will be triangulated in order to develop explanations regarding why linkage delays did or did not occur for individual patients. However, for the purposes of this study, data triangulation will not be used to establish the accuracy of interview narratives. Rather triangulation will be used to identify where concordance and contradictions emerge in order to strengthen the study's findings or identify alternate explanations.

Peer review of the data analysis methods, as well as conclusions drawn from the data will be used to further protect against bias. Peer researchers involved in collaborating quantitative and qualitative studies (see Collaboration) will be requested to review the study's data and provide input into conclusions drawn out of the data. Review of the study's findings will also be undertaken by my dissertation supervisors.

Finally, field notes will be drafted after each interview to record observations made during the interview process. Field notes are a useful tool for recalling and making sense of data during the later stage of data analysis. Furthermore, drafting of field notes during the data collection stage assists in ensuring that the researcher remains reflexive throughout this process.

Along with validity, establishing reliability is a concern that must be addressed in conducting qualitative research. Yin (2014) explains that reliability in qualitative research is concerned with the internal reliability of the study's findings and whether the findings would be reproduced if the study was repeated. As recommended by Yin and Gilson (2012), an audit trail will be developed and stored in order to strengthen the reliability of the study's results through allowing the study design, data, methods and conclusions to be audited if requested. A study database will be developed and housed within UCT's Department of Medical Microbiology. All the data extracted from patient records and interview transcripts will be stored in the database.

Limitations

A limitation of this study is that a number of patients may have died, may not be traced or may no longer be located within a study district. For most of these patients, it will not be possible to conduct a patient interview. Another limitation of this study is that clinical notes in patient records will not be consistent (Loveday et al., 2013). An additional limitation of the study is that recall bias may be present in some of the interview narratives. Some recall bias is anticipated given that the sample patients were diagnosed in early 2013.

Finally, for the purposes of this study, interviewers speaking English, Afrikaans and Xhosa will be hired. Patients and family members that do not speak one of these three languages will not be interviewed. However, given that these are the main languages spoken within the province, it is anticipated that few (if any) potential participants will not speak one of these three languages. All of the limitations will be clearly stated in the final study report.

Ethical considerations

Description of risks and benefits/ Reimbursement for participation

Risks and benefits to participants

The main benefit to individual participants will be the receipt of a R100 Shoprite voucher and refreshments during the interview. Additionally, participants that travelled away from home to participate in the study will be reimbursed for their transport costs up to R50.

Patients that have defaulted from DR-TB treatment or never initiated treatment will be encouraged to return to care through a brief treatment literacy session that will conducted by the interviewer after the interview. All participants will also be provided with a simple treatment literacy booklet explaining the importance of adhering to and completing DR-TB treatment in order to protect one's own health and prevent onward transmission.

The study will seek to prevent any personal, social or professional repercussions by ensuring that the identities of all participants remain confidential through removing their names and any other identifiable information from study reports and papers. The names of primary clinics will also be removed to ensure that participants, and particularly healthcare workers, may not be identified through study reports and papers.

Another potential risk to healthcare workers and the surrounding community is that the visits to facilities by study researchers may disrupt normal service functioning. The study will seek to minimise any disruption through communicating with facilities prior to visits in order to identify the most convenient and least disruptive times to conduct visits.

A further risk to participants is that their participation may evoke emotional anxiety or grief, as participating in the interview may raise difficult and painful memories. Careful efforts will be taken to minimise and properly address this risk, particularly when carrying out

interviews with family members or carers of patients that have died. This study will draw from the ethical standards recommended when conducting verbal autopsies with family members of patients that have died.

A key ethical consideration in conducting verbal autopsies is the training of the interviewers that are present during the interview. It is recommended that interviewers receive counselling training prior to undertaking interviews (Chandramohan et al., 2005).This is both to avoid causing distress, as well as to appropriately respond to distress that arises. The interviewers that conduct interviews for this study will undertake a short course in counselling prior to conducting the interviews. Furthermore all participants will be provided with a counselling card listing toll-free numbers that provide counselling and support, including:

The National AIDS Helpline (also provides TB assistance)	0800 012 322
The Depression and Mental Health Helpline	0800 567 567
The Social Grants Helpline	0800601011
The National HIV & TB Health Care Workers Hotline	0800 212 506
Lifeline	0861 322 322

Risks and benefits to interviewers

Another ethical consideration of this study is the risk to interviewers of contracting DR-TB during the interview process. Effort will be taken to minimise this risk by ensuring that infection control procedures are in place during interviews with DR-TB patients. Whenever possible, interviews will be conducted outside. According to the WHO, the risk of contracting tuberculosis when outdoors is very low (WHO, 2012). In the event that interviews with patients cannot be conducted outside, the interviewers will wear N95 respirators during

interviews. Patients and their family members will also be given the option to wear N95 respirators during interviews.

Informed consent process

Consent will be obtained through a multi-stage process. Prior to contacting patients or their emergency contacts to request their participation in the study, consent must be obtained from the patient or emergency contact to be contacted by study researchers. Healthcare workers responsible for sample patients' care will be asked to contact sample patients and/or their emergency contacts to request their consent to be contacted by study researchers. Patients and emergency contacts that provide consent to be contacted by study researchers will be asked to assist in identifying family members or alternate carers that may also be contacted to request their participation in the study.

Upon meeting potential participants to conduct in-person interviews, written consent must be obtained. Prior to requesting written consent, interviewers will read through the consent forms in potential participants' language of preference. The informed consent forms explain the purpose of the study, the rights of potential participants to decline participation at any point during interviews and the rights of participants to decline to respond to any specific questions. The informed consent forms will be available in English, Afrikaans and Xhosa. Potential participants must demonstrate their understanding of the informed consent form by responding to a number of questions at the end of the consent forms prior to providing consent.

Privacy and confidentiality

A key ethical consideration of this study is to ensure the confidentiality of all of the study participants, and particularly of sample patients. Given that sample patients will be selected

from the National Linkage Study cohort, it will be necessary to use named data in order to locate patient records, and to contact patients or their emergency contacts to request their consent to be contacted by study researchers. Once patient records and interviewees have been located, all names and other identifiable information will be removed from the data that is collected, stored and published by the study in order to ensure the confidentiality of sample patients and interviewees.

Each sample patient will be assigned a unique identifier code under which their medical record data and interview data will be stored. All interviewees will be given pseudonyms to ensure that their identities remain confidentially. Finally, no names of primary clinics will be included in the final study report or any published data to further protect the confidentiality of sample patients and interviewees.

Another important ethical consideration when conducting multi-perspective interviews is ensuring that there is no cross-disclosure of what one participant has said to another participant during the interview process. In other words, healthcare workers must be assured that the information that they provided regarding a patient's journey will not be disclosed to the patient or family member and vice versa. Kendall et al. (2009) highlight that when conducting multiple perspective interviews, study participants may be curious as to what other participants have said and may question this. The interviewers will be trained not to disclose what has been said in other interviews and will sign a confidentiality agreement to this regard.

Dissemination of study results

The results of this research will be useful to the Department of Health, as well as advocacy groups and funders that are concerned with improving linkage to DR-TB treatment and

thereby reducing mortality and onward transmission. The results of this study will be summarised and circulated to all relevant stakeholders in a succinct policy paper. Additionally, the study report will be submitted to journals for publication.

Collaboration

This study will be undertaken as a sub-study to the national 'Linkage to care for drug resistant TB following Xpert implementation in South Africa' study (the National Linkage Study). The National Linkage Study is run by the University of Cape Town's Department of Medical Microbiology and funded by the Bill and Melinda Gates Foundation. The primary aims of the National Linkage Study are to assess delays in initiating second-line treatment for patients with a rifampicin resistant Xpert result in South Africa, and to determine the critical points along this pathway at which delays occur. The principle investigators for the National Linkage Study are Prof Mark Nicol, University of Cape Town, Microbiology and NHLS and Prof Wendy Stevens, University of Witwatersrand, Microbiology and NHLS.

The National Linkage Study has received ethical approval from UCT's Human Research Ethics Committee (REF NO: 540/2013; REF NO: 241/2014).

Timeline

	April	May	June	July	Aug	Sep	Oct	Nov
Obtain ethical approval from UCT								
Review data from National Linkage Cohort and identify sample patients and facilities								
Request approval and access to study facilities from WC Provincial DoH and the City of Cape Town								
Initial facility visits to review patient records, interview								

healthcare workers and request assistance from healthcare workers in obtaining consent from patients and family members to be contacted								
Contact patients and family members that consent to be contacted to request their participation in the study and arrange interviews								
Interview patients and family members								
Conduct analysis								
Draft study report								

Interview schedule

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
June	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	Initial visit to Cape Town metro facilities that diagnosed and/or initiated care for 12 sample patients in the district. 12 sample patients will be selected from a maximum of 5 facilities within the Cape Town metro. During initial visits, each sample patient's records will be reviewed and interviews will be conducted with the healthcare worker(s) identified as responsible for their care. After the interviews, HCWs will be asked to contacts patients (or their emergency contacts if patients cannot be reached) to request their consent to be contacted by study researchers.						
	9	**10**	**11**	**12**	**13**	**14**	**15**
	Initial visits to Cape Town metro facilities continued…		Initial visits to the West Coast facilities that diagnosed and/or initiated treatment for 12 sample patients in the district. 12 sample patients will be selected from a maximum of five facilities. The same activities will be carried out during initial visits as described for the Cape Town Metro District.				
	16	**17**	**18**	**19**	**20**	**21**	**22**
	Initial visits to West Coast facilities continued…						
	23	**24**	**25**	**26**	**27**	**28**	**29**
	Initial visits to the Cape Winelands facilities that diagnosed and/or initiated treatment for 12 sample patients in the district. 12 sample patients will be selected from a maximum of five facilities. The same activities will be carried out during initial visits as described for the Cape Town Metro District.						
July	**30**	**1**	**2**	**3**	**4**	**5**	**6**
	Continued…		Contact sample patients and emergency contacts that consent to be contacted. Ask them to nominate an additional family member that may be interviewed. Arrange date and time for interviews.				
	7	**8**	**9**	**10**	**11**	**12**	**13**
	Continued…						

	14	**15**	**16**	**17**	**18**	**19**	**20**
	Conduct interview with sample patients and family members in the Cape Town metro.						
	21	**22**	**23**	**24**	**25**	**26**	**27**
	Continued…						
	28	**29**	**30**	**31**	**1**	**2**	**3**
Aug	Conduct interviews with sample patients and family members in the West Coast district.						
	4	**5**	**6**	**7**	**8**	**9**	**10**
	Continued…						
	11	**12**	**13**	**14**	**15**	**16**	**17**
	Conduct interviews with sample patients and family members in the Cape Winelands district						
	18	**19**	**20**	**21**	**22**	**23**	**24**
	Continued…						
	25	**26**	**27**	**28**	**29**	**30**	**31**

Expenses

The main study expenses include the cost of travel to sites, hiring Xhosa and Afrikaans speaking interviewers and translation and transcription of interview transcripts. These expenses are budgeted for under the Bill and Melinda Gates Foundation grant provided to UCT's Department of Medical Microbiology for the National Linkage Study underway (see collaboration) (HREC/NO: 540/2013; 241/2014). The study's principle researcher will receive support from a Wits Health Economics and Epidemiology Research Office (HE2RO) bursary, as well as a bursary from DAAD-NRF.

[END]

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28 May 2014

HREC/REF: 237/2014

Ms V Govender
Health Economics Unit
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Dear Ms Govender

Project Title: LINKAGE TO CARE FOLLOWING DR-TB DIAGNOSIS IN THE WESTERN CAPE (Masters - Ms C Tomlinson)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 30 May 2015.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please update the I/C documents to refer to the correct name for the Faculty of Health Sciences Human Research Ethics Committee consistently throughout the documents.

We acknowledge that the following student/s:- Catherine Tomlinson is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:237/2014

Part B:
Literature review

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Part 1: Introduction

1.1. Objectives of the study

The aim of this study is to investigate why patients diagnosed with drug resistant (DR) tuberculosis (TB) in the Western Cape frequently fail to link to timely treatment following diagnosis. Seeking to understand this phenomenon, the study will endeavour to understand what factors enabled or constrained linkage to treatment following diagnosis of rifampicin resistant (RR) TB between January and March 2013 – considering how the rollout of Xpert MTB/RIF (Xpert) diagnostic tools and ongoing decentralisation of DR-TB services, which were underway during this time, impacted on treatment linkage. DR-TB is used in this study as an encompassing term to refer to RR, multidrug resistant (MDR) and extensively drug resistant (XDR) TB.

In seeking to understand why patients do - or do not - experience treatment linkage delays and failure following RR-TB diagnosis, this study will seek to identify factors that led to: 1) expedited treatment initiation, 2) delayed treatment initiation or 3) non-initiation of treatment amongst sample patients following sputum collection on which RR-TB was diagnosed.

I will apply Coker et al.'s (2010) conceptual framework as a lens to explore contextual factors, health system mechanisms and patient factors that enabled or constrained linkage to treatment following RR-TB diagnosis between January and March 2013. For intervention monitoring and evaluation purposes, domains of treatment were categorised and defined as follows:

1) Linkage to treatment is defined as the initiation of an appropriate DR-TB regimen (according to available resistance results) following the detection of RR-TB.
2) Expedited treatment initiation is defined as the initiation of DR-TB treatment within one month of sputum collection, on which RR-TB was diagnosed.
3) Delayed treatment initiation is defined as the initiation of DR-TB treatment more than one month and less than six months after sputum collection, on which RR-TB was diagnosed.
4) Non-initiation is defined as non-initiation of DR-TB treatment within six months of sputum collection, on which RR-TB was diagnosed.

1.2. Objectives of the literature review

Part 1 of the literature review outlines the research question and literature search strategy. Part 2 of the literature review justifies the study purpose by providing an overview of the most up-to date evidence regarding DR-TB treatment linkage in South Africa and the Western Cape Province. Part 3 of the literature review provides a description of Coker et al.'s (2010) conceptual framework, which was selected as an analytic guide for this study. Part 3 also provides an overview of other conceptual frameworks considered for this study and a justification for why the Coker et al. framework was selected.

Part 4 of the literature review discusses two national health systems interventions underway to improve treatment linkage within South Africa, the evidence for these interventions and their effects on linkage so far. The two interventions of focus are 1) the rollout of Xpert diagnostics, coupled with updated DR-TB diagnostic and treatment guidelines, and 2) the decentralisation of DR-TB services in the country. Finally, part 5 of the literature

review provides an overview of available academic evidence regarding barriers and enablers to treatment linkage following DR-TB diagnosis.

1.3. Literature search strategy

Reference material for this literature review was primarily sourced from peer reviewed journals. In order to identify relevant literature, combinations of words and Boolean phrases were tested on PubMed and Google Scholar. Articles from all countries, published after 2000 and available in English were eligible for inclusion. Multiple searches were done between February 2014 and February 2015. Examples of the Boolean phrases tested are listed below. PubMed searches for these phrases yielded 12,039 results.

Table 1. Examples of search phrases used

"Linkage" and "tuberculosis"
"Linkage" and "drug resistant tuberculosis" or "DR-TB" or "MDR-TB"
"Linkage barriers" and "TB" or "DR-TB" or "MDR-TB"
"Time to diagnosis" and "TB" or "DR-TB" or "MDR-TB"
"Time to treatment" and "TB" or "DR-TB" or "MDR-TB"
"Diagnostic and treatment delays" and "TB" or "DR-TB" or "MDR-TB"
"Rapid diagnosis" or "rapid treatment" and "TB" or "DR-TB" or "MDR-TB"
"Xpert" and "DR-TB" and "South Africa"
"Decentralisation" and "DR-TB" and "South Africa"

Potentially relevant articles for inclusion were initially selected through reviewing article titles and, when available, abstracts. Articles that appeared relevant were downloaded through open access agreements or UCT's online journal database, following which the abstract and results of each article were read in order to assess each article's relevance for full review. Articles were considered relevant if they were 1) central to the disease focus of the paper, 2) considered Xpert diagnosis or decentralisation of DR-TB services, or 3) provided data on linkage barriers or enablers. Eighty nine articles were selected for full review and drawn from in this literature review.

While evidence from all countries was eligible for inclusion, evidence from South Africa is featured more strongly in this literature review. This was in part due to the dearth of literature from other high burden DR-TB countries, in comparison to the large body of literature on DR-TB in South Africa. Further, evidence from South Africa was prioritised over evidence from other countries when it provided more contextually relevant insight.

Literature published in the past 5 years (since 2010) was prioritised over older articles. During the past 5 years there have been large programmatic shifts in South Africa's efforts to treat and combat DR-TB (the rollout of Xpert diagnostics and decentralisation of services) and globally a massive increase in diagnosed RR-TB cases, coupled with a growing DR-TB treatment gap in a number of high burden countries including South Africa, has been documented (WHO, 2014, p. 141).

This literature review also draws strongly from government policy documents and grey literature (i.e. government presentations and reports). Given the recent escalation in the gap between the number of patients diagnosed with RR-TB and those initiated onto treatment, relevant academic literature is sometimes unavailable and government sources provide the most up-to date data on DR-TB treatment linkage in South Africa.

While limited academic literature on the scale of DR-TB linkage challenges in South Africa is currently available, there are a number studies underway seeking to describe and measure these challenges, including the national 'Linkage to care for drug resistant TB following Xpert implementation in South Africa' study that is being conducted by the University of Cape Town's Department of Medical Microbiology. The results of this study will be published during 2015.

Part 2. The challenge of TB and DR-TB in South Africa

2.1. Overview of TB and DR-TB in South Africa

Tuberculosis (TB) is the leading cause of natural death within South Africa. In 2011, TB accounted for 10.7% of deaths in the country (STATSSA, 2014, p. 35). According to the World Health Organisation (WHO), when adjusted for population size, South Africa has both the highest estimated incidence and prevalence of TB globally (WHO, 2014, p. 141).

The rise of the TB epidemic in South Africa has been closely related to the HIV epidemic in the country. People living with HIV are more at risk of developing active TB illness than HIV-negative people, even when stable on antiretroviral therapy (Gupta et al., 2012, p. 6). Over the past two decades, HIV prevalence has increased to 12.2% in the general population (HSRC, 2014, p. 35). During 2013, 62% of TB patients that knew their HIV status in South Africa were co-infected with HIV (WHO, 2014, p. 13). According to the WHO, South Africa has the highest number of HIV positive incident TB cases globally (WHO, 2014, p. 13).

A major challenge to South Africa's TB response is the growing epidemic of drug resistant TB. South Africa had the second largest number of diagnosed MDR-TB cases globally during 2013, falling only behind India (WHO, 2014, p. 65). The WHO estimates that 1.8% of new TB cases, and 6.7% of retreated TB cases were drug resistant in 2013 (WHO, 2014, p. 141). During 2012, the NHLS reported 14,161 laboratory confirmed MDR-TB and 1,545 XDR-TB cases, up from 7,386 and 741 respectively in 2010 (WHO & NDoH, 2014, p. 2). The WHO recently reported that the number of patients diagnosed with RR and/or MDR-TB rose to 26,023 during 2013 (WHO, 2014, p. 141)

The large increase in diagnosed drug resistant TB cases witnessed in South Africa in recent years is due to a combination of an increasing incidence of DR-TB, as well as improved case detection and diagnosis (WHO, 2014, p. 141). While the figures reported by the NHLS and WHO are likely subject to some error due to challenges with duplicate specimens and reporting (Dickson-Hall & Nicol, 2014, p. 1), what is clear is that South Africa has experienced a dramatic growth in diagnosed DR-TB cases in recent years.

This study will consider factors that enable or constrain linkage to treatment following RR-TB diagnosis in the Western Cape Province. South Africa is made up of 9 provinces, including the Western Cape Province, which has the third highest provincial burden of diagnosed RR-TB cases in South Africa (Ndjeka, 2013, p. 13 - 22).

2.2. Overview of TB and DR-TB in the Western Cape Province

The Western Cape Province is made up of the urban City of Cape Town metropolitan municipality and five rural districts: Cape Winelands, Eden, West Coast, Overberg and Central Karoo. Sixty four percent of the Western Cape Province's population resides within the Cape Town metropolitan municipality (STATSSA, 2012). During 2011, the City of Cape Town metropolitan municipality had the 2nd highest incidence of TB in the country (compared by district), falling only behind eThekwini in KwaZulu-Natal Province. However, when adjusted for population size, the City of Cape Town had the lowest TB incidence in the province at 740.6 per 100,000 (Massyn et al., 2013, p. 396 - 415).

When adjusted for population size, the highest TB incidence was seen in the West Coast district at 981.3 cases per 100,000 people, followed in descending order by the Cape Winelands, Central Karoo, Eden and the Overberg districts. All of the TB incidences reported

in Western Cape districts were far higher than the national incidence of 687.3 cases per 100,000 people (Massyn et al., 2013, p. 396 - 415).

Between January and March 2013, the largest number of rifampicin-resistant TB cases were diagnosed in the Cape Town metropolitan municipality, followed in descending order by the Cape Winelands district, the Eden district, the West Coast district, the Overberg district and, finally, the Central Karoo district.

Table 2. Rifampicin resistant diagnoses between January and March 2013 in the Western Cape

Western Cape district	Total RR-TB diagnoses	% RR-TB diagnoses
Cape Town metro	342	60.3%
Cape Winelands	82	14.5%
Eden	70	12.3%
West Coast	47	8.3%
Overberg	21	3.7%
Central Karoo	4	0.7%
Unknown	1	0.2%
TOTAL	567	100%

* *Data sourced from the National Health Laboratory Services during 2015*

2.3. The cure rate, cost and complexity of treating TB versus DR-TB

The rising rates of DR-TB in South Africa place a dramatic strain on the health system's resources. Patients with DR-TB require longer, more complex and significantly more costly treatment regimens than patients with drug susceptible (DS) TB. An economic analysis of the comprehensive costs of treating DS-TB, MDR-TB and XDR-TB in South Africa estimated that the per patient cost of treating MDR-TB is 26 times greater than per patient cost of treating DS-TB. Forty nine percent of the per patient cost of treating MDR-TB is attributable to medicine expenditure and the remainder is attributable to laboratory and hospitalisation costs (Pooran et al., 2012, p. 1 - 10). The study further found that the per patient cost of treating XDR-TB is 103 times greater than the per patient cost of treating DS-TB. Finally, while MDR and XDR-TB cases only accounted for 3% of the notified TB cases during 2010, they

accounted for approximately 45% of total national expenditure on TB (Pooran et al., 2012, p. 1 -10).

While treating DR-TB is more costly than treating DS-TB, it is also less effective (WHO & NDoH, 2014. p. 6 - 7). Between 2005 and 2011, the national TB cure rate rose from 55 – 75%. In comparison the MDR and XDR-TB treatment success rates were 40% and 18%, respectively, during 2010 (WHO & NDoH, 2014. p. 6 - 7). The lower treatment success rates are in part due to the fact that, as patients develop resistance, their options for effective treatments are reduced.

Furthermore, as patients develop resistance their treatment becomes more complex, which increases the burden on the health system. DS-TB is treated with four medicines (often combined into a single pill) taken daily for 6 months. Treating DR-TB can take up to two years, requiring patients to take around 20 pills per day, including six months of daily injections (MSF, 2012, p. 1). Patients with drug resistant TB are also more likely to require periods of hospitalisation and surgeries than patients with drug susceptible TB.

Taking account of the resources needed to treat DR-TB, it is important to curb new infections in order to contain the costs and strain placed on the country's health system.

2.4. Linkage and incidence

DR-TB disease may occur as a result of developed resistance to the medicines used to treat DS-TB. Patients may develop resistance to DS-TB medicines while being treated for TB. This risk is heightened when treatment is not taken correctly. Patients that have been previously treated for TB are more likely to be diagnosed with DR-TB, than newly diagnosed TB cases (WHO, 2014, p. xii).

DR-TB disease may also be transmitted directly from person-to-person. Therefore people that have not previously been treated for TB may contract DR-TB from someone with active and infectious DR-TB disease. Within South Africa, molecular epidemiological studies have demonstrated that the majority of new cases are a result of direct person-to-person transmission, rather than developed resistance (Streicher et al., 2012, p. 1). Within Khayelistha, an urban township in the Western Cape, DNA finger printing has shown that person-to-person transmission may account for as many as 81% of MDR-TB cases (Cox et al., 2010, p. 5). Within the Eastern Cape, an epidemiological study showed that person-to-person transmission accounted for 41% of XDR-TB cases (Kvasnovsky et al., 2011, p. 150).

Person-to-person transmission of DR-TB in South Africa is fuelled by inadequate infection control measures, poor case detection, as well as delays in diagnosing and treating DR-TB (Cox et al., 2010, p. 7; Streicher et al., 2012, p. 686). Diagnostic and treatment delays prolong the period during which patients remain infectious, thereby heightening their risk of onward transmission of DR-TB to their close contacts (Streicher et al., 2012, p. 691).

Achieving timeous linkage to treatment for people with DR-TB is therefore critical to reducing new infections, yet figures from the Department of Health suggest that South Africa is fairing extremely poorly in linking patients to care as shown in the next paragraph.

2.5. Linkage figures in South Africa and the Western Cape

Rates of linkage to treatment in South Africa are poor. According to figures from the National Department of Health, only 45.9% of patients diagnosed with MDR-TB and 45.4% of patients diagnosed with XDR-TB during 2012, were initiated onto treatment (Ndjeka, 2013, p. 13 - 22). Worryingly, the WHO recently reported a dramatic rise in the number of laboratory diagnosed

RR and/or MDR TB cases during 2013. According to WHO estimates, 26,023 patients were diagnosed with RR and/or MDR-TB during 2013, of whom only 41% linked to treatment (WHO, 2014, p. 141).

In the Western Cape, only an estimated 48.6% of diagnosed MDR-TB patients were started on treatment during 2012. The province faired far better with XDR, initiating an estimated 99% of patients onto treatment (Ndjeka, 2013, p. 13 - 22). Encouragingly, a recent study in the City of Cape Town reported far better linkage rates in the City of Cape Town, than previously reported for the province. The observational study, conducted in 10 high burden clinics, reported that between 6 and 9% of patients did not initiate treatment within 6 months of diagnosis (Naidoo et al., 2014, p. 4).

Table 3. National figures for DR-TB diagnosis and linkage to treatment during 2012

Area	Laboratory diagnosed MDR cases	MDR cases started on treatment	% of MDR cases started on treatment	Laboratory diagnosed XDR cases	XDR cases started on treatment	% of XDR cases started on treatment
National	14,161	6,494	45.9%	1,545	701	45.4%
Western Cape	2,072	1,006	48.6%	145	144	99.3%
KwaZulu-Natal	6,630	2,571	38.8%	754	267	35.4%
Eastern Cape	2,205	1,062	48.2%	477	204	42.8%
Gauteng	1,198	417	34.8%	50	26	52%
Mpumalanga	760	591	77.8%	3	8	266.7%
Free State	390	201	51.5%	31	9	29%
Northern Cape	373	243	65.1%	72	26	36.1%
North West	267	268	100.3%	10	14	140%
Limpopo	266	135	50.8%	3	3	100%

**Figures reported by the National Department of Health (Ndjeka, 2013, p. 13 – 22)*

2.6. Reporting challenges

The numbers of diagnosed DR-TB cases and patients started on treatment are subject to some reporting error. The number of annually diagnosed DR-TB cases is reported by the South African National Health Laboratory Services (NHLS). However, currently the Department of Health and NHLS do not use unique patient identifiers – such as patients' ID numbers – to recognise patients. As a result of this, duplicate specimens from one patient are sometimes reported as different cases. It is therefore expected that NHLS's reported number of annually diagnosed cases is an overestimate of the actual number of diagnosed DR-TB cases in the country (Dickson-Hall & Nicol, 2014, p. 1).

Furthermore, the numbers of patients initiated onto treatment are reported by South Africa's national electronic register for drug resistant TB patients, commonly known as the 'EDR registry'. Only patients that initiated DR-TB treatment are registered on EDR. However, some patients that start treatment are never recorded on EDR due to reporting challenges, including the centralised nature of reporting systems. As a result of reporting challenges, it is anticipated that more patients are linked to care than reflected by EDR (Dickson-Hall & Nicol, 2014, p. 1; Rose et al., 2013, p. 214). Yet, even after accounting for reporting challenges, linkage failure in South Africa remains unacceptably high.

2.7. Summary

Data from the National Department of Health, the National Health Laboratory Services and the WHO have demonstrated a growing gap within South Arica between the number of patients diagnosed with DR-TB and those initiated onto treatment. Delayed and/or failed treatment linkage fuels DR-TB mortality, as well as onward transmission of DR-TB - resulting

in an increasing strain on the health system's resources and budget. This study will seek to understand why so many patients fail to link to care through conducting an embedded case study analysis of barriers and enablers to DR-TB treatment linkage within the high-burden Western Cape Province.

Part 3: Conceptual framework

3.1 Overview of conceptual frameworks considered for this study

Health systems are inherently complex, with multiple overlapping and interacting role players, programmes and priorities. Health systems are defined as "open systems, with interlinked components that interact within the context within which the health system is situated, thereby forming a whole with properties beyond the component parts… collectively creating a 'dynamic complexity'" (Atun, 2012, p. iv4). Gilson (2012) recommends that health systems researchers utilise conceptual frameworks when conducting health systems research in order to deal with the complexity that is inherent within the system.

Three conceptual frameworks were considered as an analytical guide for this study. These frameworks were considered because they provide a lens to understand barriers and enablers to treatment linkage during a period of policy implementations – or 'scale-up' - within a complex health system.

Scale-up involves "the process of expanding the coverage of health interventions" (Mangham & Hanson, 2010, p. 1) - generally following successful pilot testing (Mangham & Hanson, 2010, p. 1). During the period of focus in this study, the implementation of two national interventions were underway: (1) the rollout of Xpert diagnostics and (2) the

decentralisation of DR-TB services (see 'Part 4: Interventions to improve linkage'). While both interventions seek to improve treatment linkage, De Savigny and Adam (2009, p. 30) explain that the outcomes of health systems interventions are often counter-intuitive and unexpected. It is therefore critical to take a systems thinking approach which considers complex causality. A systems thinking approach takes a wide lens of the health system, considering its complexity and multiple interacting sub-systems. This approach considers how the scale-up of the two interventions will affect each sub-system in the health systems and the relationships between the sub-systems (De Savigny & Adam, 2009, p. 19).

The following three conceptual frameworks, which allow for a systems thinking approach, were considered as an analytical guide for the study:

1) Agyepong et al.'s (2012) policy resistance framework (derived from Sterman's (2006) conceptual framework). *Figure 1*
2) De Savigny and Adam's (2009) conventional approach to health systems interventions using a systems perspective framework. *Figure 2*
3) Coker et al.'s (2010) framework for comparative analysis of communicable diseases interventions. *Figure 3*

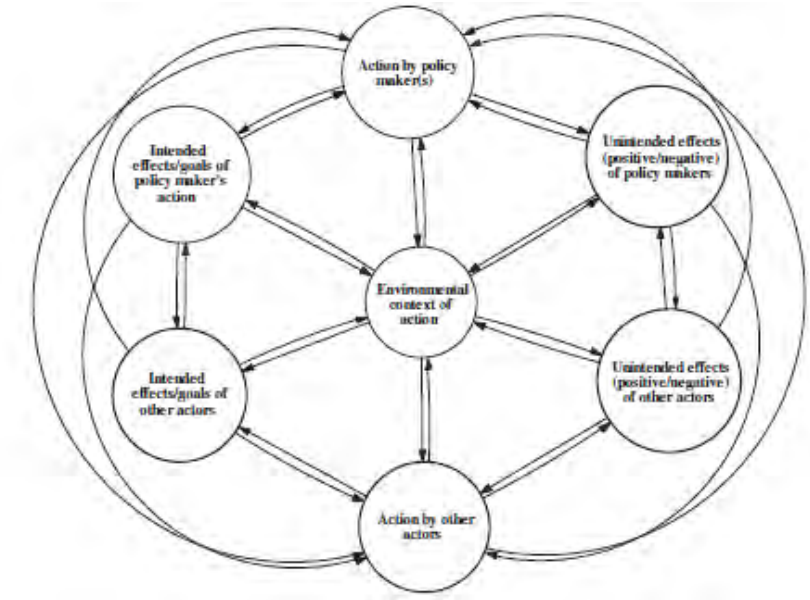


Figure 1. ***Agyepong et al. (2012). Agyepong et al.'s framework was used to identify the positive and negative effects of additional duty hours in Ghana.***

In developing their conceptual framework, Agyepong et al. (2012) drew from De Savigny and Adam's theory of health systems as complex adaptive systems. De Savigny and Adam explain that – as a complex adaptive system – the health system is self-organising and constantly changing. Additionally, dynamics and behaviours of the health system may arise spontaneously from the interactions of actors and sub-systems. De Savigny and Adam further explain that the outcome of interventions within complex adaptive systems are difficult to predict and may be counter-intuitive (2009, p. 40 – 41).

Taking a systems thinking approach, it is important to consider all of the potential positive and negative effects of an intervention on the health system. These effects, and the causal loops that contribute to them are represented in Agyepong et al.'s schematic representation of their framework. Agyepong's et al.'s framework is adapted from Sterman's (2006) theory of policy resistance which explains that an intervention may be thwarted by the health system and context in which it is implemented. The framework depicts the causal loops between actors, actions, effects and context – although it does not show the relationships between the sub-systems of the health system.

DeSavigny and Adam (2007) adopt the WHO's building blocks (or sub-systems) of the health system in their framework (WHO, 2007, p. 3). The six building blocks may enable or impede the implementation of an intervention. Furthermore, given the tightly-linked nature of complex adaptive systems, an intervention may have positive and negative effects on different building blocks (De Savigny & Adam, 2009, p. 41).

DeSavigny and Adam's (2009) framework looks at the interactions between the health systems building blocks and three measurements of health systems performance: access, coverage and utilisation. The framework also identifies a number of outcome measurements,

including: equity and health; responsiveness of the health system to the patient population; and, efficiency and cost effectiveness.

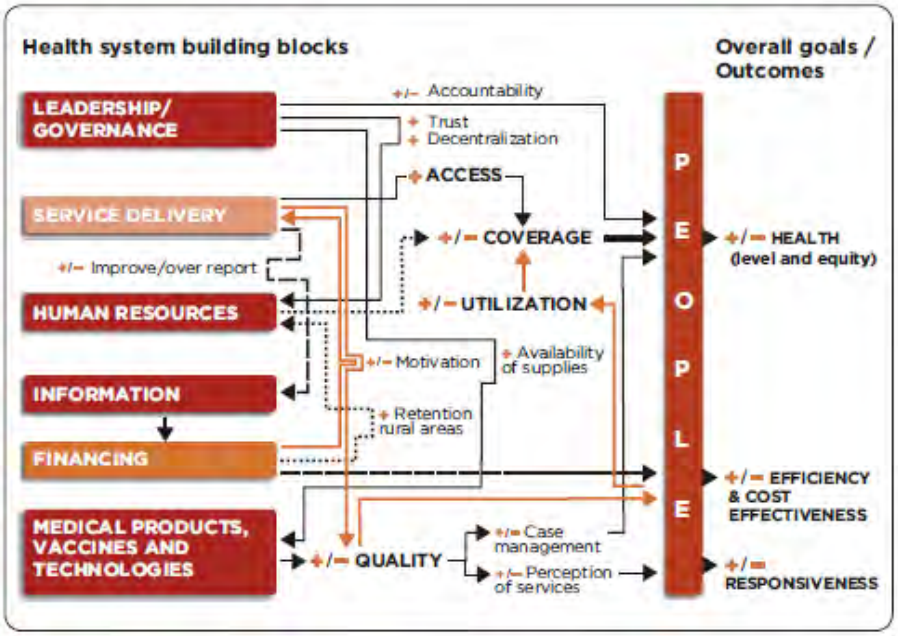


Figure 2. De Savigny & Adam (2009). DeSavigny and Adam's framework was used to explore the implementation of financial incentives for providers to improve up-take and adherence to TB treatment.

The third framework considered for this study was Coker et al.'s (2010) framework for comparative analysis of communicable disease interventions. The Coker framework was developed to allow for comparative analysis of communicable disease programmes using a systems thinking approach. Coker et al. write that the framework can be used to compare large amounts of data, both qualitative and quantitative from different health programmes, systems or countries. While the Coker et al. framework was designed to conduct large-scale, cross-comparison of communicable disease programmes, we consider it useful for conducting single-case analyses that allows for future comparative analyses.

While De Savigny and Adam adopted the WHO's health systems building blocks to enable a systems thinking approach, Coker et al. have drawn from Atun et al.'s (2004) theory of key health systems functions. Atun et al.'s six functions of the health systems include: stewardship and governance, financing, planning, service delivery, demand generation and monitoring

and evaluation. Coker et al. linked Atun et al.'s theoretical framework of health system's functions to Pawson and Tiley's (1997) framework for evaluation. Pawson and Tiley's framework identifies key elements for evaluation that seek to understand why a health programme does or does not work, while taking context into account (Pawson & Tilley, 1997). By linking the two frameworks, Coker et al.'s framework supports simultaneous analyses of health programmes and their broader, system-wide effect (Coker et al., 2010).

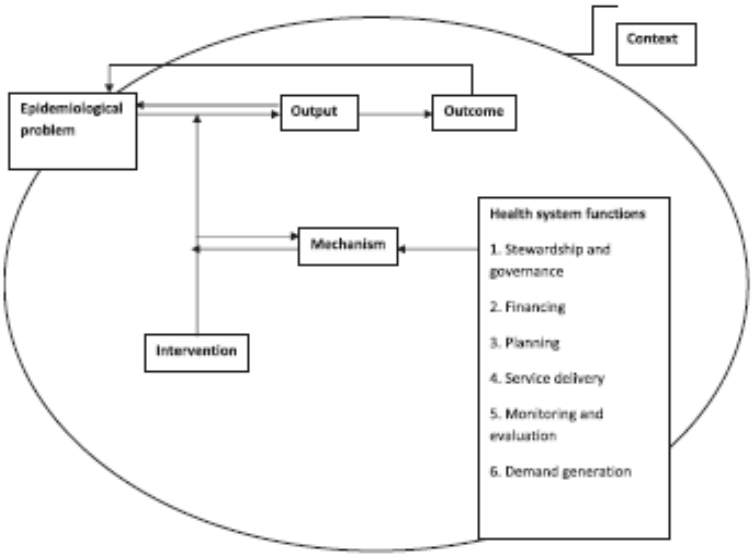


Figure 3. *Coker et al. (2010). Coker et al.'s framework was developed in order to conduct comparative analyses of communicable disease programmes.*

Drawing from Pawson and Tiley (1997), the Coker et al. framework highlights six key domains for consideration when evaluating a health systems intervention. The six domains include *context*, *epidemiological problem*, *intervention*, *mechanism*, *output* and *outcome*.

Coker et al. explain that *context* "denotes the political, legislative, social, economic and technical environments within which communicable disease control programmes sit" (p. i23). Context encompasses the local, regional and international environments in which the programme is operating, which may enable or constrain programmatic success.

Epidemiological problem "refers to infection levels and various diseases characteristics" (p. i23) that the health programme seeks to respond to. For this study, the epidemiological problem refers to large burden of DR-TB, coupled with high rates of HIV co-infection. The epidemiological problem also encompasses the low rate of treatment linkage, which drives onward transmission of DR-TB.

Intervention refers to "the intervention intended to serve public health" which are generally "recommended through clinical and policy guidelines and are evidence-based, thus lending themselves to scrutiny against gold standards" (p. i23). The interventions of focus in this study are the Xpert rollout and the decentralisation of DR-TB services.

Mechanisms refer to the "mechanism(s) by which interventions are delivered", as such it encompasses the "mechanisms within a programme, required to function effectively" (p. i23). Coker et al. link mechanisms to the health system functions - representing the functions of the health system necessary to implement the intervention.

Output refers to "public health concepts that can be measured or determined and include equity, acceptability, efficiency and effectiveness of the control programmes as a result of interventions" (p. i23). In health systems, access is commonly used as an output measurement of interventions. McIntyre et al. (2009) draw attention to the importance of defining access in order to assess it as a goal, and provide a framework that defines three key dimensions of access: availability; affordability; and, acceptability.

McIntyre et al. (2009) explain that "availability is concerned with whether the appropriate health care providers or services are supplied in [the right manner] to meet the prevailing needs of the population" (p. 184) and "affordability is concerned with the 'degree of fit'

between the full costs to the individual of using the service and the individual's ability to pay" (p. 186). They further explain that "acceptability is concerned with the fit between provider and patient attitudes towards and expectations of each other" (p. 187).

This study will use outputs of treatment linkage (expedited, delayed and non-initiation of treatment) as selection criteria for patients. Knowing patients' outputs will allow us to backward map and explore the association between these outputs and factors that influence these outputs. Knowing the outputs a priori also allows for the development of questions on how availability, affordability and acceptability as defined by McIntyre et al. (2009) might have impacted on differing linkage to treatment experiences.

Outcome in Coker et al.'s framework refers to the impact of the intervention and health programme on the epidemiological problem, "such as reduced incidence of disease or decreased mortality" (p. i23). While evaluating outcome is beyond the scope of this study, the domain has been included in the amended framework in order to retain cognisance of the ultimate aim of the health programme. A feedback loop demonstrates the impact of the outcome domain on the epidemiological problem.

Coker et al.'s framework has been further amended through the addition of a seventh domain for the *patient*. The Coker framework considers whether interventions "reach patients and populations" (p. i23). The amended framework brings patient issues to the forefront, by creating a separate domain for the patient. This study has drawn from Shippee et al.'s (2012) model of patient complexity to define the patient domain, Shippee et al. note that "patients exist at the intersection of social, personal, and clinical circumstances, and so they may face multiple complicating factors" (p. 1042). In their model of complexity, Shippee

et al. (2012) highlight the impact of patients' workloads and capacity on their experiences of care.

Patient workloads "encompasses all the demands in patients' lives, including everyday responsibilities alongside the demands of patient-hood… includ[ing] job, family, travel/transportation, childcare, scheduling and attending clinical appointments" (p. 1042).

Patient capacity "denotes the resources and limitations affecting patients' ability or readiness to do [patient-related] work, such as mental/physical functioning, unpleasant symptoms… pain, stress, or fatigue… Capacity also encompasses socioeconomic and psychological resources, literacy, language, and social support..., [as well as patients'] attitudes and beliefs about health care" (p. 1043).

In this study, the *patient* domain encompasses factors arising from patients' workloads and capacity that influence the uptake, or lack thereof, of timeous DR-TB treatment. It is crucial for policy makers to identify and consider these patient factors in order to develop more acceptable health programmes that respond to individual patient's needs and vulnerabilities in order to better link them to TB care.

3.2. Motivation for selecting the Coker framework

Following consideration of the Coker, Agyepong and DeSavigny and Adam frameworks, Coker et al.'s (2010) framework - incorporating Shippee et al.'s (2012) model of patient complexity and McIntyre et al.'s (2009) dimensions of access - was selected as an analytic guide for this study. The Coker framework was selected namely because it speaks directly to the study's aim in seeking to answer "why a programme works, for whom and under what circumstances" (Coker et al., 2009, p. i23). The framework also allows for exploration of how context, health

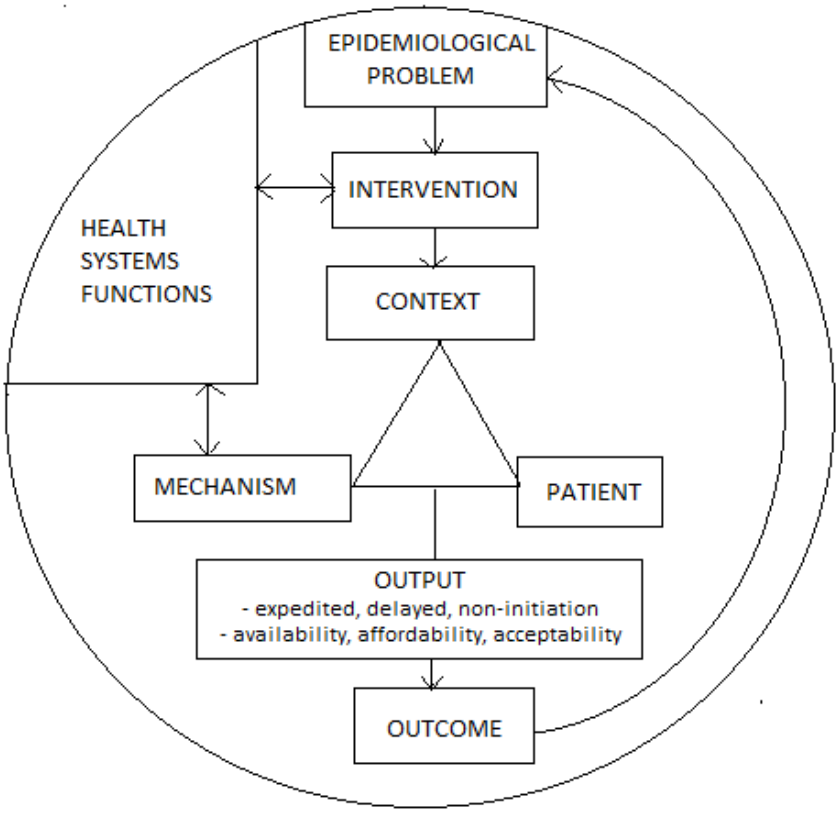
systems mechanisms and patient factors enable or constrain linkage to care during a period of intervention scale-up.

The selection of the Coker et al. (2010) framework was further motivated by its previous employment in TB and MDR-TB research in South Africa. Given the previous application of the framework, its use in this study will build on an existing body of knowledge regarding TB and DR-TB programmes within South Africa and their interactions with the health system. Previous case studies have used the Coker framework to evaluate the integration of HIV and TB services in South Africa (Loveday & Zweigenthal, 2011), as well as the impact of health systems performance on MDR-TB outcomes (Loveday et al., 2014). However, unlike previous applications of the framework (Loveday et al. 2014; Coker et al. 2010), a scoring approach will not be used to evaluate data collected for this study. Rather the framework will be applied to organise data and interpret findings. The amended framework, incorporating Shippee et al.'s model of patient complexity and McIntyre et al.'s dimensions of access, is schematically represented in Figure 4.

3.3. Summary

Following consideration of different frameworks, Coker et al.'s framework was selected as an analytical guide for this study as it allowed for exploration of "why a programme works, for whom and under what circumstances". For this study, the Coker framework was amended to incorporate aspects of Shippee et al.'s (2012) and McIntyre et al.'s conceptual models. Using the amended Coker et al. framework, this study will seek to understand how context, health system mechanism and patient factors influence linkage to treatment following the adoption of two interventions to improve linkage: the Xpert rollout and decentralisation of DR-TB care.

Figure 4. Amended Coker et al. (2010) framework incorporating Shippee et al.'s (2012) framework of patient complexity and McIntyre et al.'s (2009) dimensions of access.



Part 4: Interventions to improve linkage

During 2011, the National Department of Health embarked on the implementation of two health system interventions to improve DR-TB case detection, reduce diagnostic and treatment delays, and improve treatment outcomes. The interventions included the rollout of Xpert diagnostic tools, coupled with the adoption of updated diagnostic and treatment guidelines, and the decentralisation of DR-TB care.

Intervention 1: The Xpert rollout

The National Department of Health embarked on a national rollout of Xpert diagnostic tools following their endorsement by the WHO as an initial diagnostic tool amongst suspected DR-TB patients and patients co-infected with HIV. The recommendations were made in light of evidence that the Xpert offered significant improvements over traditional diagnostics in diagnosing TB, or DR-TB, amongst these groups (WHO, 2011).

The Xpert is often able to detect TB that is undetected by smear microscopy amongst patients with HIV. In a multi-country study, Boehme et al. (2011) reported that the sensitivity of smear microscopy in diagnosing TB amongst culture positive TB patients co-infected HIV was as low as 44.6%. In comparison, Xpert's sensitivity was 82.4%. The Xpert also offers significant reductions in diagnostic turn-around time when compared to culture diagnostics. While laboratory diagnostic turn-around time can take up to 6 weeks when using culture (FIND, 2006, p. 11) it is reduced to 2 hours when using the Xpert (Menzies et al., 2012, p. 17).

Finally, the Xpert is able to detect rifampicin resistance without additional testing using drug susceptibility testing or line probe assay, as required on sputum smear and culture tests. Rifampicin resistance is a good marker of multi drug resistance as around 90% of patients that are resistant to rifampicin are also resistant to isoniazid and are therefore categorised as MDR. Although, increasing rifampicin-mono resistance has been recently documented in the Western Cape and KwaZulu-Natal provinces (Coovadia et al., 2013, p. 1; Dlamini-Mvelase et al., 2014, p. 5; Mukinda et al., 2012, p. 4). Patients with rifampicin mono-resistance should be given isoniazid, in combination with an MDR-TB treatment regimen (NDoH, 2011b, p. 38).

South Africa has spearheaded the use of Xpert diagnostic tools to date - purchasing 56% of Xpert cartridges sold worldwide between December 2010 and June 2014 (WHO 2014). Since March 2011, the National Department of Health has placed 284 testing machines in

sites around the country and performed more than 2 million tests (NHLS, 2013, p. 3). The national Xpert rollout was coupled with the adoption of a new diagnostic algorithm that recommends the use of the Xpert as an initial diagnostic test for all patients with suspected pulmonary TB (Scott et al., 2014, p. 1818). As a result of the updated algorithm and Xpert rollout, all TB suspects should now also be screened for rifampicin resistance.

The updated diagnostic algorithm was further coupled with the adoption of updated treatment guidelines which recommend immediate initiation of MDR-TB treatment for patients diagnosed with RR-TB. Under the updated guidelines, confirmatory testing and drug susceptibility testing should still be conducted utilising line probe assay or culture drug susceptibility testing, but it should not delay the initiation of treatment. Patients diagnosed with RR-TB on Xpert should be immediately initiated onto standard MDR-TB regimens. Patients who are later identified as XDR should be switched to an XDR regimen (NDoH, 2013, p. 43).

4.1. DR-TB indicators in South Africa pre and post Xpert

4.1.1. Case detection

Substantial strides in case detection and diagnosis have been made as a result of the rollout of Xpert diagnostics. Prior to the Xpert rollout, it was estimated that as little as 63% of DR-TB cases in South Africa were diagnosed, which fuelled onward transmission of DR-TB (Streicher et al., 2012, p. 687). Following the Xpert rollout, a large increase in the number of laboratory confirmed DR-TB cases has been observed. According to NDoH figures, the number of laboratory confirmed DR-TB cases rose from 7,386 in 2010 to 14,161 in 2012 – representing an increase of 91.7% over two years. Simultaneously, the number of laboratory confirmed

XDR-TB cases rose from 741 to 1,545 – representing an increase of 108% over two years (Ndjeka, 2013, p. 13 - 22). In other words, the number of laboratory diagnosed MDR and XDR-TB cases doubled following the rollout of Xpert testing tools. A further escalation in case detection was recently reported by the WHO, who estimated that the number of laboratory diagnosed rifampicin resistant and/or MDR-TB cases rose to 26,023 during 2013 (WHO, 2014, p. 141).

4.1.2. Time to diagnosis

Prior to the rollout of Xpert diagnostics, health facilities in South Africa relied on line probe assay (LPA) or culture drug susceptibility testing (DST) in order to detect resistance. Long delays to diagnosis were documented with both methods of testing, which the Xpert rollout sought to reduce.

Line probe assay

LPA is a genotypic test that is able to detect rifampicin and isoniazid resistance within 48 hours. The WHO has endorsed the use of LPA testing on smear-positive and culture-positive sputum samples in order to detect drug resistance. In 2008, the Western Cape adopted LPA diagnostic tools to test for rifampicin and isoniazid resistance on smear- and culture-positive samples (Jacobson et al., 2013, p. 504).

While an initial demonstration study showed that LPA testing could allow for the processing of drug resistant TB results in under 2 days (Barnard et al., 2008, p. 1), this was not observed in a retrospective cohort analysis of MDR-TB results processed using LPA for patients diagnosed at Brewelskloof Hospital between 2007 and 2011. The study found an average laboratory processing time of 27 days when using line probe assay – the delays were

greatest for sputum smear negative patients whose TB was detected on culture (Jacobson et al., 2013, p. 506).

Culture DST

Prior to detecting resistance using culture drug susceptibility testing (DST), a positive TB culture must be detected which can take up to 6 weeks for laboratory processing (FIND, 2006, p. 11). Once a positive-culture result is available, the same sputum sample can be tested for drug susceptibility by exposing the sputum sample to small amounts of different medicines. This method is known as culture DST.

Two retrospective studies – conducted in KwaZulu-Natal and the Western Cape – showed laboratory processing time for MDR-TB results using culture DST took an average of 8 weeks (Gandhi et al., 2010, p. 83; Jacobson et al., 2013, p. 506). Worryingly the KwaZulu-Natal study found that 40% of MDR-TB cases and 51% of XDR-TB cases died within 4 weeks of providing sputum – before receiving their test results (Gandhi et al., 2010, p. 82).

Xpert

During 2011, Xpert diagnostic tools were adopted within South Africa in order to improve detection and diagnosis of TB and drug resistance. A multi-centre study conducted in 6 countries, including South Africa, compared the time to diagnosis using Xpert diagnostics with LPA and culture DST. The study showed that Xpert testing was able to identify rifampicin resistant TB on the same day as sputum collection, whereas LPA and culture DST took an average of 20 and 106 days, respectively (Boehme et al., 2011, p. 1495).

While the Xpert was initially lauded as a point-of-care diagnostic tool that would allow for same day diagnosis, its rollout in South Africa has been largely laboratory based due to cost

constraints (Schnippel et al., 2012, p. 109). While this placement has been criticised (Tre´bucq et al., 2011, p. 1567), large reductions in times to diagnosis of DR-TB have been observed in clinic settings. An observational study conducted in 10 high burden clinics in Cape Town, found that the time to processing drug resistant results in a lab was 1 day when testing was done with the Xpert, versus 24 days when using LPA (Naidoo et al., 2014, p. 4).

4.1.3. Time to treatment

In an effort to reduce time to treatment, the national Xpert rollout was coupled with updated treatment guidelines recommending that patients diagnosed with rifampicin resistance using the Xpert be immediately initiated onto MDR-TB treatment. Culture DST or LPA testing should still be performed and patients' treatment regimens should be amended in accordance with these results once they are available (NDoH, 2013, p. 43).

Prior to the rollout of the Xpert, mean delays of 80 days (11.4 weeks) from the date of sputum collection to treatment initiation were observed in a retrospective cohort study at Brewelskloof Hospital (Jacobson et al., 2013, p. 505). Similarly, a prospective cohort study in KwaZulu-Natal identified average delays between 72 and 93 days from the date of sputum collection to treatment initiation (Loveday et al., 2012, p. 209).

A reduction in time to treatment following the Xpert rollout has been observed in the Western Cape. According to figures from the City of Cape Town, almost half of patients diagnosed with MDR-TB during 2013 initiated treatment within 5 days of sputum collection (Caldwell, 2013, p. 27). An observational cohort study conducted in 10 high burden clinics in Cape Town showed a reduction in time to treatment following sputum collection from 43 days when using LPA to 17 days when using the Xpert. The study authors reported that 80% of the

reduction in time to treatment was due to reduced laboratory turn-around times as there were ongoing delays to treatment initiation following diagnosis. Time from diagnosis to treatment initiation was approximately 10 days when using the Xpert (Naidoo et al., 2014, p. 4).

4.1.4. Non-initiation of treatment

Following the Xpert rollout, rates of treatment initiation failed to keep pace with the increase in laboratory diagnosed DR-TB cases, which led to a large gap between the number of patients diagnosed with DR-TB and those initiated onto treatment. Between 2010 and 2012, the percentage of laboratory diagnosed MDR-TB patients that were reported to have not started treatment increased from 28% to 54%. During the same period, the percentage of laboratory diagnosed XDR-TB patients that were reported to have not started treatment rose from 17% to 55% (Ndjeka, 2013, p. 13 – 22).

Within the Western Cape, it is estimated that the percentage of laboratory diagnosed MDR-TB cases that failed to initiate treatment rose from 27% in 2010 to 51% in 2012. Yet, simultaneously the percentage of XDR patients that failed to initiate treatment declined to below 1% (Ndjeka, 2013, p. 13 – 22). An observational cohort study in Cape Town reported far lower rates of non-initiation within 10 high burden clinics (between 6 and 9%). However, there was no statistically significant difference in rates of non-initiation between patients diagnosed using LPA versus the Xpert (Naidoo et al., 2014, p. 4).

Table 4. Linkage estimates from the National Department of Health, 2014

Area	% of MDR non-initiators 2010	% MDR non-initiators 2012	% XDR non-initiators 2010	% XDR non initiators 2012
National	28%	54%	17%	55%
Western Cape	27%	51%	45%	0.7%
Eastern Cape	48%	51%	30%	57%
KwaZulu-Natal	12%	61%	0%	64%

4.1.5. Morbidity and mortality

Achieving timeous diagnosis and treatment initiation is not only important to preventing new infections, but also critical to reducing DR-TB mortality. Two KwaZulu-Natal studies conducted before the Xpert rollout showed that between one third and one half of DR-TB patients died prior to receiving there results. Furthermore, the majority of patients died within one month of providing sputum (Gandhi et al., 2010, p. 83; Heller et al., 2010, p. 424). Similarly, a Gauteng retrospective study of patients diagnosed during 2011 (during the Xpert rollout) found that one third of patients diagnosed in the province died prior to starting treatment (Ebonwu et al., 2013, p. 1046).

To date there has been no assessment of the Xpert rollout's impact on DR-TB mortality in South Africa, however this is the focus of a current study underway (Linkage to care for drug resistant TB following Xpert implementation in South Africa, Department of Medical Microbiology, N.d.). Disappointingly, however, two South African trials have shown that the Xpert rollout has not reduced morbidity and mortality amongst drug susceptible TB patients (Geffen, 2014, p. 1).

4.1.6. Summary

Following the rollout of Xpert diagnostics, significant increases in diagnosed DR-TB cases were observed (Ndjeka, 2013). Furthermore, studies have shown that diagnosis on Xpert (versus LPA or culture DST) reduces diagnostic turn-around times, as well as time to treatment (Boehme et al. 2011; Naidoo et al., 2014). However, the health system's capacity to initiate new patients onto treatment has failed to keep pace with rapid increases in diagnosed DR-TB cases, leading to a widening treatment gap (WHO, 2014; Ndjeka, 2013). This study will seek

to understand why many patients fail to link to care, despite improved diagnostic turn-around times facilitating expedited treatment initiation.

Intervention 2: Decentralisation of DR-TB services

The 2011 Xpert rollout was not introduced within a static DR-TB programme or health system. Rather, the rollout was coupled with the adoption of national guidelines recommending the decentralisation and deinstitutionalisation of MDR-TB treatment (NDoH, 2011a). The guidelines for decentralised MDR-TB care were adopted in light of evidence that decentralised, community-level care could be implemented without compromising treatment outcomes (Cox & Ford, 2013, p.1). Additionally, the guidelines were adopted in recognition of the fact that traditional centralised treatment sites were increasingly unable to accommodate the expanding patient load (Cox & Ford, 2013, p. 1; NDoH, 2011a, p. 16).

To date, three models of decentralisation have been implemented in different parts of South Africa. At its most basic, 'decentralisation' has involved the extension of DR-TB services to district hospitals. According to current guidelines, at least one decentralised DR-TB unit should be available within each district (NDoH, 2013, p. 15). The Eastern Cape Province, for instance, is in the process of decentralising MDR-TB treatment to one hospital per district (communication with the ECDoH, May 2014). National policy guidelines recommend that complicated MDR-TB patients and smear-positive patients be hospitalised at a decentralised DR-TB unit for up to eight weeks, or until they have received two consecutive, smear-negative microscopy results (NDoH, 2013, p. 5).

Along with at least one decentralised DR-TB unit per province, each province should have at least one centralised DR-TB unit or 'provincial centre of excellence'. The centralised DR-TB

unit is responsible for initiating XDR-TB patients, as well as assessing and overseeing DR-TB patients receiving decentralised care in the province (NDoH, 2013, p 5).

The second model of decentralisation seen in South Africa, has been the extension of DR-TB services to primary care clinics. This model of decentralisation has been implemented across the Western Cape and parts of KwaZulu-Natal. National policy guidelines recommend that primary care clinics initiate MDR-TB treatment and provide daily injections to smear negative MDR-TB patients. Clinics should also provide ongoing treatment to DR-TB patients discharged from hospital. XDR-TB patients and patiens with complicated MDR-TB should still be referred by primary clinics to centralised and decentralised DR-TB units for hospitalised treatment initiation (NDoH, 2013, p. 16).

The third and least common model of decentralisation seen in South Africa is home based DR-TB treatment. National policy guidelines recommend that patients who are unable to reach treatment facilities be treated in their homes by mobile injection teams (NDoH, 2013, p. 17). Integrated home-based MDR-TB and HIV treatment was successfully piloted in Tugela Ferry in KwaZulu-Natal – a community with a dual high burden of HIV and DR-TB – without compromising treatment outcomes (Brust et al., 2012, p. 998).

4.2. DR-TB indicators in centralised versus decentralised settings

4.2.1. Case detection and treatment linkage

The decentralisation of DR-TB treatment in South Africa has led to improvements in case detection and linkage to care. In Khayelitsha, an urban township in the Western Cape, an increase in case detection was observed with the decentralisation of DR-TB services to primary clinics (Cox et al., 2014, p. 445). The decentralisation of DR-TB services in Khayelitsha

also improved linkage to treatment for DR-TB patients in the area. An estimated 85% of patients diagnosed with DR-TB in the area initiated treatment - far above the national average of 42%. This success was credited to shortened time to diagnosis, better tracing systems and improved access to treatment (Cox et al., 2014, p. 445 - 446).

4.2.2. Time to treatment

Two KwaZulu-Natal studies have demonstrated reduced times to treatment in decentralised sites, versus centralised sites. Time to treatment was reported at 84 days at the community-based hospital in KwaZulu-Natal, versus 106.5 days at the centralised, provincial hospital (Heller et al., 2010, p. 420). Similarly, median time to treatment initiation was reported 72 days at decentralised sites using mobile injection teams versus 93 days at the centralised hospital (Loveday et al., 2012, p. 209). In Khayelitsha in the Western Cape, decentralisation of DR-TB services to primary clinics led to reductions in time to treatment from over 2 months to 27 days (Cox et al. 2014, p. 441).

4.2.3. Distance and access to decentralised treatment sites

A number of studies have demonstrated reduced times to treatment initiation following the decentralisation of DR-TB services (Cox & Ford, 2013; Heller et al., 2010; Loveday et al., 2012). However, the implementation of decentralised care to date has been slow and varied across provinces.

In the City of Cape Town, an estimated 80% of patients are now initiating MDR-TB treatment at a primary clinic (Caldwell, 2013, p. 4). The average time to treatment commencement for patients diagnosed in the City of Cape Town by the Xpert is 17 days (Naidoo et al. 2014, p 1). However in rural parts of the Western Cape Province, many patients

are unable to access primary clinics for daily injections due to distance and lack of transport. These patients must continue to be hospitalised during the injectable phase of treatment (Theron, 2013; Kendal et al., 2013). It can be anticipated that access to decentralised care is even worse in other parts of the country where efforts to decentralise have been slower than in the Western Cape.

Surprisingly, given evidence that decentralisation improves linkage to care, a recent KwaZulu-Natal study that collected data at four DR-TB treatment initiation sites did not find any association between patients' times to treatment and the distances between diagnosing and treatment initiating facilities (Smith et al., 2013, p. 1). This finding may be due to inadequate decentralisation to date.

4.2.4. Treatment outcomes and mortality

Studies in South Africa have shown that decentralised programmes have had similar, if not better, treatment outcomes than centralised programmes. A Khayelistsha study showed improved survival rates amongst patients receiving decentralised care, whereas a KwaZulu-Natal study showed no significant difference in survival following treatment initiation (Cox et al., 2014, p. 446; Loveday et al., 2012, p. 209). Another KwaZulu-Natal study reported shorter times to sputum smear and sputum culture conversion amongst patients receiving decentralised treatment, when compared to patients receiving centralised treatment (Heller et al., 2010, p. 420). Importantly, however, an in-depth analysis of treatment outcomes at 4 decentralised DR-TB sites in KwaZulu-Natal reported significant differences in treatment outcomes, including rates of mortality, between decentralised facilities (Loveday et al., 2014, p. 3).

4.2.5. Summary

Decentralisation of DR-TB services can reduce time to treatment and improve rates of treatment linkage without negatively impacting on treatment outcomes (Cox et al., 2014; Loveday et al., 2012). However, access to decentralised treatment sites remains varied within the country and the Western Cape Province. This study will seek to identify barriers and enablers to treatment linkage during a period of ongoing scale-up of decentralised care. This study will further seek to identify variations in barriers and enablers to DR-TB treatment linkage across urban and rural areas with varying level of decentralised care.

Part 5: Factors that enable or impede timeous treatment linkage

Previous studies have demonstrated that rates of treatment initiation and time to treatment following DR-TB diagnosis are influenced by the type of diagnostic test used, as well as initiation of treatment at a centralised versus decentralised site. However, these factors overlap and interact with a numerous other factors, including factors falling within Coker et al.'s (2010) context, mechanisms and patient domains. The overlapping factors that influence DR-TB treatment linkage, identified in academic literature, are outlined below.

5.1. Death and loss to follow up

Previous studies have demonstrated that death prior to treatment linkage and loss to follow-up are the most prevalent drivers of linkage failure within South Africa. Loss to follow-up may occur due to a combination of health systems and patient factors. Death prior to treatment

linkage occurs due to failures of the health system to rapidly process diagnostic results and/or link patients to treatment.

5.1.1. Death prior to treatment linkage

Prior to the rollout of the Xpert and decentralisation, long delays to treatment initiation resulted in many patients dying prior to starting treatment. A retrospective study in KwaZulu-Natal reported that 40% of MDR and 51% of XDR TB patients died prior to receiving their diagnosis (Gandhi et al., 2010, p. 80). In Gauteng, 21% of patients diagnosed between 2004 and 2007 died between diagnosis and referral to specialist treatment sites (Marais et al., 2014, p. 411). High rates of death prior to treatment initiation were also reported in Mongolia between 2012 and 2013, where average time to treatment initiation was measured at 137 days (Ganzaya et al., 2013, p. 1).

Despite efforts to reduce times to treatment through the decentralisation of DR-TB services and the rollout of Xpert testing tools, many patients still die prior to starting treatment. Following the decentralisation of DR-TB services, death continued to be the most common reason for non-initiation of treatment in the area (Cox et al., 2014, p. 443). Similarly, two recent studies in Gauteng and KwaZulu-Natal highlighted death as one of the most common reasons for non-initiation of treatment. Thirty one percent of non-linkers in Gauteng and 24% of non-linkers in KwaZulu-Natal diagnosed in 2011 died prior to starting treatment (Dlamini-Mvelase et al., 2014, p. 4; Ebonwu et al., 2013, p. 1046). The high rates HIV co-infection in South Africa contribute to the high rates of death prior to DR-TB treatment initiation (Cox et al., 2014, p. 447; Nkosi et al., 2013, p. 3).

5.1.2. Loss to follow up

Patients that are defined as 'lost to follow up' are patients that cannot be traced by the health system. Loss to follow up may occur due to health system and patient factors, and the interactions between these factors. This may occur when inadequate information is collected from patients in order to locate and communicate with them further. This may also occur when health facilities' procedures and systems for tracing patients are inadequate.

Loss to follow up has been highlighted as one of the most common reasons for linkage failure amongst drug resistant and drug susceptible TB patients. It is estimated that 25% of sputum smear-positive TB patients in South Africa are lost to follow up prior to starting treatment (Churchyard et al., 2014, p. 245). Amongst MDR-TB patients that fail to link to care, rates of loss to follow up have been reported to be as high as 46.4% and 72% (Ebonwu et al., 2013, p. 3; Nkosi et al., 2013, p. 1046).

A prospective study of TB patients in Stellenbosch in the Western Cape reported that patients that were lost to follow up could not be traced because incomplete information was collected by health facilities during their initial health facility visit (Botha et al., 2008, p. 1). Similar challenges were reported in a Vietnam study, which also reported patients purposefully provide wrong names and incorrect addresses (Buu et al., 2003, p. 737).

5.2. Factors related to health system mechanisms

Mechanisms are the elements of a health system that are required for a programme to function effectively. Mechanisms are also the processes of intervention that are often shaped by actors and the circumstances in which they operate (May, 2013, p. 3). Previous studies

have shown that health system mechanisms to link patients to treatment impact on linkage outcomes.

5.2.1. Location of diagnosis and tracing procedures

Studies have demonstrated that patients' location of treatment initiation impact on linkage outcomes. Patients who initiate treatment at decentralised sites tend to have shorter times to treatment than patients that initiate treatment at centralised sites. Yet, there is increasing evidence that it is not only where patients initiate treatment that influences linkage, but also where they are diagnosed.

A Gauteng cohort study of patients diagnosed with MDR-TB in 2011 found that patients that were referred to initiate DR-TB treatment from a hospital were 8 times less likely to initiate treatment than patients referred from a clinic. Reasons for non-initiation of treatment included death and loss to follow up (Ebonwu et al., 2013, p. 1046). Another Gauteng study found that patients referred to initiate DR-TB treatment from a hospital were more likely to be lost to follow-up and not initiate treatment than patients referred from a primary care clinic (Nkosi et al., 2013, p. 3).

The different procedures for tracing patients diagnosed with DR-TB at hospitals versus at clinics likely contribute to the different rates of treatment linkage between these two types of facilities. Hospitals tend to rely on phone calls to follow up with patients, while primary clinics will often go beyond this by arranging home visits for patients that cannot be reached via phone (Nkosi et al., 2013, p. 3). Relying solely on phone calls may be problematic as some patients, particularly in rural areas, do not have phones (Jacobson et al., 2013, p. 507). While clinics fair batter than hospitals in tracing patients, a Gauteng study noted that tracing

procedures could be improved at clinics by increasing staffing levels and clarifying staff's roles and responsibilities (Nkosi et al., 2013, p 4).

5.2.2. Human resources

A KwaZulu-Natal study reported that rapid and constant turnover of staff undermines the consistency and quality of MDR-TB care. The authors reported that facilities with more consistent staffing were more likely to notice missed appointments and follow up with DR-TB patients when necessary (Loveday et al., 2014, p. 4). A Gauteng study, similarly noted that ongoing rotation of staff likely undermines treatment linkage. The study authors recommended clarification of staff responsibilities and additional training to improve treatment linkage (Nkosi et al., 2013, p. 4).

In Cape Town, the employment of nurses at a sub-district level to trace patients and ensure treatment initiation contributed to improved linkage. A study of 10 high burden clinics reported that 6 and 9% of patients diagnosed using the Xpert and LPA, respectively, did not initiate treatment (Naidoo et al. 2014, p. 4). This is far below government's national and provincial estimations for non-initiation.

5.2.3. Health care worker attitudes

A Gauteng study found that patients that reported previously having negative experiences at primary clinics were less likely to link to care following diagnosis of TB (Edginton et al., 2005, p. 401). Similar challenges have been identified in Vietnam (Buu et al., 2003, p. 1). Patients' negative perceptions of health care worker attitudes also contribute to default following DR-TB treatment initiation in South Africa (MRC, 2009, p. 8).

5.2.4. Adherence to guidelines

Health care workers' knowledge of, and adherence to, policy guidelines can enable or impede treatment linkage. Over recent years, the National Department of Health has published a number of updated diagnostic and treatment guidelines, yet many health care workers report being unaware of or not having seen the updated guidelines (Loveday et al., 2014, p. 6; Nkosi et al., 2013, p. 3). In Gauteng, 86 and 64% of staff interviewed at primary care clinics and hospitals, respectively, reported being unaware of the MDR-TB guidelines (Nkosi et al., 2013, p. 3). A KwaZulu-Natal study reported that poor adherence to clinical guidelines in decentralised DR-TB sites is associated with poor treatment outcomes (Loveday et al., 2014, p. 6). Additionally, many eligible patients are not provided with Xpert testing due to poor adherence to diagnostic algorithms and therefore continue to face diagnostic delays (Churchyard et al., 2014, p. 245; Dlamini-Mvelase et al., 2014, p. 3).

5.2.5. Systems for processing and returning results

Sputum samples collected at clinics are sent to National Health Laboratory Services (NHLS) labs for processing. Large discrepancies in the times to diagnosis have been reported depending on the type of testing done (Xpert, LPA or culture DST). Operational delays at NHLS labs may contribute to delayed treatment initiation. A Western Cape study of patients diagnosed using LPA and culture DST, reported delays of approximately 1 week between processing DST results and returning them to clinics. Further delays were reported between the time results were returned to clinics and when patients were contacted to return for treatment (Jacobson et al., 2013, p. 1).

NHLS's systems for returning results to facilities can influence facility level delays. One tactic that the NHLS is exploring to reduce these delays is the use of cell phone messaging to promptly alert both health care workers and patients of TB results. To improve follow up on diagnostic results, a cell phone system was piloted by TB/HIV Care in KwaZulu-Natal, which used text messages to inform community health care workers of new TB diagnoses. After receiving text messages, community health care workers were responsible for contacting patients to inform them of their results and refer them to clinics for treatment. The project reported initiating 89% of patients onto treatment within 5 days of diagnosis (TB/HIV Care, n.d.).

5.2.6. Counselling and education

The availability and quality and of counselling and education in facilities and communities can also influence treatment linkage. Poor awareness and understanding of MDR-TB within communities contributes to diagnostic delays and may lead patients to seek care from alternative providers (MRC, 2009, p. 8; Niekerk et al., 2013, p. 1). Without proper counselling and education, patients may not be aware of the importance of starting treatment (Buu et al., 2003, p. 1; Voss De Lima et al., 2013, p. 5) and face a greater risk of default (MRC, 2009, p. 8).

5.2.7. Availability of beds

The 2011 adoption of policy guidelines for decentralised MDR-TB treatment was undertaken in recognition of the fact that hospitals are increasingly unable to accommodate the growing number of DR-TB patients. Waiting lists for hospital beds of up to 120 days have been documented in KwaZulu-Natal (Brust et al., 2012, p. 2). In the 2011 guidelines, the National

Department of Health stated that “waiting lists for patients [who] need to be admitted to centralised units are long, delaying the initiation of treatment in some provinces for three or four months. In addition, several patients die before starting treatment” (NDoH, 2011a, p. 5).

Waiting lists for beds likely continue to delayed treatment initiation in areas where decentralisation has not been fully implemented. Additionally, waiting lists may delay treatment initiation for XDR-TB patients, and patients with complicated MDR-TB, who still require hospitalisation during the initial intensive phase of treatment.

5.2.8. Leadership

Leadership is a key component of health systems and may influence whether or not an intervention is effectively implemented. Facility managers and local leaders play a crucial role in supporting policy implementation, both in terms of making sense of the challenges that the policy seeks to respond to and its potential benefit, as well as creating a culture of accountability (Gilson et al., 2014, p. 1.).

The 2011 decentralisation guidelines called for the appointment of district DR-TB coordinators to support DR-TB services in the district. A recent KwaZulu-Natal study reported that facilities with visible leadership, including regular visits from district coordinators, had better treatment outcomes (Loveday et al., 2014, p. 4). Regular visits by the district coordinators “led to increased accountability and a commitment to patient care resulting in improved adherence and a higher number of successful [treatment outcomes]” (Loveday et al., 2014. p. 7).

5.3. Patient factors

Developing responsive and acceptable health programmes is a key component of demand generation, identified by Atun et al. (2004) as one of the six key functions of the health systems. Understanding patient factors that impact on linkage to treatment is crucial to developing health programmes that are responsive to the needs and vulnerabilities of different patient groups. Patient factors encompass factors arising from patients' capacity and workloads that influence the uptake, or lack thereof, of timeous DR-TB treatment.

Patient capacity encompasses individual socio-economic factors, mental and physical factors that impact on patients' ability and willingness to initiate treatment. Patient workloads encompass patient's individual employment, financial and household responsibilities, they also encompass the work required to initiate treatment, such as daily clinic visits.

5.3.1. Factors related to patient capacity

5.3.1.1. Socio-demographic and economic status

A number of studies have sought to identify whether socio-demographic and economic factors influence treatment linkage. A Johannesburg study showed that not having a formal education results in a two-fold increase in one's risk of delayed or failed linkage to TB care (Voss De Lima et al., 2013, p. 5). This finding was supported by a systematic review (Storla et al., 2008, p. 6).

Previous research has also shown that age and gender may impact on TB treatment linkage (Farah et al., 2006; Rojpibulstit et al., 2006; Storla et al., 2008). However, a recent KwaZulu-Natal study did not observe any differences in rates of treatment initiation between

age or gender groups (Naidoo et al., 2014, p. 1). Similarly, a Gauteng study did not find any difference in rates of treatment initiation between gender groups. However the study did observe that patients over 65 had an increased risk of linkage failure when compared to other groups (Ebonwu et al. 2013, p. 1046).

A Johannesburg study showed that non-South Africans are less likely to link to TB treatment than South African citizens following diagnosis (Voss De Lima et al. 2013, p. 4). This finding was supported by a systematic review that found that patients with a history of immigration, and illegal residents, are more likely to face TB diagnostic and treatment delays (Storla et al. 2008, p 6), suggesting poor access for these groups.

5.3.1.2. Substance abuse

Substance abuse has repeatedly been highlighted as a major driver of South Africa's high DR-TB default rates (Holtz et al., 2006; Kendall et al., 2013; MRC, 2009). Substance abuse has also been shown to increase diagnostic and treatment delays amongst drug susceptible TB patients (Storla et al., 2008, p. 1). Taking these findings into account, it is likely that substance abuse also negatively influences DR-TB treatment linkage.

5.3.1.3. Beliefs and attitudes

A participatory research study in Cape Town found that people with TB may avoid or delay TB diagnosis due to fears around anticipated HIV-stigma (Murray et al., 2013, p. 1). In Cape Town, TB is seen as related to squalor and dirt over which people living in poverty may have little control. The sense of lack of control, combined with the anticipation of HIV-stigma, discourages people from actively seeking TB diagnosis and treatment (Murray et al., 2012, p. 1).

5.3.1.4. Disease and health related patient factors

Site of TB illness

A Western Cape study reported that patients with extra-pulmonary MDR-TB had shorter delays to treatment initiation than patients with pulmonary MDR-TB. The authors posited that this is because patients with extra-pulmonary disease tend to be more ill when they are diagnosed and may already admitted as hospital in-patients, which allows for immediate treatment initiation upon diagnosis (Jacobson et al., 2013, p. 507). While having extra-pulmonary TB was associated with quicker treatment initiation following diagnosis, it may have the opposite effect on time to diagnosis. A systematic review of studies of patients with drug susceptible TB, found that patients with extra-pulmonary TB have longer delays to diagnosis than patients with pulmonary TB (Storla et al., 2008, p. 3).

Smear status

A patient's TB smear status may also impact on their time to treatment. Smear positive DR-TB patients diagnosed using LPA have significantly shorter times to diagnosis and treatment than smear negative patients (Jacobson et al., 2013, p. 506). This is because a positive smear, removes the necessity of a positive culture prior to identifying drug resistance. Positive smear status has also been shown to reduce time to diagnosis and treatment amongst patients with drug susceptible TB (Chiang et al., 2005, p. 1; Storla et al., 2008, p. 1). However, for patients diagnosed using the Xpert, smear status should no longer impact on time to diagnosis and treatment.

HIV co-infection

A Gauteng study found that HIV positive patients were more likely to initiate MDR-TB treatment following diagnosis than HIV negative patients. This is likely due to the integration of HIV and TB services, which has also been shown to improve MDR-TB outcomes in KwaZulu-Natal (Ebonwu et al., 2013, p. 1047; Loveday et al. 2014, p. 1). However, a Cape Town study found that HIV contributed to non-initiation of treatment amongst patients diagnosed with LPA (Naidoo et al., 2014, p. 4). Two studies further demonstrated that HIV does not increase a patient's risk of treatment default but does increase the risk of death (Cox et al., 2014, p. 444; Kendall et al., 2013, p. 4).

Previous TB treatment, other health conditions and smoking

A recent Gauteng study reported that 84% of patients that did not initiate MDR-TB treatment were previously treated for TB and these patients faced a greater risk of death (Ebonwu et al. 2013, p. 1045). Additionally, patients failing drug susceptible TB treatment may face diagnostic delays due to being ineligible for Xpert testing according to diagnostic algorithms (Niekerk et al., 2013, p. 1).

Other health conditions may also impact on time to diagnosis and treatment initiation, including the presence of a chronic cough or lung disease (Storla et al. 2008, p. 3). In the Western Cape smoking currently, or in the past, is associated with delays to treatment initiation (Jacobson et al., 2013, p. 506).

5.3.2. Factors related to patient workloads

5.3.1.1.. Employment and household responsibilities

Balancing employment and family responsibilities is particularly difficult during the initial phase of DR-TB treatment, as patients must visit clinics daily for injections or be hospitalised.

Two Cape Town studies reported that patients sometimes miss appointments or delay initiating treatment due to family, financial and employment responsibilities (Naidoo et al., 2014, p. 8; Niekerk et al., 2013, p. 1).

The National Department of Health further noted that patient's household responsibilities may contribute to treatment delays amongst patients referred to centralised services (NDoH, 2011a, p. 17). For patients that take care of young children in single headed households, initiating in-patient care may not be feasible. Importantly, a study in the KwaZulu-Natal found that 75% of MDR-TB patients' households were headed by females (Marra, 2009, p. 11).

5.4. Contextual factors

Contextual factors further impact on whether or not patients link to care. Contextual factors refer to the context in which the DR-TB programme is operating and encompass "the political, legislative, social, economic and technical environments within which communicable disease control programmes sit" (Coker et al., 2010, p. i23).

5.4.1. Rural versus urban residence

A systematic review of factors that impede DS-TB treatment linkage, showed that living in a rural area increases one's risk of diagnostic and treatment delays (Storla et al., 2008, p. 1). Similarly, two Western Cape studies reported that patients with a farm address are less likely to initiate treatment following MDR-TB diagnosis than patients with a town address (Jacobson et al., 2013, p. 506; Kendall et al., 2013, p. 5).

Interestingly, a Gauteng study detected significant differences in MDR-TB patients' likelihood of linking to treatment between different urban districts. The reason for this is

unknown. The Gauteng study also showed that patients living in Gauteng's central business districts were less likely to initiate treatment than people living in the suburbs or informal settlements (Ebonwu et al., 2013, p.1047).

Part 6: Conclusion

In recent years, South Africa has witnessed rapid increases in the number of diagnosed DR-TB cases. This is due to a combination of increasing incidence and improved diagnostics (WHO, 2014, p. 141). However, rapid increases in diagnosed DR-TB cases have outpaced the capacity of the country to initiate and treat patients, resulting in a widening treatment gap. According to WHO estimates, 59% of patients diagnosed with RR and/or MDR TB during 2013 were not linked to care (WHO, 2014, p. 141).

This study will seek to understand why patients frequently fail to link to DR-TB care through conducting an embedded case study within the Western Cape. The Western Cape was selected as the site of this case, to allow for exploration of variation in barriers and enablers to treatment linkage in high-burden urban and rural areas with varying levels of decentralisation. While wide-scale access to decentralised care has been observed in the urban City of Cape Town (Caldwell, 2013, p. 4), access remains limited in rural parts of the province (Theron, 2013, p. 5).

While a number of previous studies have identified factors that influence treatment linkage, they have also highlighted research gaps. To date, there has been little exploration of patients' perspectives regarding factors that impact on treatment linkage and there is limited understanding of how patient factors impact on linkage to care. Additionally, there has been no analysis of barriers and enablers to treatment linkage in the current environment of policy

scale-up, which can have unexpected consequences that impact on linkage to care (De Savigny & Adam, 2009, p. 4).

This study will apply Coker et al.'s (2010) conceptual framework as a lens to explore the impact of context, health system mechanisms and patient factors on linkage to treatment during a period of policy intervention. By adopting a systems thinking approach (De Savigny & Adam, 2009, p. 19), this study aims to generate insight into the complex dynamics of DR-TB treatment linkage and develop useful and feasible recommendations for reducing the treatment gap.

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Part C:
Manuscript

Title page:

Linkage to treatment following RR-TB diagnosis in the Western Cape during the rollout of Xpert diagnostics and ongoing decentralisation of DR-TB services

Note for examiners:
This dissertation has been developed according to the specifications of BMC Health Services. BMC Health Services Instructions for Authors are provided in the Appendices.

Abstract

Background: Patients diagnosed with rifampicin resistant (RR) tuberculosis (TB) in South Africa frequently fail to link to appropriate drug resistant (DR) TB treatment. The aim of this study was to explore barriers and enablers to expedited treatment linkage following RR-TB diagnosis in the Western Cape Province, within the context of ongoing decentralisation of DR-TB services and the scale-up of Xpert MTB/RIF diagnostics.

Methods: An embedded case study approach, using qualitative research methods, was employed to explore barriers and enablers to expedited treatment linkage following RR-TB diagnosis. The case of investigation in this study was 'treatment linkage following RR-TB diagnosis in the Western Cape Province during the ongoing decentralisation of DR-TB services and scale-up of Xpert diagnostics'. DR-TB is used in this study as an encompassing term to refer to RR, multidrug resistant (MDR) and extensively drug resistant (XDR) TB. The embedded units of analysis in this study were patients' linkage outputs, defined as: (1) expedited treatment initiation, (2) delayed treatment initiation and (3) non-initiation of treatment following the collection of sputum on which RR-TB was diagnosed. Seventeen patient, 8 family member, 49 healthcare worker and 4 key informant open-ended, in-depth interviews were conducted and 59 patient folders were reviewed. A framework approach using an adapted version of Coker et al.'s (2010) conceptual framework was applied for analysis.

Results: This study identified multiple factors that enabled and constrained expedited treatment linkage following RR-TB diagnosis. Enabling factors included: 1) the availability of clinic level DR-TB counsellors and tracers, 2) living in walking distance of decentralised services and 3) having a strong social support network. Constraining factors included: 1) low usage of Xpert diagnostics, 2) delays in acting on results and missed (or unseen) results, 3)

rotation of nurses or the lack of dedicated TB nurses in clinics, 4) limited clinic-level administrative support, 5) information systems challenges and 6) waiting lists for beds and limited access to transport services in rural areas.

In linking to treatment, patients commonly face challenges due to competing subsistence needs and household or employment responsibilities. Substance addiction, having a history of treatment interruption, demonstrating hopelessness regarding treatment, as well as not having a stable place to stay or social support may increase a patient's risk of linkage failure.

Conclusion: Within the Western Cape Province there is significant opportunity to improve linkage to treatment through strengthening the health systems mechanisms to link patients to treatment following RR-TB diagnosis. Expanding access to psychosocial services (substance abuse rehabilitation and psychosocial evaluations) following RR-TB diagnosis may assist in linking high risk patients to treatment. Additionally, the provision of food support (in addition to social grants) should be evaluated as a tactic to improve treatment linkage and adherence.

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Keywords

Drug resistant tuberculosis, rifampicin resistant tuberculosis, linkage, decentralisation, Xpert MTB/RIF, health system

Background

The World Health Organisation's 2014 Global TB Report drew attention to the growing gap between the number of patients diagnosed with drug resistant (DR) tuberculosis (TB) and those initiated onto treatment in a number of high burden countries, including South Africa. According to the Global Report, during 2013 only 41% of patients diagnosed with rifampicin resistant (RR) TB in South Africa linked to treatment [1]

Treatment linkage is defined in this study as the initiation of an appropriate DR-TB treatment regimen (according to available resistance results) following the detection of RR-TB. DR-TB is used in this study as an encompassing term to refer to RR, multidrug resistant (MDR) and extensively drug resistant (XDR) TB.

RR-TB requires 18 to 24 months of MDR-TB treatment (in combination with isoniazid for rifampicin mono-resistant patients) [2] and is a good indicator of MDR-TB, which is defined as resistance to rifampicin and isoniazid [3,4]. According to South Africa's treatment guidelines, patients diagnosed with RR-TB should be immediately initiated onto an MDR-TB regimen, while awaiting the results of further resistance testing [5].

The DR-TB treatment gap has rapidly grown in recent years as rates of treatment linkage have failed to keep pace with escalating rates of diagnosed RR-TB cases. Diagnosed RR-TB cases increased by 252% in South Africa between 2010 and 2013, due to a combination of improved diagnostics and increasing incidence [1,6].

Studies in South Africa have demonstrated that increasing incidence is largely driven by person-to-person transmission, rather than acquired resistance [6,7]. Reducing the periods during which DR-TB patients remain infectious by decreasing delays to diagnosis and treatment initiation and improving rates of treatment linkage is therefore critical to reducing DR-TB incidence [7].

In an effort to reduce diagnostic and treatment linkage delays, South Africa's National Department of Health (NDoH) embarked on two ambitious national policy interventions during 2011: the rollout of Xpert MTB/RIF (Xpert) diagnostics and the decentralisation of DR-TB services [5,8].

Xpert diagnostics were adopted following demonstration studies that showed Xpert significantly reduced diagnostic turn-around times for detecting RR-TB, when compared to line probe assay and culture drug susceptibility testing [9]. The Xpert rollout was coupled with the adoption of a new diagnostic algorithm recommending Xpert as an initial diagnostic test for all TB suspects, and the establishment of a policy target to initiate all newly diagnosed RR-TB patients onto MDR-TB treatment within 5 days of diagnosis [5,10].

National guidelines recommending the decentralisation of DR-TB services were adopted in recognition of the fact that the traditional hospitalised system was increasingly unable to cope with rising patient numbers and in light of evidence that decentralisation could improve treatment linkage [11–13].

Treating DR-TB typically involves six months of daily injections and tablets during the intensive phase of treatment, followed by eighteen months of tablets during the continuous phase of treatment.[1] Prior to the adoption of decentralisation guidelines, patients were hospitalised during the intensive phase of treatment. The decentralisation guidelines removed the requirement for hospitalisation, allowing for clinic-level treatment initiation and management during the intensive phase of treatment [8].

[1] The intensive phase refers to the initial phase of treatment during which medicines to treat DR-TB are taken in combination with daily injections. Patients must be hospitalised or visit clinics daily in order to receive injections. This phase generally last around 6 months. After the intensive phase, patients initiate the continuous phase. During the continuous phase, which generally lasts 18 months, patients must continue to take medicines daily but no longer require injections daily.

The decentralisation guidelines recommend clinic-level treatment initiation and management for low grade transmission risk, smear negative MDR-TB patients with stable social circumstances, as well as patients that refuse hospitalisation. These patients must visit clinics daily for injections throughout the intensive phase of treatment. XDR-TB patients, smear positive MDR-TB patients, severely ill and complicated patients, as well as patients whose social circumstances preclude them from ambulatory care should continue to be hospitalised during the intensive phase of treatment [8]. This study defines decentralised care as clinic-level treatment initiation and centralised care as hospital-level treatment initiation.

This study qualitatively explored barriers and enablers to DR-TB treatment linkage within the Western Cape Province in the context of the national Xpert rollout and ongoing decentralisation of DR-TB services using an adapted version of Coker et al.'s (2010) conceptual framework as an analytic lens.The Coker framework was designed for evaluating infectious disease programmatic interventions within health systems [14]. Using an adapted version of this framework, this study explored how issues of context, health systems mechanisms, patient factors, and the inter-relationships between these factors impacted on patients' linkage to treatment outputs. Linkage to treatment outputs included: expedited initiation of treatment, delayed initiation of treatment and non-initiation of treatment following sputum collection on which RR-TB was diagnosed.

Methods

Research design

This study employed a single, embedded case study design to explore enablers and barriers to DR-TB treatment linkage following RR-TB diagnosis. An embedded case study involves

more than one unit of analysis, which are situated within the wider case [15]. The embedded units of analysis in this study were linkage to treatment outputs, defined as: (1) expedited treatment initiation, (2) delayed treatment initiation and (3) non-initiation of treatment following sputum collection on which RR-TB was diagnosed.

A case study design was applicable for this study as it allowed for exploration of enablers and barriers to expedited treatment linkage within a contemporary field setting over which the researchers did not have behavioural control [15]. The case of analysis in this study was 'DR-TB treatment linkage following RR-TB diagnosis within the Western Cape Province, during a period of treatment decentralisation and rollout of Xpert diagnostics'.

Qualitative data collection and analysis techniques were employed in order to gain rich insight into patients' 'real life' [16] linkage experiences following diagnosis of RR-TB. Qualitative research techniques were selected as they allow for exploration and interpretive analysis of complex phenomena that are influenced by context, actors and the inter-relationships between the different aspects of the phenomena [17].

Study setting

The Western Cape Province was selected as the setting for this case study in order to explore variation in linkage barriers and enablers across urban and rural areas in a high-burden province with varying levels of decentralisation across districts. The Western Cape Province has the third highest burden of DR-TB nationally. According to national estimates, only 49% of patients diagnosed with RR-TB during 2012 linked to DR-TB treatment [18]. However, a recent observational study conducted in 10 high burden clinics in the City of Cape Town reported that more than 90% of patients diagnosed with RR-TB between 2008 and 2012 linked to treatment within 6 months of diagnosis [19].

The Western Cape Province is made up of the urban Cape Town metropolitan municipality and the following rural districts: West Coast, Cape Winelands, Eden and Central Karoo. The province began piloting decentralised DR-TB care in 2007 in partnership with Médecins Sans Frontières[2] within an urban township in the Cape Town metropolitan municipality [13]. Following the adoption of national policy guidelines in 2011, the province sequentially rolled out Xpert diagnostics to all provincial sub-districts and expanded decentralised DR-TB treatment initiation and management to rural parts of the province [8,20].

Sampling criteria for patients and re-categorisation following data collection

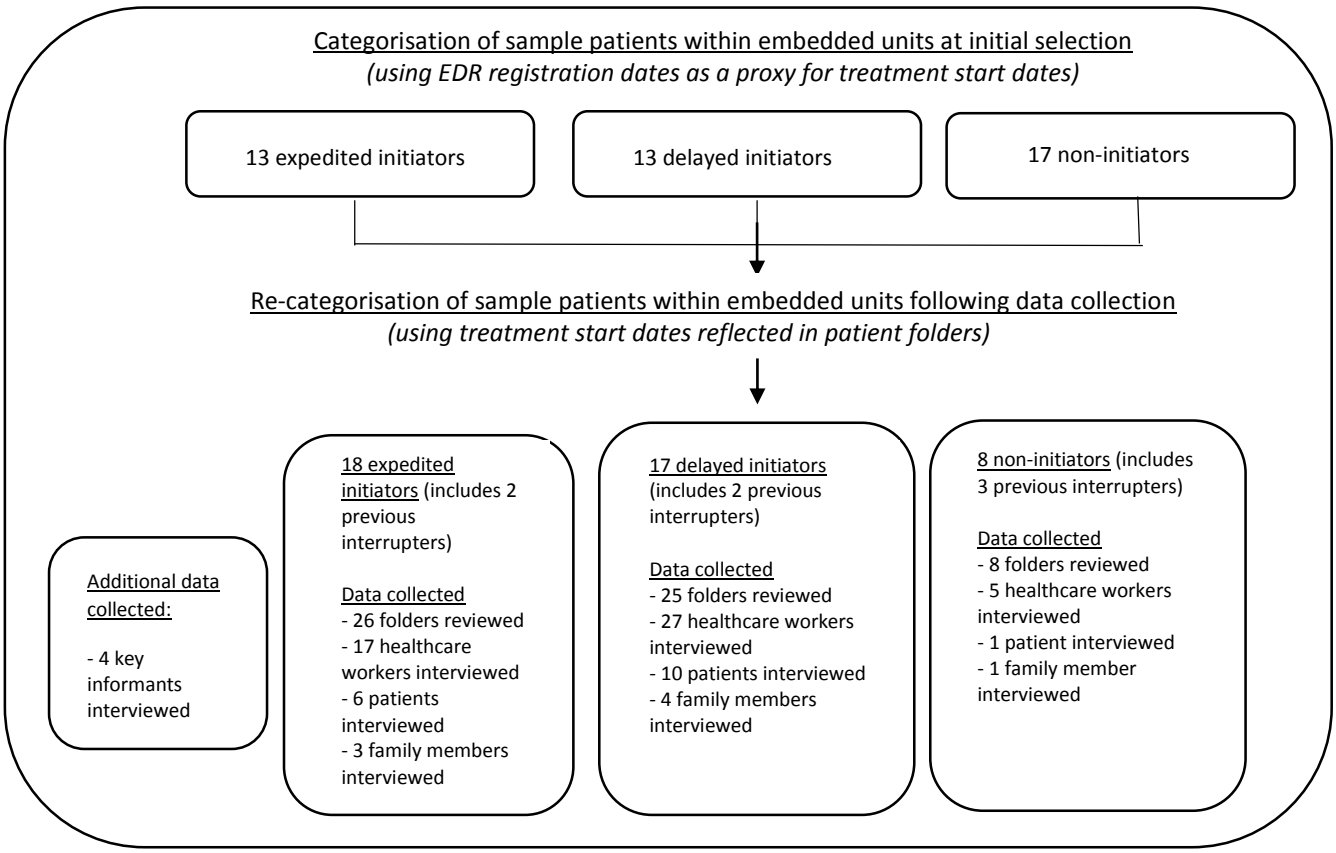
Forty three patients were purposefully sampled from the National Health Laboratory Services (NHLS) diagnostic records from January to March 2013 and the national electronic DR-TB registry (EDR). Purposive sampling involves the identification and selection of key individuals who are able to provide unique insight into the topic of investigation [21]. Purposive sampling was used to identify sample patients for each embedded unit: expedited treatment initiators, delayed treatment initiators and non-initiators in each study district. At initial selection, patients' EDR registration dates and locations were used as a proxy for treatment start dates and locations.

Patients that linked to treatment within one month of the date of sputum collection on which RR-TB was diagnosed were categorised as expedited initiators. Patients that started treatment more than one month and less than six months after sputum collection were categorised as delayed initiators. Patients that did not initiate treatment within six months of sputum collection on which RR-TB was diagnosed were categorised as non-initiators.

[2] Médecins Sans Frontières is an international non-governmental organisation that provides health services in a number of countries including South Africa.

Following record review, patients were re-categorised as expedited initiators, delayed initiators and non-initiators according to the more accurate treatment start dates reflected in their folders. Re-categorisation is visually depicted in Figure 1.

Figure 1. Sample patients (and sources of data) at initial selection and following re-categorisation



A limitation of this study was that a number of patients initially selected as non-initiators had to be re-categorised as expedited or delayed initiators following data collection from patient record reviews – leading to low patient numbers in the non-initiator embedded unit. Effort was made to identify additional non-initiators after re-categorisation. Two of the 43 sample patients were purposefully selected following initial re-categorisation in order to increase the number of non-initiators included in this study.

Following completion of data collection, 7 patients were further categorised as previous interrupters as they previously interrupted DR-TB treatment. This is unsurprising given the complicated pathways of DR-TB patients and the high rates of treatment interruption in the country [22]. Previous interrupters were categorised as expeditors, delayers or non-initiators according to their times to treatment, following their RR-TB diagnosis on sputum collected between January and March 2013.

Sample patients were purposively sampled from the City of Cape Town metropolitan municipality, the West Coast district and the Cape Winelands district to explore variation in linkage pathways across urban and rural areas. All patients diagnosed in a City of Cape Town facility were categorised as 'urban' and all patients diagnosed in a Cape Winelands or West Coast facility were categorised as 'rural'. All of the purposively sampled patients were diagnosed and, if relevant, initiated onto treatment in 21 facilities within the three study districts, excluding 1 patient who was diagnosed and initiated onto treatment in prison. Patients were selected from these facilities to examine the linkage pathways of: (1) patients that were diagnosed and initiated onto treatment at a clinic; (2) patients that were diagnosed and initiated onto treatment at a hospital; and (3) patients that were diagnosed at a clinic and referred to hospital to initiate treatment. The number of facilities visited in each district to perform record reviews and interviews are listed in Table 1.

Table 1. Facilities visited in this study to conduct HCW interviews and review patient records

	Mobile clinics	Clinics	Non-designated TB hospitals	Designated TB hospitals
Cape Town	0	5	2	1
Cape Winelands	0	4	0	1
West Coast	1	5	1	1

Non-designated TB hospitals refer to district and tertiary hospitals that are not designated to provide in-patient DR-TB treatment. Designated TB hospitals refer to hospitals that are designated to provide in-patient DR-TB treatment. There are 6 designated TB hospitals located within the Western Cape, 3 of which were included in the study.

In addition to patients' linkage to treatment outputs and locations of diagnosis and treatment initiation, gender and age were considered in selecting sample patients. Effort was made to identify a similar number of male and female patients from a wide age range. This was done to allow for consideration of how gender and age impact on treatment linkage. The selection of patients by gender and age, as well as urban versus rural location is depicted in Table 2.

Table 2. Distribution of sample patients across age, gender and rural versus urban categories

	Expedited initiators (n 18)	Delayed initiator (n 17)	Non-initiators (n 8)	Total sample patients (n 43)	
	N	N	N	N	%
Urban	7	6	2	15	35
Rural	11	11	6	28	65
Female	8	10	3	21	49
Male	10	7	5	22	51
Age range	22 - 59	23 - 75	21 - 51	21 -75	
Median age	39	46	34	38	

Selection criteria for healthcare workers and family members recruited to the study

Healthcare workers (HCWs) at diagnosing and treatment initiating facilities were recruited to be interviewed regarding sample patients' journeys. Doctors, nurses and community health workers were eligible to be included in this study if they had provided DR-TB diagnostics

and/or treatment services to a sample patient and were able to speak to the sample patient's experience of diagnosis and/or treatment linkage.

Patients and/or their emergency contacts were asked to identify family members that could be recruited to the study. The only criteria requested from patients and or their emergency contacts in identifying family members was that they be: 1) over 18 years of age; 2) willing to be contacted by study reseachers; 3) aware of the sample patient's DR-TB status; and 4) able to speak to the patient's experiences between diagnosis and treatment initiation.

Recruitment and data collection

Multiple-perspective, in-depth interviews and folder reviews were conducted in order to explore linkage barriers and enablers. For each sample patient, effort was made to explore multiple perspectives through requesting interviews with the patient, a family member and a treating HCW, as well as conducting folder review. This approach was selected to allow for exploration of various perspectives, and in anticipation of the fact that some sample patients would have died or not be traceable. All interviews and folder reviews were conducted between June and September 2014.

Interviewers fluent in English, Xhosa and Afrikaans were recruited and trained to conduct interviews with patients, their family members and HCWs using interview guides. The themes covered in the interview guides were informed by available literature on DR-TB linkage [4,13,23–25]. Coker et al.'s conceptual framework [14], as well as the researchers' professional knowledge of the South African health system.

A sequential approach was used to recruit participants and collect data. The sequential approach is visually depicted in Figure 2. Initial facility visits were conducted at the facilities where patients were diagnosed with RR-TB, as well as the facilities where patients

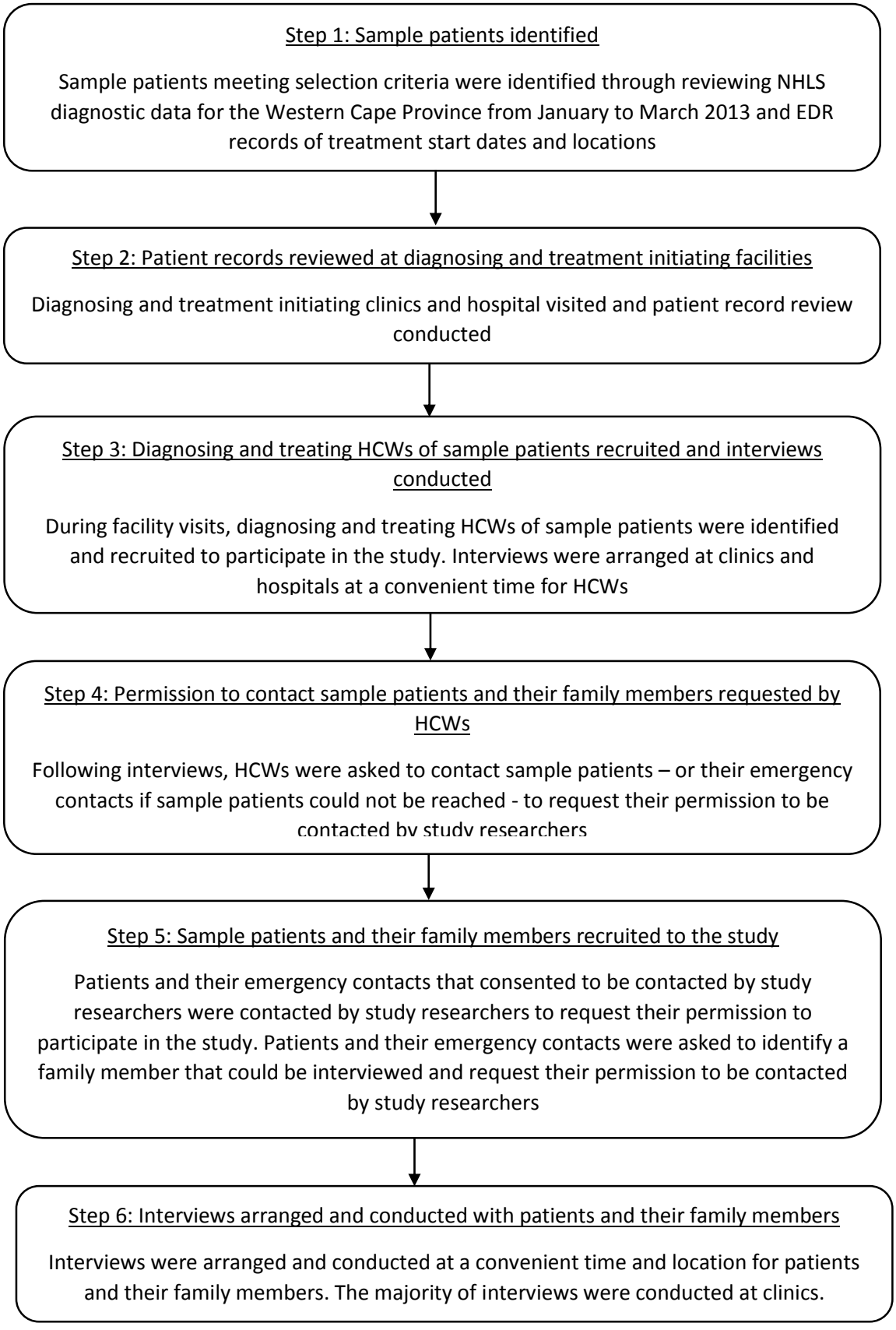
were initiated onto treatment. Twenty two sample patients were initiated onto treatment at the same facility where they were diagnosed. Thirteen sample patients were initiated onto treatment at a different facility from where they were diagnosed and the remaining 8 patients were not initiated onto treatment.

During initial facility visits, 59 patient folders were reviewed and 49 interviews were conducted with 31 HCWs, including 23 nurses, 7 doctors and 1 community care worker. A greater number of HCW interviews were conducted than the total number of HCWs who participated in the study, as some HCWs were interviewed regarding more than one sample patient. Additionally, a greater number of folders were reviewed than sample patients as some patients had folders at more than one facility.

Using open-ended interview guides, interviewers asked HCWs to describe their perceptions of sample patients' experiences following diagnosis, as well as any factors that they felt impacted on patients' linkage to treatment ouputs. HCWs were asked about sample patients' interactions with the health system following sputum collection on which RR-TB was diagnosed, including: whether tracing was required at any point; whether counselling was provided; whether the patient was referred between facilities; and, if so, whether transport was provided. HCWs were asked whether they perceived any barriers or enablers arising due to health system factors that impacted on patients' linkage to treatment outputs. HCWs were also questioned regarding whether they had insight into patients' personal lives and, if so, to describe from their perspectives how personal factors impacted on patients' linkage to treatment outputs. HCWs that had difficulty in recalling patients were given patients' folders to review during interviews. This approach was used to minimise the impact of recall bias on the study's results. HCWs were also questioned about their general

perceptions of barriers and enablers to treatment linkage in the facilities and districts where they worked.

Figure 2. Sequential approach used to recruit patients and collect data



During initial facility visits, HCWs were asked to contact sample patients to request their consent to be contacted by study researchers. All but three HCWs agreed to do this. The three HCWs that would not contact their patients explained that the patients were too ill to be interviewed and did not have emergency contacts. An additional 4 patients could not be contacted as no contact information was known to the facility. HCWs attempted to reach the remaining 36 patients and/or their emergency contacts via phone (22 patients), via community care workers (9 patients) or during facility visits (5 patients).

Seventeen of the 43 sample patients were located and interviewed. Reasons for not interviewing all 43 purposively sampled patients included: loss to follow up (16 patients), death (5 patients), ill health (3 patients), refusal (1 patient) and relocation (1 patient). Patients that could not be contacted by HCWs via phone, community care workers or due to having no known contact details were categorised as lost to follow up.

Eight family members of sample patients were recruited to the study and interviewed. Of the 8 family members interviewed, four were interviewed jointly with a sample patient and four were interviewed individually.

During interviews, patients and were asked to describe their experiences of diagnosis and linking to treatment. Family members were asked to describe the experiences of the patient. Open-ended questions were used during patient and family member interviews to explore the challenges that patients faced in linking to treatment, as well as enabling factors that assisted them in linking to treatment. Questions explored patients' experiences in interacting with the health system between diagnosis and treatment initiation and how this impacted on their linkage to treatment outputs. Questions also explored patients' personal circumstances – including household responsibilities, employment, social support and economic status - and whether factors related to personal circumstances impact on their

linkage to treatment outputs. Patients that did not link to treatment were asked to describe what happened following diagnosis and why they never linked to treatment.

Interviews were also conducted with four key informants (1 provincial and 3 district) in order to complement and compare our understanding of enablers and barriers to treatment linkage of individuals in leadership positions with those of front line providers. This allowed us to pool knowledge to understand the Western Cape more broadly. Key informants (KIs) included senior managers at district and provincial levels, as well as senior clinicians operating across districts. All four KIs approached for interviews agreed to participate. KIs were questioned about challenges faced in facilities diagnosing and treating DR-TB, as well as what - from their perspectives – works well and enables patients to rapidly link to treatment. All groups of participants (patients, family members, HCWs and KIs) were asked to give recommendations for how facilities could improve rates of treatment linkage and reduce treatment linkage delays and failure.

Data collected from interviews and folder review was supplemented by a review of NHLS diagnostic records for all RR-TB diagnoses processed in the Western Cape between January and March 2013 and data on dates of Xpert installation within Western Cape sub-districts. This was done to explore how the type of diagnostics tool used, as well as access to Xpert diagnostics impacted on linkage to treatment outputs.

It was determined that data saturation was achieved with regards to the health system mechanisms that impacted on treatment linkage, as participants' responses became repetitive at the end of the interview process, and KIs' explanations of barriers and enablers to treatment linkage echoed previously described phenomena [26]. However, data saturation was not achieved with regards to patient factors that contributed to linkage failure, given the

small number of interviews conducted with patients (or their family members) that failed to link to treatment.

Data analysis

Data analysis was guided by Coker et al.'s conceptual framework, which was adapted for the study [14]. The framework approach facilitated a combination of thematic analysis and cross-synthesis of data across embedded units, perspectives and districts. Unlike previous applications of the framework, a scoring approach was not used to evaluate data [14,27]. Rather the framework was applied to organise data and interpret findings – related to the treatment linkage output data we already had.

All recorded interviews were transcribed and interviews conducted in Xhosa and Afrikaans were translated into English. Interview transcripts and data extracted from patient folders were coded in Nvivo using a combination of inductive and deductive coding. Deductive codes were drawn out from an extensive literature review and Coker et al.'s framework. Inductive codes were drawn from emerging findings recorded in field notes kept throughout the data collection process, as well as themes that emerged during the coding process.

Following the completion of coding, each data source (interview transcripts and record notes) was reviewed again for each sample patient and a summary of barriers and enablers faced by each patient was drafted. The summarised enablers and barriers were then organised into matrix tables for each embedded unit by sample patient and perspective (see annexure 1). "The matrix is a tabular format that collects and arranges data for easy viewing in one place, permits detailed analysis, and sets the stage for later cross case-analysis with other comparable cases or sites" [16: 111].

Tactics recommended by Miles, Huberman and Saldana (2013) were used to draw meaning from the embedded unit matrices [16]. Within unit analysis was done for each embedded unit and patterns and themes were noted. Constant comparison and contrasts were used to identify patterns and themes across embedded units. Additionally, counting was used to compare the presence of a variable (such as being employed, having a stable place to stay or having access to Xpert) with patients' linkage to treatment outputs [16].

Following embedded unit analyses, case-level analysis was conducted using thematic matrices. Thematic matrices were used to organise data from all embedded units which allowed for visual comparison of the data across the case as a whole. Case-level thematic matrices organised all coded data falling within the theme of analysis by: (1) perspective (patient, family member, HCW, KI); (2) district (Cape Town, Cape Winelands, West Coast); and (3) focus (reported barriers and enablers faced by individual patients versus reported general barriers faced in facilities and districts) (see annexure 2).

Data was organised according to perspective to explore agreement and discrepancy between patients', family members', HCWs' and KIs' perspectives of barriers and enablers. Data was organised according to district to explore variation in barriers and enablers across rural and urban districts. Finally, data was organised by focus to determine whether participants' general perceptions of barriers and enablers matched those reported for individual patients.

Miles, Huberman and Saldana explain that "there are no fixed canons for constructing a matrix" [16: 113] and that a creative and systematic procedure should be used to develop a matrix that effectively responds to your research questions.

A framework synthesis approach was used to synthesize data compiled in thematic matrices according to the key domains of Coker et al.'s adapted framework for interpretive

analysis. The framework synthesis approach utilises a previously identified conceptual framework "to extract and synthesise findings" [28]. Emerging findings from thematic matrices were organised by domain for interpretive analyses and write up.

Use of theory and triangulation were applied as principles to ensure rigour during the data analysis process [17]. Coker's framework was used to synthesize and interpret finding from the data. Data was triangulated across sources of data, perspectives, and focus in order to identify where ideas converged or not. At an individual level, triangulation of data extracted from patient records, NHLS record and transcripts from HCW, KI, patient and family member interviews allowed us to piece together different perspectives and sources of information to have a more comprehensive understanding of patients' journeys and factors that impacted on their linkage to treatment outputs. At a group level, data triangulation allowed us to identify common and conflicting perspectives shared within and across groups of participants, as well as variation in challenges and enablers across rural and urban areas.

Using a framework approach to triangulate data allowed us to manage large amounts of data in a systematic way, using data reduction and data display tactics recommended by Miles, Huberman and Saldana [16], to demonstrate how reported findings were interpreted from the data. Data reduction tactics were used to manage large amounts of data through coding and drafting summaries of data to be inputted into tables (provided in the annexures) for data display. The combination of data reduction and data display tactics allowed us to test and draw conclusions from the data.

Ethics

Permission to conduct the study was granted by the University of Cape Town and the Western Cape Department of Health. Study participants were given a R100 grocery store voucher and

their travel costs were reimbursed. The names of sample patients and other study participants were removed from patient records and interview transcripts to protect their identities and, when necessary, pseudonyms were used in quotations. Effort was made to minimise any disruption to health services through arranging visits and interviews at convenient times identified by health facilities. To protect the health of interviewers, an infection control training was conducted and N95 masks were worn during interviews perfomed inside with sputum smear or culture positive patients. All interviewers received counselling training prior to conducting interviews, which was arranged to equip interviewers to respond any emotional distress demonstrated by participants during interviews.

Conceptual framework

In their framework, Coker et al. (2010) identify the following domains for consideration when evaluating an infectious disease programmatic intervention: (1) *epidemiological problem*, (2) *intervention*, (3) *context*, (4) *mechanisms*, (5) *outputs* and (6) *outcomes*. For this study, the framework was adapted to include a seventh domain for the (7) *patient*, in order to explore how patient factors impact on linkage to treatment.

Coker et al. define *epidemiological problem* as "infection levels and various disease characteristics" and *intervention* as "the intervention intended to serve public health" [14: i23]. In this study the *epidemiological problem* refers to the drastic increase in reported RR-TB incidence and poor treatment linkage fuelling onward transmission. The *intervention* refers to the rollout of Xpert diagnostics and decentralisation of DR-TB services. Both of these domains have been described in detail in the study background.

Outputs are defined in Coker at al.'s framework as "public health concepts that can be measured or determined" [14: i23]. In this study the scope of the output domain was

amended to incorporate aspects of McIntyre et al.'s framework that defines three key dimensions of access: availability, affordability and acceptability [50]. The *outputs* of interest in this study are patients' linkage to treatment outputs, including: expedited initiation, delayed initiation and non-initiation of treatment. Using patients' linkage to treatment outputs as an initial selection criteria, backward mapping was performed to explore the impact of context, mechanisms and patient factors on patients' linkage to treatment outputs. Backward mapping involves working backwards from endpoints (generally desired endpoints) to answer a policy evaluation question [29]. Knowing the linkage to treatment outputs a priori also allowed for the development of questions and exploration of how our other outputs of interest, namely availability, affordability and acceptability, [50] shaped patients' linkage to treatment journeys.

Definitions of the *context*, *mechanisms* and *patient* domains, as well as factors encompassed in these domains are described in detail in the study results.

Finally, Coker et al.'s *outcome* domain considers the impact of the interventions on the epidemiological problem. For example: has the programme successfully reduced incidence of the disease? While evaluating *outcomes* is beyond the scope of this study, this domain has been preserved in the diagram to retain recognition of the ultimate aim of the programmatic interventions. The amended framework and its application in this study is visually depicted in Figure 3.

Results

Backward mapping from patient's linkage to treatment outputs, this study explored how factors encompassed in the *context*, *mechanisms* and *patient* domains impacted on linkage to treatment.

Context domain

Coker et al. explain that contextual environments may enable or constrain the success of programmatic interventions. The *context* domain encompasses "the political, legislative, social, economic and technological environments within which communicable disease control programmes sit" [14: i23].

All KIs and multiple HCWs noted social and economic contextual factors that negatively impact on linkage to treatment, including: high rates of poverty, high rates of substance abuse, poor community knowledge regarding DR-TB, as well as seasonal labour migration in rural areas. While this study was unable to draw conclusions regarding the impact of these contextual factors on linkage to treatment in the province, these factors were explored at an individual level and are discussed further under the *patient* domain.

This study was able to identify factors relating to the technological, environmental and financing contexts that negatively impacted on linkage to treatment. At the outset of this study, it was expected that all facilities had access to Xpert diagnostics between January and March 2013. However, this study found that low Xpert usage amongst sample patients contributed to linkage delays. To better understand why few sample patients were diagnosed using Xpert, data was requested from the National Department of Health on the rollout of Xpert diagnostics and a review of all RR-TB diagnoses processed by the NHLS in the Western Cape between January and March 2013 was performed.

Data from the NDoH showed that Xpert diagnostics were rolled out sequentially to Western Cape sub-districts between January and March 2013 [20]. Xpert diagnostic tools were installed in NHLS laboratories in the City of Cape Town (excluding Mitchells Plain) and the West Coast prior to 2013. Whereas, in the Cape Winelands, Xpert diagnostics were only installed during February 2013 [20]. Data from the NHLS revealed low usage of Xpert between

January and March 2013, even in areas where Xpert was installed (see Table 3). The reasons for low usage are discussed under the *mechanisms* domain.

Table 3. RR-TB diagnoses processed between January and March 2013 in the Western Cape Province by diagnostic tool and district

	Test type						Total tests performed	
	Xpert		Line probe assay (LPA)		Culture DST		**N**	% of provincial total
Location	N	%	N	%	N	%		
City of Cape Town	191	55,4%	152	44,1%	2	0,58%	345	60,6%
Cape Winelands	12	15,0%	68	85,0%			80	14,1%
Eden	34	48,6%	36	51,4%			70	12,3%
West Coast	10	20,4%	39	79,6%			49	8,6%
Overberg	3	14,3%	18	85,7%			21	3,7%
Central Karoo	0	0,0%	4	100,0%			4	0,7%
WC provincial total	250	43,9%	317	55,7%	2	0,4%	569	100,0%

* Data compiled from NHLS diagnostic records

Three KIs and several healthcare workers further observed that efforts to decentralise services in rural areas have been hampered by factors related to the environmental context. Participants explained that, for many patients, clinic-level treatment initiation is not feasible as they live beyond walking distance of clinics capacitated to initiate and manage DR-TB care. In addition to environmental challenges, this study found that the perception of some KIs and HCWs that hospitalised services are superior to clinic services contributes to an ongoing reliance on hospitalised services for rural patients that are eligible for, and able to access, decentralised services.

> **Barrier:**
> *"We've always admitted patients [to hospital] for the first four to six months of treatment - everybody. We wouldn't start patients outside [of hospitals] on treatment, because our initial experience was bad outcomes… When the decentralised model of National came out we realised that we cannot keep people here for four to six months. They don't want to be here… So we made a decision to at least admit them for the first two months of treatment."* (Senior clinician 1 and sub-district manager, Rural TB hospital)

Finally, funding constraints within the province led to clinic-level staffing reductions that negatively impacted on linkage to treatment. Clinic-level staffing reductions are described under the *mechanisms* domain.

Mechanisms domain

The mechanisms domain refers to "the mechanisms within a programme, required to function effectively". Coker et al. link the mechanisms domain in their conceptual framework to Atun et al.'s key functions of the health system [29] explaining that the "functions [of the health system] consist of mechanisms that enable interventions to impact upon the health of populations" [15: i23]. Atun et al.'s six functions of the health systems include: stewardship and governance, financing, planning, service delivery, monitoring and evaluation, and demand generation.

While the functions establish the mandates of the health system, the mechanisms are the means by which they are delivered. Within the DR-TB programme, multiple interacting mechanisms must come into play in order to link patients to timeous treatment.

This study identified the following factors - falling within the mechanisms domain - that impacted on linkage to treatment, including: (1) diagnostic delays, action delays and missed results, (2) human resource challenges, (3) information system challenges, (4) availability of hospital beds and (5) availability of transport.

Diagnostic delays, action delays and missed results

Diagnostic delays are defined as delays between the collection of sputum and the processing of results. As found by previous studies [10,20], diagnostic delays contributed to overall delays to treatment initiation amongst patients diagnosed on line probe assay (LPA). Only 1 of the

16 patients categorised as delayed initiators was diagnosed using the Xpert. Diagnostic delays contributed to almost half of the overall delays to treatment initiation for this group.

Table 4. Time to diagnosis and treatment initiation following sputum collection by embedded sub-unit and diagnostic tool

	Expeditors (n 18)		Delayers (n 17)		Non-initiators (n 8)		Total sample patients (n 43)		Median time to diagnosis by diagnostic tool **
Diagnosis on Xpert	9	50,0%	1	5,9%	1	12,5%	11	25,6%	<1 days
Diagnosed on LPA	9	50,0%	16	94,1%	7	87,5%	32	74,4%	17 days
Median time to diagnosis following sputum collection by linkage category *	3 days		19 days		16 days				
Median time to treatment following sputum collection by linkage category *	6 days		43 days						

* expeditors, delayers, non-initiators. ** Xpert versus LPA.

Of the 43 sample patients included in this study, 32 were diagnosed on LPA. This is in part due to the sampling method used, as patients were selected according to their linkage to treatment outputs. The reasons as to why 32 sample patients were diagnosed on LPA (as opposed to Xpert) were assessed to better understand the factors contributing to diagnostic delays. Amongst the 32 patients diagnosed on LPA the reasons for not using Xpert included: ineligibility due to receiving drug susceptible TB treatment (13 patients) or due to previous interruption of DR-TB treatment (2 patients); non-adherence of HCWs to diagnostic algorithms (5 patients); no access to Xpert diagnostics (7 patients); and failure of Xpert to detect TB (2 patients).

Seven HCWs reported not having access to Xpert diagnostic tools between January and March 2013. Access issues occurred due to the phased nature of the rollout and should now be resolved as the Xpert rollout has been completed [20]. One doctor explained that

non-adherence was largely due to the learning curve required for HCWs to switch to these new diagnostics. Two KIs noted that low levels of confidence in Xpert results of some HCWs in the early days of the Xpert rollout further contributed to non-adherence – this was observed in some HCW interviews. The failure of Xpert to detect rifampicin resistance further contributed to diagnostic delays.

> **Barrier:**
> *"Usually we would take a culture… we don't actually diagnose them on the GeneX… We have patients that are GeneX 'RIF' here and then they are not 'RIF- resistant'."*
> (Nurse 15, Rural clinic)

Action delays and missed results further contributed to overall linkage delays and failure. Action delays are defined as delays between processing diagnostic results and recalling patients. Missed results are defined as results that were never seen by HCWs at diagnosing and/or referral facilities. Action delays and missed results were assessed through triangulating data collected from patients' medical and diagnostic records with healthcare worker and patient interviews. For instance, action delays were identified if a patient reported returning immediately to the clinic after receiving an urgent phone call, yet this phone call was weeks or months after results were processed.

Action delays and missed results contributed to overall delays amongst 5 patients categorised as delayers (out of a total of 17 delayers), and linkage failure amongst 2 patients categorised as a non-initiators (out of a total of 8 non-initiators). An urban patient categorised as a delayer experienced delays of one month and six months, respectively, in initiating MDR and XDR-TB treatment due to action delays. Her doctor explained that both delays were due to her results being missed (never seen) by HCWs at the clinic where she was diagnosed with MDR, and subsequently XDR, TB. A rural patient categorised as a non-initiator was treated for regular TB and discharged. Her doctor explained that her resistance

result was missed by HCWs at the clinic that diagnosed her - despite the fact that her husband was simultaneously receiving MDR-TB treatment at the same clinic.

All KIs and 9 HCWs reported that delays in acting on results and missed results occur due human resources and/or information system challenges described below.

Information systems

Within the Western Cape, sputum samples are collected by courier daily and sent to NHLS laboratories for testing. Once diagnostic results are ready they are uploaded to NHLS's electronic database (www.disa) and faxed to facilities [19]. In this study, all KIs and several HCWs reported that information systems challenges contributed to action delays following the processing of results. Information systems challenges included: limited access to the internet, limited access authorisation to NHLS's diagnostic database, broken fax machines, paper and ink stock-outs, as well as the lack of unique patient identifiers[3].

> **Barrier:**
> *"I think last week when I was up in [that clinic] I moaned about results not [being] available… That lady hasn't got an admin assistant, nothing… And sometimes their faxes doesn't work at the clinics…. They say the computers are there but nobody has got an email address, so they are still trying to get the email addresses to them or to get - to give them access to NHLS on the computer."*
> (Senior clinician 2, Rural TB hospital and clinics)

Availability of staff

The availability of dedicated TB nurses, DR-TB counsellors and tracers, as well as support staff were highlighted by HCWs and KIs as a critical mechanisms for linking patients to treatment.

The rotation of nurses between disciplines, or the lack of a dedicated TB nurse, was highlighted as a challenge contributing to linkage to treatment delays and failure by 3 KIs

[3] Unique patient identifiers would allow HCWs to view all previous diagnostic reports for patients from all facilities visited in the province or country.

and 9 HCWs. HCWs reported that the rotation of nurses results in an ongoing loss of skills in the TB programme and a breakdown in consistency of services. KIs explained that nurses are rotated between disciplines in order to achieve better integration of services, which is a policy goal of the Department of Health [31]. The provincial KI further observed that the lack of a dedicated person in clinics for receiving and signing off on results contributes to missed results and delays in acting on results.

> **Barrier:**
> *"One of our MDR patients who has died, she came to do a sputum last year and her sister came to get the result and what the patient told us subsequently this year was that she was told that the sputum was negative – [that] she didn't have TB. I think that somebody looked at the smear so if you have a change of staff or you suddenly get an untrained staff member, they look at a smear result. They didn't then look at the GeneXpert result. They were two separate results. She came back ill this year, so I mean that is months and months later."* (Doctor 1, Urban clinic)

According to all KIs and 4 HCWs, facility level administrative backlogs further contributed to missed results and delays in acting on results. Backlogs were exacerbated by the removal of TB clerks from a number of facilities. Two KIs explained that TB clerks (who previously provided administrative support to TB nurses in clinics) were phased out in early 2013 due to budget constraints.

> **Barrier:**
> *"TB is a very administratively difficult programme that involves lots of paper work. There are not enough hands [in clinics] to keep paper work up to date."* (Notes from interview with district manager of the TB programme, Urban)

The budget constraints also led to a removal of TB assistants – previously responsible for tracing patients and linking them to treatment. Two KIs explained that TB assistants were phased out in early 2013 and their roles were meant to be absorbed by community care workers hired through NGOs. In facilities where community care workers were trained and funded to trace DR-TB patients, nurses and doctors reported that tracing was working well. However, community care workers' roles were not consistent across facilities visited. Five

out 14 clinics visited did not have community care workers that were trained or allowed to trace DR-TB patients.

Enabler:
"We've got the community carers. We ask them to go and trace out the patient for us. We luckily in our facilities there are people that are staying mos in the community so they know the patients then … like our... [community care] worker, she knows most of the persons, most of the people in this community. Then sometimes when we struggle then we just go to her. Then we tell her that 'Gogo, we are looking for this patient, don't you know?' And then she'll say, 'Yes, I know and I know where she stays'. Then she must go to get the patient." (Sister 11, Rural clinic)

Barrier:
"The one I know, it's this follow-up, because the system we are using here which is the CCWs, if someone is missing the appointment and all that stuff, it could be easily recalled back to the clinic. But when it comes to the MDR patient, we don't have that system of recalling. It's only the MDR counsellor but who's working for all [the] district, not only based on the facility that can do that… and even before, the counsellor here at the clinic, they were not doing the counselling on MDRs, only on TB." (Community care worker 1, Urban clinic)

While the removal of TB clerks and assistants reduced staff capacity within clinics during a period of decentralisation, KIs highlighted parallel efforts underway to strengthen support for clinics to manage DR-TB care. DR-TB coordinators were appointed at a sub-district level during 2011 to support clinics in tracing patients and assist with data collection and monitoring. Additionally, in rural areas, doctor outreach programmes – involving monthly visits by doctors located at TB hospitals to clinics – were underway.

The availability of DR-TB counsellors at a clinic-level further emerged as a factor influencing linkage to treatment. HCWs frequently emphasised the role of counselling as a critical mechanism for linking patients to treatment. Patients' reports of receiving counselling were inconsistent and contradictory. However, the messages that patients most likely learnt through counselling and education enabled treatment linkage, as patients repeatedly noted concerns regarding their health and infecting others as motivating factors for initiating treatment.

Enabler:
"So she was the one that didn't want to come every day but we did try to give education and counselling every time. She didn't want, she didn't want to go to hospital… when we told her that she is going to be admitted - it was not an easy… It was a very, very big challenge for us because we have to counsel her several times… we did try to convince her… we told her that at least if she can start the treatment then at least [she] will be very much better." (Nurse 11 on delayed initiator, Rural clinic)

Barrier:
"You can see he is ill. He refuses [treatment] and he is still on drugs… Maybe he doesn't maybe know the seriousness of this TB he has… Or I will say he is not educated on it because no-one did speak actually with him about this resistant TB… He wasn't counselled about it or, you see… We don't got [an] MDR counsellors in the clinic facility… So when we recalled him the sister explained to him, but not - she didn't went into it." (Nurse 22 on non-initiator, Urban clinic)

Healthcare worker attitudes

Patients were questioned about the treatment that they received from HCWs following diagnosis. Overall, patients reported having good relationships with HCWs and that HCWs were a source of support in initiating and continuing treatment. Three patients reported being treated poorly by a HCW. These three patients engaged in the following actions to avoid the HCWs that treated them poorly: (1) switching to another clinic, (2) purposefully seeking care from another HCW at the clinic and (3) interrupting treatment.

Enabler:
"I can't complain, the Sister treats me well. Sometimes I get here and there are a lot of people sitting there then they call me first and they help me. I am happy. I told them the other day and I thanked them for treating me so well. I told the Sister that I notice that when she sees me sitting there then it is never long before she calls me and helps me." (Patient 10, Expeditor, Rural)

Barrier:
"I was scared of the sisters because they shout and I also understand that I am wrong in the way I take my treatment because in the two days that I did not go and go on the third day, they tell me and scold me and say what I'm doing is just not on. So when it happens again and don't go for about a week." (Patient 16, Non-initiator [this patient was categorised as a non-initiator due to experiencing a delay of over 6 months in initiating treatment], Rural)

Clinic versus hospital initiation of treatment

Table 5 summarises the location of diagnosis and treatment initiation for sample patients according to their linkage to treatment outputs and urban versus rural location. Sample

patients from the City of Cape Town are categorised as urban and sample patient from the Cape Winelands and West Coast are categorised as rural.

Table 5. Location of diagnosis and treatment initiation by facility type and embedded sub-unit

Location of diagnosis and treatment initiation		Expeditors			Delayers			Non-initiators		
		Urban (n 7)	Rural (n 11)	Total (n 18)	Urban (n 6)	Rural (n 11)	Total (n 17)	Urban (n 2)	Rural (n 6)	Total (n 8)
Location of diagnosis	Clinic	4	8	12	5	10	15	1	4	5
	Hospital	2	3	5	1	1	2	1	2	3
	Prison	1	0	1	0	0	0	0	0	0
Location of treatment initiation	Clinic	3	8	11	4	1	5			
	Hospital	3	3	6	2	10	12			
	Prison	1	0	1	0	0	0			

Clinic-level treatment initiation enabled expedited linkage to treatment amongst sample patients. Eleven of 18 patients categorised as expeditors initiated treatment at a clinic. Six of 18 patients categorised as expediters initiated treatment at a hospital. For all 6 expediters that started treatment in a hospital, mitigating circumstances were identified that assisted them in rapidly linking to treatment. Four patients were diagnosed with RR-TB while admitted to hospital (designated and non-designated TB hospitals) and immediately initiated onto treatment. One patient was sent to hospital before his results were processed due to his history of DR-TB treatment interruption and another patient was able to arrange his own transport to access the hospital - circumventing waiting periods for transportation.

Availability of transportation, beds and mobile clinics

While clinic-level treatment initiation enabled expedited treatment linkage, access to decentralised services remained limited in rural areas due to vast distances between patients' homes and clinics capacitated to manage DR-TB care [32]. HCWs' and rural district KIs' perceptions that hospitalised services are superior to clinic-level services further contributed to an ongoing reliance on hospitalised services in rural areas (see context domain).

Given limited access to decentralised services in rural areas, the mechanisms to link patients to hospitalised treatment emerged as critical factors influencing rural patients' linkage to treatment outputs. Eight HCWs and 2 KIs explained that severely limited access to transport services contribute to linkage delays and failure in rural areas.

Barrier:
"[Transportation] is the main problem… So they book [a bed] for the next Friday but then the transport / health-net transport, the bus is full, so they wait for the next Friday and sometimes for the next one. So that is where your three weeks and a month comes in before they start treatment." (Senior clinician 2, Rural TB hospital and clinics)

Waiting lists for beds at designated TB hospitals further emerged in this study as a barrier to expedited treatment linkage within rural areas. In urban areas, HCWs were generally able to circumvent this challenge through initiating out-patient treatment or referring patients to non-designated TB hospitals to manage treatment while waiting for beds at designated TB hospitals.

Enabler:
"Then just bear in mind that sometimes there are some clients that are on the waiting list for a bed, so you give the client the treatment while she is waiting for a bed. And some people actually recover very quickly when they start here." (Nurse 2, Urban clinic)

Barrier:
"From then I stayed home from the 4th of March, and in April I was still waiting for a place and they said there was no bed, and I only got there on 30th May. [The sister] phoned and said they said there was a bed available but she could not get hold of me, so I missed out on that week. I waited the next week and the vehicle of Health-net was full and I did not have a place, so I came on the 30th May and started treatment for pre-XDR in June'." (Patient 16, Non-initiator [this patient was categorised as a non-initiator due to experiencing a delay of over 6 months in initiating treatment], Rural)

Mobile clinics operating in some rural areas played an important role in linking patients living on farms and in remote areas to treatment, although patients diagnosed by mobile clinics were prone to linkage delays. Two HCWs and 1 KI explained that mobile clinics undertake monthly routes to collect sputum and recall patients. Patients that do not have phones and

are diagnosed by mobile clinics therefore have to wait for the next monthly route to receive their diagnostic results.

Patient domain

In an effort to bring patient issues to the forefront of this study, Coker et al.'s framework was amended to include a patient domain. Shippee et al.'s (2012) model of patient complexity was used as a framework to identify patient factors that impact on linkage to treatment outputs [33]. In their model, Shippee et al. explain that patient complexity occurs due to a combination of factors, categorised under patient *workloads* and *capacity.*

Patient workloads encompass "all the demands in patients' lives" [33: 1042], including demands resulting from employment, household and financial responsibilities, and the demands of patient-hood, such as daily clinic visits for injections. Patient capacity "denotes the resources and limitations affecting patients' ability or readiness to do [patient-related] work" [33: 1043]. Capacity issues encompass a range of influences, including mental health, mobility and pain, social support, literacy, as well as beliefs and understandings regarding DR-TB.

Barriers and enablers related to patients' workloads

Employment and household responsibilities

Employment responsibilities were noted as challenges in initiating treatment by several patients and their family members. For the most part, HCWs in this study were empathetic to linkage challenges resulting from employment responsibilities, raising them in their descriptions of patients' linkage journeys.

In this study, being self-employed or having a supportive employer that allowed patients to take time off for hospitalisation or daily clinic visits enabled expedited treatment linkage. However, five patients reported having to quit their jobs to initiate treatment, due to: being refused time off by employers for daily clinics visits or hospitalisation, or being too ill to continue working, or being instructed by HCWs that they could no longer work. Three HCWs and 2 KIs further noted seasonal employment as a barrier to treatment linkage, as seasonal workers frequently relocate and cannot be traced to link them to treatment.

Enabler:
"I went to work and I explained it to my boss and … I said to her she must also go and check herself out… but she was very supportive of me and she speaks to her husband and they said, 'No, as long as you go for your treatment we have no problem'. And she was supportive of me all the way up till now she still does." (Patient 1, Expeditor, Urban)

Barrier:
"We have seasonal workers here, you know, they travel all over the Western Cape… So they will work here for a couple of months… Now they come to the hospital or the clinic. They get diagnosed, h'm, and then, but when you look for them on the farm they already have moved to another town." (Nurse 19, Rural non-designated TB hospital)

Household responsibilities were further identified as a barrier to initiating treatment for patients requiring hospitalisation by several patients, HCWs and KIs. These challenges were faced by patients in all linkage categories, and contributed to delays for 3 patients categorised as delayers. While household responsibilities contributed to delayed linkage, having dependents enabled treatment linkage as 6 patients noted concern for dependents as a motivating factor for initiating treatment following diagnosis.

Enabler:
"What motivated me is that my child does not have a father. The father passed away, so when I looked at my child, I always thought I would rather die when he is older than while he is still young. He is 6 years old. So when I look at him I always think it will be better if I die and he's older and he's educated than while he is young. I don't have a mother or father so I can't leave him." (Patient 5, Delayer, Rural)

Barrier:
"She had a problem when she came, that she's got a daughter that is sick at home so she don't know what is she going to do if she is admitted to the hospital. [Eventually] she told us that… her sister came from Eastern Cape to look after her daughter." (Nurse 13 on delayer, Rural clinic)

Competing subsistence needs and grant support

Competing subsistence needs including food insecurity and/or not having a stable place to stay were raised as challenges by 9 of 17 patients interviewed and/or their family members. Grant support assisted patients in managing these needs, but did not always remove them entirely as some patients reported being unable to stretch grants to cover monthly subsistence needs. The impact of competing subsistence needs and grant support on linkage could not be judged as patients in all linkage categories reported these challenges and grant support was generally only available weeks to months after initiating treatment. However, participants from all categories recommended the provision of food support to improve rates of treatment linkage, adherence and completion.

> **Barrier**
> *"He did not have food and [would] be weak to walk because at that time he had nobody to support him and he was not working and staying alone, so he always came to me and I would give him whatever I had… [But] there [are] many people who are poor and have no food at their homes. Maybe if every morning they can be given soup when they arrive and again at about 13:00 they [can] be given bread and be encouraged in that way [then] they will come [to the clinic]."* (Family member 5 of delayer, Urban)

Patients' beliefs and concerns regarding DR-TB

For the most part, patients' beliefs and concerns regarding DR-TB and the services provided by public health facilities positively contributed to treatment linkage. Only 2 out of 17 patients interviewed reported seeking out alternative care from traditional or faith healers. Both of these patients only sought out alternative treatment after initiating DR-TB treatment. Overall, patients indicated good confidence in the services provided from public sector facilities. However, the difficult regimens required for treating DR-TB were noted by all groups of participants as a barrier to treatment initiation and adherence.

Patients that successfully linked to treatment also demonstrated a good understanding of DR-TB disease. All but 1 of the interviewed patients that linked to treatment

reported concerns regarding their health and/or infecting others as motivating factors for initiating treatment. Although, 2 patients further noted stigma and fear of being blamed for spreading DR-TB as an impetus for starting treatment.

> **Enabler:**
> *"I thought about the children in the house, my family, I could infect them. That is why I went back, never mind the lot of tablets."* (Patient 17, Expeditor, Rural)

Patient characteristics, risk factors and social support

HCWs frequently noted patients' characteristics as factors influencing treatment linkage. Patients that initiated expedited treatment were described as responsible and reliable, whereas patients that experienced long delays or failed to link to treatment where described as unreliable. Patients that were described as unreliable, experienced one or more of the following risk factors that contributed to delayed or failed linkage to treatment: history of treatment interruption (HIV and TB), alcohol and/or drug addiction, participation in criminal activity, lack of social support, or lack of concern or hopelessness regarding treatment.

All participant groups perceived patients' support networks as a key factor influencing their linkage to treatment outputs. The role of support networks also emerged in narratives of patients' linkage journeys. After receiving their DR-TB diagnosis, patients generally reported being frightened and distressed and drawing on their support networks who encouraged them to initiate treatment. Support networks were also drawn on to manage competing subsistence needs through treatment periods.

Enabler:
"When I started treatment [my boyfriend] was the one that always encouraged me to go to the clinic, and I would say, wait about the clinic. He would remind me that he had long been asking me to go to the clinic and he could see that I was losing weight and not wanting to go to the clinic…. I can say he is the one that always supported me because he always gave me the tablets even now that I am taking treatment he is also cooking porridge for me and giving me tablets when it is time". (Patient 3, Delayer, Urban)

Barrier:
"He told us he was stabbed. That was years ago and at the time… they found out that he had TB… Maybe it was resistant [at] that time or maybe it was susceptible that time and converted to MDR… He just refused [treatment]… I think it is for the everyday coming and the injection and the two years - it seems for him too long… and the gangster-related story he won't be able to walk up and down every day. They are always in hideout. He is a gangster in his own area… And when they are on drugs they believe the drug keep the pain away. So for him he don't see the need to start the treatment." (Nurse 22 on non-initiator, Urban clinic)

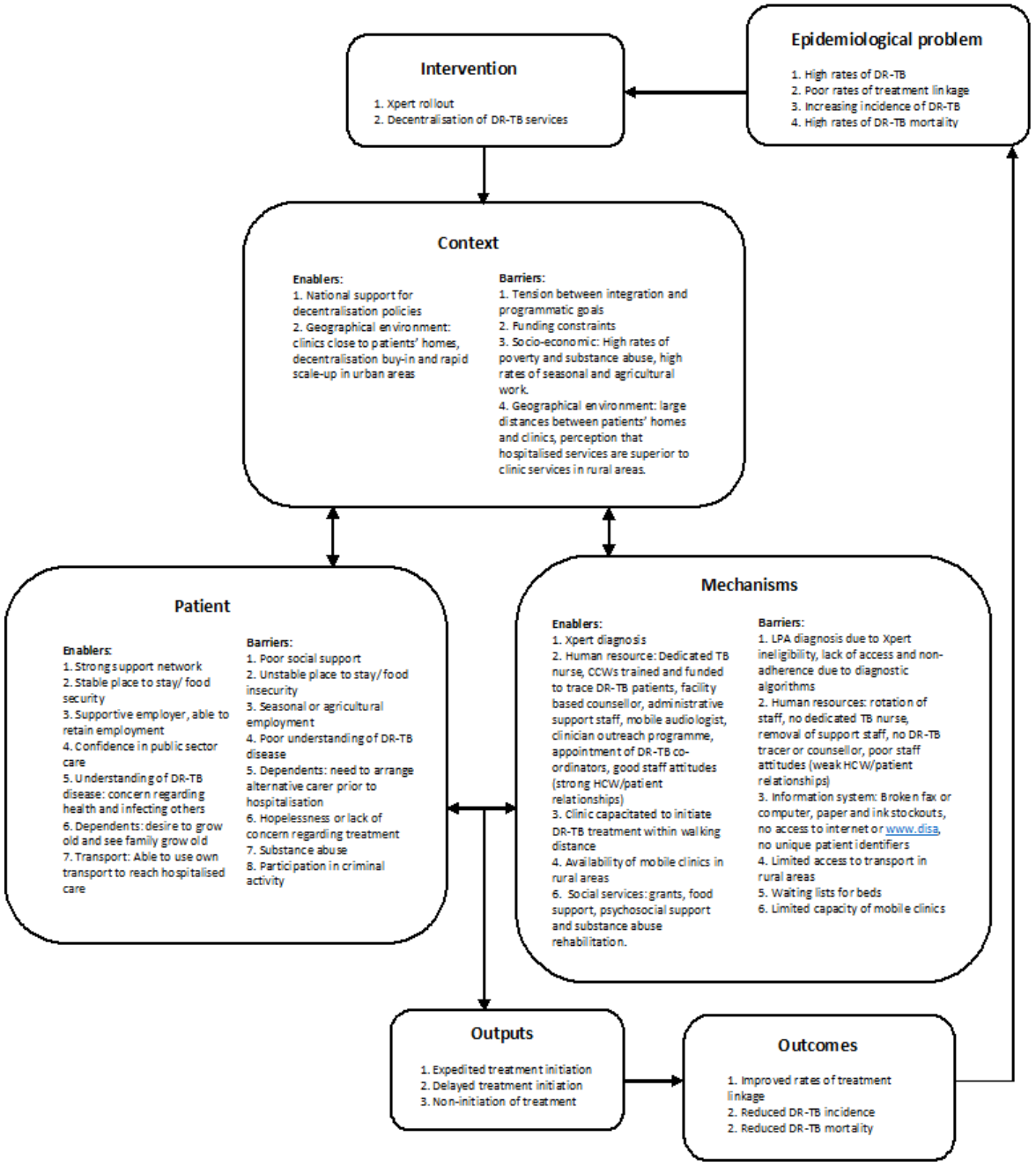
Discussion

This study identified multiple factors falling within the *context*, *mechanisms* and *patient* domains that enabled and constrained expedited treatment linkage following RR-TB diagnosis. The enablers and barriers to expedited treatment linkage identified in this study are visually depicted in the amended Coker et al. framework in Figure 3. Enabling factors and constraining factors were experienced by patients in all linkage categories and it was often not a single factor, but the combination of multiple interacting factors that determined patients' linkage to treatment outputs.

Between January and March 2013, limited access to Xpert diagnostics emerged as barrier to expedited linkage, most commonly amongst patients that were ineligible for Xpert diagnosis according to diagnostic algorithms. Limited access due to the phased nature of the Xpert rollout further contributed to delays. This challenge should now be resolved as the rollout has been completed [20]. Amongst eligible patients with access to Xpert diagnostics, non-adherence by HCWs to diagnostic algorithms and failure of Xpert to detect rifampicin resistance further contributed to delays. A recent retrospective study conducted in Khayelitsha township, in the Western Cape, reported that between 2012 and 2013 only half

of patients diagnosed with RR-TB were diagnosed on Xpert [54]. The most common reason for this was the failure of Xpert to detect RR-TB and subsequent culture diagnostics [54].

Figure 3. Barriers and enablers to expedited treatment linkage identified in this study organised according to the amended Cocker et al. framework



Previous studies have also documented poor adherence to the Xpert diagnostic algorithms within South Africa [4,34]. Dlamini-Mvelase et al. suggested that poor adherence to the

diagnostic algorithm occurred due to limited training prior to the Xpert rollout [4] and Churchyard et al. recommended a simplification of the diagnostic algorithm to improve adherence [34]. Participants in this study reported that poor adherence was due to the learning curve required to switch to the new diagnostic tools, which was exacerbated by ongoing rotation of staff, as well as low levels of confidence in Xpert results by some HCWs.

This study found that the ongoing rotation of staff contributed to action delays and missed results following RR-TB diagnosis. Similarly, Loveday et al. reported that rotation of staff between disciplines contributes to a loss of skills from the DR-TB programme in South Africa and a breakdown in consistency of services [23]. Given the complexity of interpreting TB results, rotation of staff can contribute to missed results and delays in acting on results, as new staff may have difficulty in interpreting results and may be less likely to follow up on pending results. Action delays and missed results were exacerbated by the recent removal of TB clerks from a number clinics in this study, resulting in greater administrative workloads for nurses.

The ongoing rotation of nursing staff and removal of TB specific support staff revealed the tensions that exist between the health system's goals to integrate health services versus DR-TB programmatic goals [35,36]. These challenges further highlighted disconnect between financing priorities and policy mandates, as a number of clinics experienced reductions in TB support staff at the same time as their workloads and responsibilities for managing DR-TB care rapidly increased.

Information systems challenges further contributed to action delays and missed results. The lack of a unique identifier to allow HCWs to review all of a patient's previous diagnostic results has been repeatedly highlighted as a challenges in South Africa, including in the NHLS's strategic plan [34,37,38]. Implementing unique patient identifiers would

improve diagnostic follow up for patients that move between facilities, districts and provinces. Within clinics, broken fax machines, paper and ink stock-outs, internet connectivity challenges and limited staff access to NHLS's diagnostic database contributed to delays. Similar challenges have been previously documented in South African clinics, negatively impacting on the provision of antiretroviral therapy [39].

Within the Western Cape, the decentralisation of DR-TB services has been shaped by the context in which it has been implemented. Widespread access to decentralised services has been achieved in the City of Cape Town, but in rural areas decentralised treatment initiation remains unrealistic for many patients that live beyond walking distance of clinics capacitated to manage DR-TB care [32,40]. Additionally, the perception of some HCWs and some KIs that hospitalised services are superior to decentralised services contributed to an ongoing reliance on hospitalised services in rural areas - highlighting the importance of generating buy-in from front line providers when implementing health systems interventions [41,42].

Amongst rural patients referred to hospitalised care, limited access to transport and waiting lists for beds at designated TB hospitals contributed to delays. Previous studies have reported similar challenges [11,43–45]. Additionally, in a recent costing study Sinanovic et al. observed that decentralised services may not be appropriate for all groups of patients in South Africa [46]. Sinanovic et al. stressed that proper referral systems between clinics and hospitals continue to be necessary to link XDR, complicated MDR and patients in low density, rural areas in South Africa to treatment [46].

Hospital diagnosis *during an in-patient stay* was identified as an enabler to expedited treatment linkage. This finding may be due to the small sample size and was only relevant to patients that were diagnosed while admitted to hospital. Previous studies provide strong

evidence that, in general, DR-TB diagnosis within a hospital, as opposed to a clinic, increases a patients' likelihood of linkage failure [24,25]. Ebonwu et al. demonstrated that in Gauteng MDR-TB patients diagnosed in hospitals are 8 times less likely to link to treatment than patients diagnosed in clinics and that the high rates of death amongst patients diagnosed by hospitals contributed to linkage failure for this group [25]. Nkosi et al. further theorised that hospitals may be less effective than clinics at tracing patients, resulting in higher rates of linkage failure [24].

In this study, HCWs at hospitals reported relying on phone calls or clinics to trace patients that failed to return for results or treatment, whereas clinics generally utilised community care workers to trace patients at their homes. However, some facilities were unable to trace DR-TB patients at their homes as community care workers (hired through non-profit organisations) were not trained, funded or allowed to visit DR-TB patients.

This study further highlighted reporting challenges within the DR-TB programme as more than half of patients initially selected as non-initiators from EDR were later re-categorised as treatment initiators. Reporting challenges within the DR-TB programme have been previously documented [47] and likely contribute to overestimates of the treatment gap [48]. One participant noted that reporting challenges can result in demotivation of HCWs providing DR-TB care, as their successes are often punished rather than rewarded. Franco et al. emphasize the importance of collecting quality information and providing proper feedback and recognition when seeking to improve HCW motivation [49].

For the most part, in this study HCWs attitudes positively contributed to acceptability of services. However, difficult treatment regimens negatively impacted on the overall

acceptability of services. McIntyre et al. define acceptability as "the fit between provider and patient attitudes towards and expectations of each other" [50: 187].

Food insecurity was repeatedly noted as a key concern of patients and their family members, negatively impacting on the acceptability of services. Similar challenges have been documented amongst patients with HIV/AIDS. Weiser et al. note that "food insecurity and other competing subsistence needs are associated with worsened access and adherence to care" [51: 1773s]. Food insecurity remained a concern even amongst patients receiving social grants, as grants could often not be stretched to cover food costs for the entire month.

Patients' household and employment responsibilities further emerged as challenges in linking to treatment. Similarly, a previous study conducted in the City of Cape Town reported that patients contribute to delays to treatment initiation by missing appointments, often due to family, financial and employment responsibilities [52]. In this study a number of patients reported having to quit their jobs in order to initiate treatment. This is concerning as a Western Cape cohort study recently demonstrated that steady employment reduces ones' risk of DR-TB treatment interruption [22].

Other psychosocial and economic challenges faced by patients in linking to treatment included: not having a stable place to stay or social support, substance abuse and hopelessness regarding treatment. Patients with unstable social circumstances and substance addictions not only face challenges in linking to treatment, but also face a high risk of default following treatment initiation [22,53]. Kendall et al. highlight that policy guidelines recommend psychosocial evaluation, substance abuse rehabilitation, and food aid following treatment default. They recommend that resources are rather allocated to provide adherence-focussed interventions prior to treatment default for high risk patients [22].

Expanding these services to high risk patients following RR-TB diagnosis may further assist in improving linkage to treatment.

Conclusions

This study identified a number of barriers to expedited treatment linkage related to health systems mechanisms to link patients to treatment. Within the Western Cape there is significant opportunity to improve linkage to treatment through strengthening these mechanisms. At a clinic-level, staffing and information systems challenges impeded on expedited linkage to treatment. In rural areas, access to decentralised, clinic-level services remained limited and waiting lists for beds at designated TB hospitals, as well as limited access to transportation services impeded on expedited linkage to treatment.

In linking to treatment, patients commonly face challenges due to competing subsistence needs and household or employment responsibilities. Additionally, substance addiction, having a history of treatment interruption, hopelessness regarding treatment, as well as not having a stable place to stay or social support may increase patients' risk of linkage failure. Expanding access to psychosocial services (substance abuse rehabilitation and psychosocial evaluations) following RR-TB diagnosis may assist in linking high risk patients to treatment. Additionally, the provision of food support (in addition to social grants) should be evaluated as a tactic to improve treatment linkage and adherence.

Limitations

There are a number of limitations to the findings reported in this study. Firstly, many of the patients initially selected as non-initiators were recategorised as expedited or delayed

initiators following data collection - leading to low patient numbers in the non-initiator group. Data saturation was therefore not achieved regarding contributing factors to non-initiation.

An additional limitation of this study was that a number of sample patients from all embedded units and their family members could not be located. As a result of this, the factors identified as barriers and enablers to treatment linkage in this study are more representative of the views of HCWs than those of patients and their family members.

Additionally, data collection occurred between 15 months and 18 months after patients were diagnosed with RR-TB. Therefore the findings of this study may contain some recall bias. To minimise the impact of recall bias on the study's findings, patient folders were reviewed prior to data collection and participants were questioned regarding the timeline reflected in folders. Additionally, HCWs that had difficulty in recollecting events were provided patient folders to refer to during interviews.

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Annexure 1

1. Example of matrix outline used for embedded unit matrices

Expedited initiators								
	Barriers reported by				Enablers reported by			
	HCW	Patient	Family member	Folder	HCW	Patient	Family member	Folder
Patient 1								
Patient 2								
Patient 3								
…								

Annexure 2

2. Example of matrix outline used for case-level thematic matrices

Theme: Transport				
	Focus of coded text (individual patient versus general)			
	Expedited initiators	Delayed initiators	Non-initiators	General barriers and enablers
	District: Cape Town			
Patient perspective				
Family member perspective				
HCW perspective				
KI perspective				
	District: Cape Winelands			
Patient perspective				
Family member perspective				
HCW perspective				
KI perspective				
	District: West Coast			
Patient perspective				
Family member perspective				
HCW perspective				
KI perspective				

Part D:
Policy brief

Health system challenges and opportunities to strengthen linkage to care following RR-TB diagnosis in the Western Cape

Key points:

- There is significant opportunity in the Western Cape to improve linkage to treatment following RR-TB diagnosis through addressing staffing, information system, infrastructure and transport challenges.
- There is also opportunity to leverage and build on mechanisms that facilitate linkage to care following RR-TB diagnosis in the Western Cape by increasing usage of Xpert diagnostics and improving perceptions of decentralised services, as well as mechanisms to link patients to hospitalised services in rural areas.

Introduction

During the past few years, South Africa has experienced a growing gap between the number of patients diagnosed with RR-TB and those initiated onto treatment. According to estimates from the World Health Organisation (WHO), only 41% of patients diagnosed with RR-TB in South Africa during 2013 initiated treatment.

The Western Cape Province has the third highest burden of RR-TB, after KwaZulu-Natal and the Eastern Cape. Estimates of treatment linkage in the Western Cape are similarly low to the rest of the country. According to estimates from the National Department of Health, only 45.9% of patients diagnosed with MDR-TB in the Western Cape during 2012 linked to treatment.[i]

However, a recent study reported that high burden clinics in the City of Cape Town fare significantly better than provincial estimates in linking patients to treatment – reporting that around 90% of patients in 10 high burden Cape Town clinics linked to treatment within 6 months of diagnosis [1].

Rifampicin resistant (RR) TB is a good indicator of MDR-TB. According to treatment guidelines, patients diagnosed with RR-TB should be immediately initiated onto treatment – while undergoing further resistance and confirmatory testing. Additionally, the National Strategic Plan on HIV, TB and STI's (2012 – 2016) established a target to initiate all RR-TB patients onto MDR-TB treatment within 5 days of diagnosis.

Methodology

To understand why patients diagnosed with RR-TB in the Western Cape frequently fail to link to treatment, we conducted an embedded case study to explore barriers and enablers to treatment linkage following RR-TB diagnosis within the context of ongoing decentralisation of DR-TB services and the rollout of Xpert diagnostics.

What is an embedded case study?

A case study is a research method that involves in-depth analysis of a particular case. A case may be a person, place, process or situation. The case in this study is linkage to treatment following RR-TB diagnosis in the Western Cape. An embedded case study is a case study with more than one natural unit of analysis. The embedded units that were analysed in this study were patients' linkage outcomes.

To better understand enablers and barriers to expedited treatment linkage, we conducted an in-depth analysis of 43 patients' journeys following RR-TB, considering multiple perspectives on the factors that influenced their linkage outcomes.

The journeys of 43 patients diagnosed with RR-TB between January and March 2013 were explored through reviewing their NHLS records, reviewing clinical notes in their folders at facilities and conducting interviews with 31 healthcare workers that oversaw their care at diagnosing and treatment initiating facilities. When possible interviews were also conducted with sample patients and/or a family member.

National interventions to improve treatment linkage

1. The rollout of Xpert diagnostics
During 2011, the NDoH embarked on a national rollout of Xpert diagnostics. The rollout was coupled with the adoption of a new diagnostic algorithm recommending Xpert as an initial diagnostic test for all TB suspects. Xpert significantly reduced diagnostic turn-around time for detecting RR-TB in comparison to line probe assay (previously used to detect RR-TB in the Western Cape). A recent study conducted in the City of Cape Town reported that average diagnostic turn - around time for detecting RR-TB was < 1 day for the Xpert versus 24 days for line probe assay [1].

2. The decentralisation of DR-TB services
During 2011, the NDoH adopted a national policy for the decentralisation of DR-TB services, recognising that traditional hospitalised services were increasingly unable to accommodate rising RR-TB patient numbers. Previous experience in piloting decentralised services in an urban township in the City of Cape metropolitan showed that decentralisation of services could improve linkage to treatment and reduce delays to treatment initiation following diagnosis [2].

The 43 sample patients included: 18 patients that started treatment within one month of sputum collection on which RR-TB was diagnosed; 17 patients that started treatment more than one month and less than six months after sputum collection on which RR-TB was diagnosed; and 8 patients that did not start treatment within six months of sputum collection on which RR-TB was diagnosed.

All sample patients were diagnosed and (when relevant) initiated onto treatment in the urban City of Cape Town metropolitan municipality, the rural Cape Winelands district and the rural West Coast district. We selected sample patients from these districts in order to explore variation in treatment linkage barriers and enablers across urban and rural areas with varying level of decentralisation. In this study, decentralisation was defined as clinic-level MDR-TB treatment initiation, in line with the commonly accepted definition of decentralisation in the Western Cape.

This study also aimed to understand barriers and enablers to treatment linkage in Western Cape facilities and districts beyond our sample patients' experiences. All 31 HCWs interviewed regarding sample patients were also asked to describe their general perceptions of barriers and enablers to treatment linkage following RR-TB diagnosis in the facilities and districts where they worked. The 31 HCWs included in this study worked at 21 health facilities in the City of Cape Town, the Cape Winelands and the West Coast. The 21 health facilities included: 1 mobile clinic, 14 clinics, 3 non-designated TB hospitals (district and tertiary) and 3 designated TB hospitals.

In addition to the 31 HCWs that we spoke to, we also interviewed 4 key informants (1 provincial and 3 district) in order to complement and contrast the perspectives of enablers and barriers to treatment linkage of individuals in leadership positions with those of front line providers. Key informants included senior managers at district and provincial levels, as well as senior clinicians operating across districts.

Findings

This study explored barriers and enablers related to 1) the Western Cape context, 2) the mechanisms of the health system to link patients to treatment and 3) patient related factors. Multiple barriers and enablers related to the health system mechanisms to link patients to treatment were identified - illuminating opportunities to improve treatment linkage following RR-TB diagnosis through strengthening these mechanisms. Some barriers and enablers were relevant to both urban and rural areas, and some were unique to rural areas.

Barriers and enablers related to mechanisms of the health system in urban and rural contexts:

Barrier 1: Low Xpert usage

Low Xpert usage contributed to linkage delays amongst sample patients. Low Xpert usage is this study was due in part to the phased nature of the rollout, as not all facilities had access to Xpert diagnostics prior to 2013. However, where Xpert diagnostics were available, low usage remained a challenge. Low usage occurred due to:

i) Ineligibility: Patients already receiving treatment for regular TB were ineligible for Xpert diagnosis according to diagnostic algorithms.
ii) Poor adherence to diagnostics algorithms: A number of patients that were eligible for Xpert diagnosis were not diagnosed on Xpert due to poor adherence of HCWs to diagnostic algorithms.
iii) Failure of Xpert to detect RR-TB: Xpert did not detect RR-TB on two patients.

HCWs and key informants reflected that the learning curve required to switch to Xpert diagnostics, as well as low levels of confidence of some HCWs in Xpert results during the early stages of the rollout contributed to poor adherence. Additionally, HCWs and key informants reflected that the ongoing rotation of staff likely contributed to poor adherence to diagnostic algorithms, as it often takes time for HCWs to become confident with complicated TB diagnostics algorithms.

Barrier 2: Delays in acting on results and missed results

Delays in acting on diagnostic results after they were returned to facilities, as well as missed (unseen) results contributed to linkage delays and failure amongst sample patients. HCWs and key informants explained that delays in acting on results and missed results occurred due to the following challenges:

1) Rotation of staff: New staff rotated into the TB programme may have difficulty in interpreting complex TB results and may

be less likely to follow up on pending results.

2) Administrative backlogs: Limited administrative support and the lack of a dedicated person for receiving and signing off on results in clinics contributed to backlogs in seeing and acting on results.
3) Information systems challenges: Broken fax machines, paper and ink stock-outs, limited internet access, and limited HCW access to NHLS's diagnostic database led to delays in seeing and acting on results.
4) No unique patient identifiers: The lack of unique patient identifiers prevented healthcare workers from reviewing all previous diagnostics results for patients that moved between facilities.

Enabler 1: Access to decentralised services

Initiation of treatment at a clinic, as opposed to a hospital, contributed to expedited treatment linkage amongst sample patients. In urban areas, decentralised services were widely available, yet in rural areas access remained limited (see right column).

Enabler 2: Availability of DR-TB counsellors and tracers

The availability of clinic-level DR-TB counsellors and tracers enabled treatment linkage – particularly for patients that were resistant to starting treatment or failed to return for diagnostic results or treatment. However, not all clinics included in this study had clinic-level DR-TB counsellors or tracers.

Enabler 3: Good patient/ provider relationships

Good patient/ provider relationships positively contributed to treatment linkage and retention.

Barriers and enablers related to mechanisms of the health system unique to rural contexts:

Barrier 1: Limited access to, and negative perceptions of, decentralised services

Limited access to decentralised services constrained expedited treatment linkage in rural areas. Access was limited by distances between patients' homes and clinics, as many patients live beyond walking distance of clinics that have the capacity to initiate and manage MDR-TB treatment.

Negative perceptions of decentralised services of some HCWs and key informants also negatively impacted on treatment linkage. As a result of negative perceptions, some patients that are eligible for[ii] and able to access decentralised services continue to be referred to hospitalised services.

Barrier 2: Waiting periods for beds

Waiting periods for beds at designated TB hospitals contributed to linkage delays for rural patients requiring hospitalised treatment initiation. Waiting periods of up to a few weeks were commonly reported.

Barrier 3: Limited access to transport services

Limited access to transport services constrained expedited treatment linkage for rural patients requiring hospitalised treatment initiation. HCWs and key informants explained that, due to limited availability of transport, ambulances are often full and patients must sometimes wait for weeks before receiving transport. HCWs and key informants also reported that ambulance pick up points are often far from

patients' homes and often very difficult for patients to access.

Additional challenges: food insecurity

Food insecurity throughout treatment periods was repeatedly raised as a key concern of patients. Food insecurity was a concern for patients with and without social grants, as social grants could often not be stretched to cover monthly expenses. Patients, their family members, HCWs and key informants all recommended the provision of food support to improve treatment linkage and adherence.

Limitations

The findings of this study give us a lens into the life of patients who need care and help us to build the knowledge to improve services in the WC, these findings however, due to the sample size, cannot be generalised to the Western Cape as a whole.

A limitation of this study is that a number of sample patients and their family members could not be located, and therefore the findings of this study are more representative of the views of HCWs and key informants than those of patients and their family members. An additional limitation of this study was that very few patients and family members of patients that did not initiate treatment within 6 months were interviewed, due to difficulties in identifying and locating these patients.

Policy recommendations

This study identified a number of barriers and enablers to expedited treatment linkage following RR-TB diagnosis in the Western Cape in the context of the introduction of Xpert diagnostics and decentralisation of DR-TB services. The barriers and enablers identified in this study demonstrate that there is significant opportunity in the Western Cape to improve linkage to care through strengthening the health systems mechanisms for linking patients to treatment. Based on the findings of this study, the following policy recommendations are made:

Staffing interventions:

- The Western Cape Department of Health (WCDoH) should assess different models of rotating staff in and out of TB programme as the current model negatively impacts on linkage to care. Additionally, the WCDoH should ensure that clinics have adequate administrative support to deal with the administrative workloads of the TB programme. For a 'quick win' the WCDoH could ensure that all clinics have an assigned staff member responsible for receiving and signing off on TB diagnostic results.

- DR-TB counsellors and tracers[iii] play an important role in linking patients to treatment. Ensuring that all clinics have staff that are trained and funded to provide DR-TB counselling and tracing could improve linkage to care.

- While decentralised treatment initiation is not feasible for all rural patients, generating buy-in for decentralisation from healthcare workers and TB programme managers in rural areas would assist in increasing use of decentralised services by patients that are eligible for, and able to access, decentralised sites (recognising that some factors are associated with the social determinants of health and will need inter-sectoral collaboration). Educating front-line providers regarding the reasons for decentralisation, ensuring their ongoing participation in the policy process and adapting the policy to the local context can assist in generating buy-in.

Information systems interventions:

- To reduce linkage delays and failure, broken fax machines must be urgently dealt with and adequate supplies of ink and paper must be available in all clinics. Additionally, the WCDoH should urgently deal with internet connectivity and NHLS access issues (limited staff log-ins and email addresses) to ensure that staff can rapidly access patients' diagnostic reports.

- Working together with the NHLS, the National Department of Health should implement unique patient identifiers to allow health care workers to view all previous diagnostic results of patients. This would assist in reducing linkage failure and delays, as well as curb costs of repeated testing.

Infrastructure interventions:

- Given limited access to decentralised care in rural areas, the WCDoH should assess the ongoing need for beds at designated TB hospitals and consider increasing bed capacity in the province relative to need.

Transport interventions:

- The WCDoH and HealthNET emergency transportation services must jointly tackle transportation challenges in rural areas as a critical intervention to improve treatment linkage. Increasing the frequency of ambulance routes and expanding pick-up locations to improve accessibility for patients would assist in reducing linkage delays and failure in rural areas.

Food support interventions:

- The WCDoH should evaluate the provision of food support (in the form of vouchers, food parcels or daily meals) in addition to social grants as a strategy to improve treatment linkage and ongoing adherence.

This study was conducted towards the fulfilment of a Master's degree at the University of Cape Town (UCT) under the supervision of UCT's Health Economics Unit. The study was completed as part of the requirements for the 'Linkage to care for drug resistant TB following Xpert implementation in South Africa' that is being conducted by the University of Cape Town's Department of Medical Microbiology. This study was funded by the Bill and Melinda Gates Foundation, as well as bursary support for the master's student from the Wits Health Economics and Epidemiology Research Office (HE2RO) and DAAD-NRF.

References:

1 Naidoo P, du Toit E, Dunbar R, Lombard C, Caldwell J, Detjen A, et al. A Comparison of Multidrug-Resistant Tuberculosis Treatment Commencement Times in MDRTBPlus Line Probe Assay and Xpert® MTB/RIF-Based Algorithms in a Routine Operational Setting in Cape Town. Nicol MP, editor. PLoS One. Public Library of Science; 2014;9(7):e103328. A

2. Cox H, Hughes J, Daniels J, Azevedo V, McDermid C, Poolman M, et al. Community-based treatment of drug resistant tuberculosis in Khayelitsha, South Africa. Int J Tuberc Lung Dis. International Union Against Tuberculosis and Lung Disease. 2014;18(4):441–8.

[i] Estimates for linkage are subject to some error due to reporting and monitoring challenges in the TB programme.

[ii] The decentralisation guidelines recommend clinic-level treatment initiation and management for low grade transmission risk, smear negative MDR-TB patients with stable social circumstances, as well as patients that refuse hospitalisation. These patients must visit clinics daily for injections throughout the intensive phase of treatment. XDR-TB patients, smear positive MDR-TB patients, severely ill and complicated patients, as well as patients whose social circumstances preclude them from ambulatory care should continue to be hospitalised during the intensive phase of treatment.

[iii] DR TB tracing may be performed by CCWs or TB assistants.

Part E:
Appendices

Includes:

1) Participant information and consent form
2) Interview guides 1 – 7
3) Patient record data extraction form
4) Patient treatment literacy pamphlet
5) BMC Health Services Instructions for Authors

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences

DIVISION OF CLINICAL LABORATORY
SCIENCE/MEDICAL MICROBIOLOGY

PARTICIPANT INFORMATION AND CONSENT FORM

Consent form for participation in an in-depth interview regarding [*your* / *your family member or friend's* / *your patient's*] **experience following diagnosis with rifampicin or drug resistant tuberculosis**

Study Title: *Linkage to Care for Drug Resistant TB Following Xpert Implementation in South Africa*

Investigators:

- *University of Cape Town, South Africa:* Prof Mark Nicol (Principal Investigator), Dr Helen Cox (Co-Investigator), Dr Lindy Dickson-Hall (Co-Investigator)
- *National Health Laboratory Service/University of Witwatersrand, South Africa:* Prof Wendy Stevens (Co-Principal Investigator)
- *University of Amsterdam/Amsterdam Institute for Global Health and Development:* Prof Frank Cobelens (Co-Investigator), Dr Anja van't Hoog (Co-Investigator)
- *London School of Hygiene & Tropical Medicine, UK:* Prof Alison Grant (Co-Investigator)

Collaborators:

- *National Department of Health:* Dr David Mametja, Dr Norbert Ndjeka, Dr Lindiwe Mvusi, Ms Nontobeko Mtshali, Ms Lorna Nshuti
- *Eastern Cape Department of Health:* Dr John Black

Researcher (MPH Student):

- *University of Cape Town, South Africa:* Ms. Catherine Tomlinson

Research supervisor:

- *University of Cape Town, South Africa:* Ms. Veloshnee Govender

Introduction:
Good day, my name is _____, and I am a researcher with the Linkage to Care study team. We would like to invite you to take part in a research study that is investigating why patients that are diagnosed with DR-TB do or do not start treatment, and why the patients that start treatment do or do not experience a delay in starting treatment.

Research is the process to learn the answer to a question. We are seeking to understand what factors influence whether and when patients start treatment by learning more about patients' experiences through interviewing patients, family members and friends of patients, as well as health care workers.

You are free to decide whether you wish to participate in the study or not. Before you decide this, it is important that you understand why the research is being done and what it will involve. This information sheet explains our study and what participation in the study entails. Please feel free to ask me questions at any stage if there is anything which is not clear. If you decide to take part in the study then we will ask you to answer a few simple questions to demonstrate that you understand what your participation in the study will entail. We will also ask you to sign a form to demonstrate that you consent (agree) to be interviewed.

Your decision to take part in the study or not will not affect [*your/ your family member or friend's/ your patient's*] healthcare in any way.

Why are we doing this study?
Drug-resistant Tuberculosis (TB) is a major health problem in South Africa, but most forms of TB can be cured if treated early and well. In our study we want to find out:

- what factors contribute to whether a patient starts treatment after being diagnosed
- what factors contribute to when a patient starts treatment after being diagnosed

This study is a national study that will look at a number of health facilities and patient experiences across South Africa, and will take one year to complete. The study is funded by the Bill and Melinda Gates Foundation. A report from this study will also be submitted to the University of Cape Town towards the fulfilment of a Master's Degree in Public Health.

Who will be asked to participate in the study?
DR-TB patients, friends and family members of DR-TB patients, as well as health care workers responsible for providing care to DR-TB patients will be asked to participate in this study. Key informants that oversee or provide services for DR-TB may also be interviewed.

If I take part in this study, what will happen?
Through agreeing to participate in this study, you are agreeing to be interviewed regarding [*your/ your family member or friend's/ your patient's*] experience following diagnosis with drug resistant TB. During the interview the researcher will ask you a series of questions regarding whether or not [*you / your family member or friend / your patient*] started treatment following diagnosis. In the case that [*you / your family member or friend/ your patient*] did start treatment, the researcher will ask a series of questions regarding whether or not a delay was experienced between diagnosis and treatment initiation. Finally, the researcher will ask questions in order to gain an understanding of why the person diagnosed with DR-TB did or did not start treatment and/or experience a delay. Each interview will last approximately 30 to 40 minutes.

Who may choose to be interviewed together with another participant?
Some of the study participants will be given the option to be interviewed on their own, or together with another participant. The following study participants will be given the option to be interviewed individually or together with another participant:

- In the event that a patient, as well as a family member or friend of the patient consent to be interviewed then they may choose to be interviewed jointly.
- In the event that a patient has died or cannot be traced and a family member or friend consents to be interviewed then he/she may choose to be interviewed jointly with another family member or friend.

- In the event that more than one health care worker at the facility provided care to a single patient, then the health care workers may choose to be interviewed jointly regarding this patient's experience.

What are the risks and benefits of taking part in this study?
This study poses little to no risk to you if you agree to take part. All the information that you give us will be kept confidential. You will not benefit medically from participating in this study, however you will be able to share your experiences with us and so broaden our understanding of the challenges faced by patient's following diagnosis.

Reimbursement:
Healthy snacks will be provided during the interview. Additionally you will be given a once off R100.00 food voucher for Shoprite Checkers to compensate for your time. Patients and their family members that are interviewed away from their homes or regular clinic visits will also receive transport reimbursement of up to R50.

What happens if I do not agree to take part in this study?
You do not have to take part in this study. If you do not take part, this will not affect the medical care that you receive. You can stop taking part in the study at any time, without giving a reason.

How will the information collected during this study be recorded?
If you take part in the study, your interview will be recorded using an audio recording device and the interviewer may write some notes on paper during the interview.

How will the information collected during this study be kept confidential?
Audio recordings and notes from your interview will be kept securely and confidentially in locked suitcases by study staff during transportation of the information from the study site until it is brought back to the research station at the University of Cape Town. Upon reaching the University, the audio and paper records will be transferred to a securely, locked cabinet. The audio recordings and paper records will also be uploaded to an electronic database that is securely password protected. Only restricted University staff members will have access to the locked cabinet and secure database.

Study information may be reviewed by the Ethics Committee and independent monitors to check that the study procedures were done correctly and the information is correct. Your information will remain confidential, unless we are required by law to release information. The records from your interview will be destroyed either 6 years after study is finished if the research findings are not published, or after 2 years if the findings are published.

Will what I say during the interview appear in the study report or any published papers?
With your permission, we might quote things you say during the interview. If you are quoted in the study report, your name will be replaced by a pseudonym to protect your identity. Your name or any other identifiable information will not be included in any reports about the study or published papers.

If I am interviewed jointly with another participant, how will the information be kept confidential?
The researchers will ensure that there is no cross disclosure of what is said during interviews to other participants, unless the participants choose to be interviewed jointly. In other words, what you say during your interview will not be disclosed to [*your patient* / *your family member or friend* / *your health care worker*].

If you choose to be interviewed jointly with another participant, you must indicate that you understand that we cannot ensure that the person with whom you are jointly interviewed does not disclose what was said during the interview. However, we ask that you both agree to protect each other's confidentiality by not disclosing what was said during the interview by the participant with whom you were jointly interviewed.

What if I have questions about this study?
If you have any questions about this study, please feel free to ask me now. If you have questions later you may contact Dr Lindy Dickson-Hall at 021 406 6616. The committee reviewing this study is the Research Ethics Committees of the University of Cape Town. If you have any questions or concerns about your rights as a person taking part in a research study, or if you wish to make a complaint about the study, you may contact Professor Marc Blockman, Chairperson of the University of Cape Town, Human Research Ethics Committee, at 021 406 6338.

We will give you a copy of this sheet which explains the study to take away with you. If you would like a copy of a report on this study, and you give us an email or postal address, we will send you a report. The final results may not be available until 1 year from now.

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences

DIVISION OF CLINICAL LABORATORY SCIENCE/MEDICAL MICROBIOLOGY

Participant Informed Consent Form **Study ID No: _____**

Study title: Linkage to Care for Drug Resistant TB Following Xpert Implementation in South Africa

Investigators:

- *University of Cape Town, South Africa:* Prof Mark Nicol (Principal Investigator), Dr Helen Cox (Co-Investigator), Dr Lindy Dickson-Hall (Co-Investigator)
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- *Eastern Cape Department of Health:* Dr John Black

Researcher (MPH Student):

- *University of Cape Town, South Africa:* Ms. Catherine Tomlinson

Research supervisor:

- *University of Cape Town*, *South Africa:* Ms. Veloshnee Govender

Participant's Understanding:

- *I understand that my participation is voluntary* *(Yes/ No)*
- *I understand that I will not be identified by name in the finished study report or in any published papers* *(Yes/ No)*
- *I understand that the interview will be recorded* *(Yes/ No)*
- *I acknowledge that the contact information of the researcher and the researching institution have been made available to me* *(Yes/ No)*
- *I understand that I may withdraw from this study at any time without giving a reason and without affecting my normal care and management* *(Yes/ No)*
- *I have had the opportunity to ask questions about the study and any questions I have asked have been answered to my satisfaction* *(Yes/ No)*
- *I agree to take part in the study* *(Yes/ No)*

<u>For participants that are interviewed jointly:</u>

- *I agree not to disclose what was said during the interview by the person with whom I was jointly interviewed to anyone outside of the interview* *(Yes/ No)*

Study participant name (printed)	Signature/mark/thumbprint	Date

My questions concerning this study have been answered by:

Research staff name (printed)	Signature	Date
Research staff name (printed)	Signature	Date

If the information sheet and consent form were translated or explained to the participant, enter the name of the translator here and their signature:

Translator name (printed)	Signature/mark/thumbprint	Date

If the participant gave verbal consent (with a thumb print), enter the name of the person who witnessed the consent here and their signature:

Witness name (printed)	Signature/mark/thumbprint	Date

INTERVIEW GUIDE COVER PAGE

INTERVIEW GUIDE 1

This guide should be used to interview health care workers (HCWs) at the **diagnosing** facility of patients that have initiated treatment (this facility may or may not have initiated treatment)

INTERVIEW GUIDE 2

This guide should be used to interview health care workers (HCWs) at the facilities that initiated treatment following diagnosis and **referral** from elsewhere

INTERVIEW GUIDE 3

This guide should be used to interview health care workers (HCWs) of patients that never initiated treatment following diagnosis

INTERVIEW GUIDE 4

This guide should be used to interview patients that started treatment

This guide may also be used to do joint interviews with patients that started treatment and their family members

INTERVIEW GUIDE 5

This guide should be used to interview patients that never started treatment

This guide may also be used to do joint interviews with patients that never started treatment and their family members

INTERVIEW GUIDE 6

This guide should be used to interview family members of patients that started treatment

INTERVIEW GUIDE 7

This guide should be used to interview family members of patients that never started treatment

INTERVIEW GUIDE 1

This guide should be used to interview health care workers (HCWs) at the **diagnosing** facility of patients that have initiated treatment (this facility may or may not have initiated treatment).

To interview HCWs of patients that did not start treatment, use interview guide 3.

To interview HCWs who initiated treatment following diagnosis and referral from another facility, use interview guide 2.

INTERVIEW GUIDE 1 INSTRUCTIONS:

1. SKIP INSTRUCTIONS ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *red, italicised text*

2. PROBES AND EXAMPLES ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *blue, italicised text*

3. IF THE PARTICIPANT RESPONSES ARE UNCLEAR, USE FOLLOW UP QUESTIONS TO FIND OUT MORE

   Examples:
   - Why?
   - Can you tell me more?

4. BEFORE STARTING THE INTERVIEW QUESTIONS, CLARIFY THE FOLLOWING FOR THE HEALTH CARE WORKER
   - When and where the patient was diagnosed
   - When and where the patient started treatment.

INTERVIEW GUIDE 1 QUESTIONS:

1) What do you remember about this patient?

2) What was this person like as a patient?

3) Do you think the length of time that passed between the patient being diagnosed with Drug Resistant Tuberculosis (DR-TB) and started treatment was good, bad or acceptable?

   Follow up: Why?

4) Do you think anything else could have been done to shorten the time between when the patient was diagnosed and started treatment?

   Follow up: If no, why?
   Follow up: If yes, what could have been done?

5) Can you describe what happened to the patient between receiving their diagnosis and starting treatment?

If the HCW ask for more clarity, ask them to describe whatever they can recall about the patient's journey and the steps they took to start treatment

6) Do you know whether the patient faced any challenges in starting treatment?

Examples:
Lack of transport
No beds available for patients requiring hospitalisation
Delays in receiving diagnostic results, records unavailable
Doctor unavailable when visiting treatment site
Medicine shortages
No one to take care of children
Unable to take time off work to visit the facility
Other…

Follow up: If the patient did experience challenges, did the challenges impact on when the patient started treatment?
Follow up: How?

7) Do you know what factors enabled this patient to start treatment, when many other patients that are diagnosed with DR-TB never start care?

Examples:
Started treatment close to home
Unemployed or able to take time off work
Transport available
Received social grant
Had a good understanding of DR-TB, received counselling and education
Good social and emotional support system
Doctor available
Other…

Follow up: Did any of these factors impact on when the patient started treatment?
Follow up: If yes, how?

8) Do you have any insight regarding what happened in the patient's personal life between finding out their diagnosis and starting treatment and how this might have impacted on the time to treatment?

Examples:
Dependants (new caregiver needed)
Employment (quit or lost job)
Place and location of residence (moved)
Substance abuse
Use of traditional or alternative medicines
Other…

INSTRUCTIONS: If the patient was referred to a different facility to start treatment after diagnosis, ask questions 9 through 16. If the patient initiated treatment at this facility, skip to question 17 (page 6)

9) Under what circumstances are patients usually referred elsewhere (to another facility) to start treatment following diagnosis at the facility where you work?

Examples:
All patients are referred elsewhere
Sputum positive patients are referred elsewhere
XDR and children are referred elsewhere
Patients with substance abuse issues are referred elsewhere
Other…

10) In general, how does referral impact on time to treatment?

11) Why was this patient referred elsewhere for treatment and did this influence time to treatment?

    Follow up: If yes, how was their time to treatment impacted?

12) Do you know how this patient reached the referral site and whether the patient experienced any difficulties in reaching the site?

13) Are there any services available to assist patients in reaching referral sites (ie. ambulances)?

    Follow up: If yes, why were they or were they not provided to this patient?

14) Are there any systems to track whether patients referred elsewhere, reach the referral site and initiate treatment?

    Follow up: If yes, please describe

15) Was there any follow up for this patient following their referral?

    Follow up: If yes, please describe

INSTRUCTIONS: Ask question 17 through 21 for patients that were initiated onto treatment at this facility

16) Under what circumstances are patients initiated onto treatment at this facility versus being referred elsewhere?

17) In general, how does referral impact on time to treatment?

18) Why was this patient initiated onto treatment at this facility rather than being referred elsewhere?

19) Do you have systems to follow up with patients that fail to initiate treatment at this facility following diagnosis?

    Follow up: If yes, please describe

20) Was there any follow up for this patient, following their diagnosis?

    Follow up may be done by a HCW from the health facility, or a city/provincial environmental health officer

    Follow up: If yes, please describe

INSTRUCTIONS: Ask all HCWs questions 22 – 24

Note: If the HCW has already responded to these questions for a previous patient, then you do not need to ask them again. Simply note on the recording that the HCW has already responded to these questions in a previous interview.

21) What is the average (usual time) that passes between diagnosis and treatment initiation for patients that are diagnosed with DR-TB at your facility?

22) Do you face any challenges personally in dealing with DR-TB patients and linking them to treatment?

23) Do you have recommendations for how your facility, organisation, or district could improve linkage to treatment following DR-TB diagnosis in your area?

INTERVIEW GUIDE 2

This guide should be used to interview health care workers (HCWs) at the facilities that initiated treatment following diagnosis and referral from elsewhere.

INTERVIEW GUIDE 2 INSTRUCTIONS:

1. SKIP INSTRUCTIONS ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *red, italicised text*

2. PROBES AND EXAMPLES ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *blue, italicised text*

3. IF THE PARTICIPANT RESPONSES ARE UNCLEAR, USE FOLLOW UP QUESTIONS TO FIND OUT MORE

   Examples:
   - Why?
   - Can you tell me more?

4. BEFORE STARTING THE INTERVIEW QUESTIONS, CLARIFY THE FOLLOWING FOR THE HEALTH CARE WORKER
   - When and where the patient was diagnosed
   - When and where the patient started treatment

INTERVIEW GUIDE 2 QUESTIONS:

1) What do you remember about this patient?

2) What was this person like as a patient?

3) Do you think the length of time that passed between the patient being diagnosed with Drug Resistant Tuberculosis (DR-TB) and started treatment was good, bad or acceptable?

   Follow up: Why?

4) Do you think anything else could have been done to shorten the time between when the patient was diagnosed and started treatment?

   Follow up: If no, why?
   Follow up: If yes, what could have been done?

5) Can you describe what happened to the patient between receiving their diagnosis and starting treatment?

   If the HCW asks for more clarity, ask them to describe whatever they can recall the patient's journey and the steps they took to start treatment

6) Do you know whether the patient faced any challenges in starting treatment?

Examples:
Lack of transport
No beds available for patients requiring hospitalisation
Delays in receiving diagnostic results, records unavailable
Doctor unavailable when visiting treatment site
Medicine shortages
No one to take care of children
Unable to take time off work to visit the facility
Other…

Follow up: If the patient did experience challenges, did these impact on when the patient started treatment?
Follow up: How?

7) Do you know what factors enabled this patient to start treatment, when many other patients that are diagnosed with DR-TB never start treatment?

Examples:
Started treatment close to home
Unemployed or able to take time off work
Transport available
Received social grant
Had a good understanding of DR-TB, received counselling and education
Good social and emotional support system
Doctor available
Other…

Follow up: Did any of these factors impact on when the patient started treatment?
Follow up: If yes, how?

8) Do you have any insight regarding what happened in the patient's personal life between finding out their diagnosis and starting treatment and how this impacted on their time to treatment?

Examples:
Dependants (new caregiver needed)
Employment (quit or lost job)
Place and location of residence (moved)
Substance abuse
Use of traditional or alternative medicines
Other…

9) Under what circumstances are patients referred to your facility to start treatment?

10) Why was this patient referred to your facility for treatment?

11) How far away is your facility from the facility where this patient was diagnosed?

12) Do you know how this patient reached your facility and whether the patient experienced any difficulties in doing so?

13) Are there any services available to assist referred patients in reaching your facility (ie. ambulances)?

Follow up: If yes, why were they or were they not provided to this patient?

14) Are there any systems to track or follow up with patients that are referred to your facility to start treatment, but do not arrive?

Follow up: If yes, please describe

15) Was there any follow up for this patient, following their referral?

Follow up: If yes, please describe

Follow up may be done by a HCW from the health facility, or a city/provincial environmental health officer

Note: If the HCW has already responded to questions 16 - 18 for a previous patient, then you do not need to ask them again. Simply note on the recording that the HCW has already responded to these questions in a previous interview.

16) What is the average (usual time) that passes between diagnosis and treatment initiation for patients that are initiated onto DR-TB treatment at your facility?

17) Do you face any challenges personally in dealing with DR-TB patients and linking them to treatment?

18) Do you have recommendations for how your facility, organisation, or district could improve linkage to treatment following DR-TB diagnosis in your area?

INTERVIEW GUIDE 3

This guide should be used to interview health care workers (HCWs) of patients that never initiated treatment following diagnosis

INTERVIEW GUIDE 3 INSTRUCTIONS:

1. SKIP INSTRUCTIONS ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *red, italicised text*

2. PROBES AND EXAMPLES ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *blue, italicised text*

3. IF THE PARTICIPANT RESPONSES ARE UNCLEAR, USE FOLLOW UP QUESTIONS TO FIND OUT MORE

   Examples:
   - Why?
   - Can you tell me more?

4. BEFORE STARTING THE INTERVIEW QUESTIONS, CLARIFY THE FOLLOWING FOR THE HEALTH CARE WORKER
   - When and where the patient was diagnosed

INTERVIEW GUIDE 3 QUESTIONS:

1) What do you remember about this patient?

2) What was this person like as a patient?

3) Can you describe what happened to this patient following their diagnosis with Drug Resistant Tuberculosis (DR-TB)?

4) In your opinion, why did this patient never start treatment?

5) Do you have any insight regarding what happened in the patient's personal life after finding out his/her diagnosis and whether this affected why the patient never started treatment?

Examples:
Dependants (new caregiver needed)
Employment (quit or lost job)
Place and location of residence (moved)
Substance abuse
Used traditional or alternative medicines
Other

Follow up: If yes, please describe

6) Is failure to initiate treatment following DR-TB diagnosis a common challenge in this area?

7) Do you think the reasons that this patient did not start treatment are typical of most patients in the area that fail to initiate care?

   Follow up: Why or why not?

8) Following diagnosis, was the patient referred elsewhere to start care?

   Follow up: If yes, why?
   Follow up: If yes, how far away is the facility that the patient was referred to?

9) Under what circumstances are patient referred elsewhere to start treatment?

10) Are there any systems to track whether patients referred elsewhere, reach the referral site and initiate treatment?

    Follow up: If yes, please describe

11) Are there any services available to assist patients in reaching referral sites (ie. ambulances)?

    Follow up: If yes, why were they or were they not provided to this patient?

12) Are there any systems to trace or follow up with patients that do not start treatment?

    Follow up may be done by a HCW from the health facility, or a city/provincial environmental health officer

    Follow up: If yes, please describe

13) Was there any follow up for this patient?

    Follow up: If yes, please describe
    Follow up: If no, why not?

14) What is the average (usual time) that passes between diagnosis and treatment initiation for patients that are diagnosed with DR-TB at your facility?

15) Do you face any challenges personally in dealing with DR-TB patients and linking them to treatment?

16) Do you have recommendations for how your facility, organisation, or district could improve linkage to treatment following DR-TB diagnosis in your area?

INTERVIEW GUIDE 4

This guide should be used to interview patients that started treatment

This guide may also be used to do joint interviews with patients that started treatment and their family members

INTERVIEW GUIDE 4 INSTRUCTIONS:

1. SKIP INSTRUCTIONS ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *red, italicised text*

2. PROBES AND EXAMPLES ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *blue, italicised text*

3. IF THE PARTICIPANT'S RESPONSES ARE UNCLEAR, USE FOLLOW UP QUESTIONS TO FIND OUT MORE

   Examples:
   - Why?
   - Can you tell me more?

4. WHEN DOING JOINT INTERVIEWS, ASK FOLLOW UP AND PROBING QUESTIONS TO FIND OUT MORE FROM THE FAMILY MEMBER REGARDING THE PATIENT'S RESPONSES

   Examples:
   - Would you like to add anything?
   - Can you tell me more?

5. WHEN DOING JOINT INTERVIEWS, OPEN UP QUESTIONS TO BE INCLUSIVE WHEN APPROPRIATE

   Examples:
   - Change: Do you have recommendations…
   - To: Do either of you have recommendations…

INTERVIEW GUIDE 4 QUESTIONS:

1) Where did you first find out that you had Drug Resistant Tuberculosis (DR-TB)?

2) How were you informed of your DR-TB diagnosis?

Examples:
The patient may have been asked to return a few days after sputum collection to receive their diagnosis
The patient may have returned to the facility many times after giving sputum before receiving their diagnosis
The patient may have received a phone call or home visit where they learnt about their diagnosis

3) Did you experience any symptoms of TB before being diagnosed with DR-TB?

Examples:
Bad cough
Coughing up blood or sputum/ phlegm
Pain in chest
Fever and/or chills
Night sweats
Weakness and fatigue (tired)
Weight loss
Other…

Follow up: If yes, for how long did you experience these symptoms?
Follow up: If the patient experienced symptoms for more than a couple of weeks, ask why they were not tested for TB sooner.

Examples:
The patient visited a facility sooner but was not tested for TB because:
Test not offered
The wait at the clinic was too long
The health care worker was not available
Other…

The patient put off visiting the facility because he/she was:
Afraid that health care workers would be rude (may have previously defaulted)
Afraid of being diagnosed with TB (may have been previously treated for TB)
Unable to get time off work or find a caregiver for children
Too ill to travel to the health facility
Other…

4) After being diagnosed with DR-TB, what were you told to do in order to start treatment?

Examples:
Was the patient told to go to the hospital
Was the patient told he/she could start treatment from home
Was the patient told he/she could start treatment immediately or was there a waiting list

5) How were you treated by health care workers after you were diagnosed with DR-TB?

6) Did the facility that diagnosed you provide you with any educational materials or counselling sessions explaining DR-TB and the importance of starting and completing treatment?

Follow up: If yes, please describe

7) How did you feel after finding out you had DR-TB?

8) What did you do after you found out you had DR-TB?

Ask the interviewee to describe anything that they can recall - there are no wrong answers.

9) How much time passed between finding out your diagnosis and starting treatment?

10) Can you describe what happened during this time?

Ask the patient to describe anything that they recall about this time – there are no wrong answers.

17) What were the main challenges you faced in starting treatment?

These may be personal challenges or challenges related to the facility
Examples:
Employment
Dependents
Housing
Fear about medicines or death
Stigma from others in the community
No beds, waiting lists at facilities
Shortages of medicines
Other…..

Follow up: Did any of these challenges impact on when you started treatment?
Follow up: If yes, how?

18) Were there any factors that helped you in starting treatment?

These may be personal challenges or challenges related to the facility
Examples:
Strong support system
Able to take time off work
Good understanding of DR-TB
Able to start treatment from home
Received grant
Other…

Follow up: Did any of these factors impact on when you started treatment?
Follow up: How?

19) Did you have to make any changes to your personal life in order to start treatment?

Examples:
Quit job
Found caregiver for dependents
Moved
Stopped drinking or using drugs
Other

20) Who supported you in starting treatment?

21) At any point after finding out your diagnosis, did you choose to delay starting treatment?

Follow up: If yes, why?

22) At any point between learning your diagnosis and starting treatment did you seek out care from a private provider, traditional healer, alternative practitioner or faith healer?

Follow up: If yes, from where?

9) At any point, between learning your diagnosis and starting treatment, did you receive a home visit or call from the diagnosing facility or anyone else?

   Follow up: If yes, by whom and what was the purpose of this contact?

10) Did you start treatment from a hospital or from your home with daily facility visits?

   Follow up: Where would you have preferred to start treatment?

11) How far from your home was the facility where you started treatment?

   (Time according to mode of transport used, i.e. 30 minutes by foot)

12) Did you face any difficulties in travelling to the facility where you started treatment?

   Follow up: If yes, please describe

13) Overall, what was the most difficult thing about starting treatment?

14) Do you have any suggestions for how facilities could make it easier for patients to start DR-TB treatment?

15) Are you still on treatment today?

   Follow up: If no, why not?

INSTRUCTIONS: *When doing joint interviews with family members, direct the question at the family member*

16) What were the biggest challenges that your family faced as a result of your diagnosis?

INTERVIEW GUIDE 5

This guide should be used to interview patients that never started treatment

This guide may also be used to do joint interviews with patients that never started treatment and their family members

INTERVIEW GUIDE 5 INSTRUCTIONS:

1. SKIP INSTRUCTIONS ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *red, italicised text*

2. PROBES AND EXAMPLES ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN *blue, italicised text*

3. IF THE PARTICIPANT RESPONSES ARE UNCLEAR, USE FOLLOW UP QUESTIONS TO FIND OUT MORE

   Examples:
   - Why?
   - Can you tell me more?

   WHEN DOING JOINT INTERVIEWS, ASK FOLLOW UP AND PROBING QUESTIONS TO FIND OUT MORE FROM THE FAMILY MEMBER'S REGARDING THE PATIENT'S RESPONSES

   Examples:
   - Would you like to add anything?
   - Can you tell me more?

   WHEN DOING JOINT INTERVIEWS, OPEN UP QUESTIONS TO BOTH INTERVIEWEES WHENEVER APPROPRIATE

   Examples:
   - Change: Do you have recommendations…
   - To: Do either of you have recommendations…

INTERVIEW GUIDE 5 QUESTIONS:

1) Where did you first find out that you had Drug Resistant Tuberculosis (DR-TB)?

2) How were you informed of your DR-TB diagnosis?

Examples:
The patient may have been asked to return a few days after giving sputum to receive their diagnosis
The patient may have returned to the facility many times after giving sputum before receiving their diagnosis
The patient may have received a phone call or home visit where they learnt about their diagnosis

3) Did you experience any symptoms of TB before being diagnosed with DR-TB?

Examples:
Bad cough
Coughing up blood or sputum/ phlegm
Pain in chest
Fever and/or chills
Night sweats
Weakness and fatigue (tired)
Weight loss
Other…

Follow up: If yes, for how long did you experience these symptoms?
Follow up: If the patient experienced symptoms for more than a couple of weeks, ask why they were not tested for TB sooner

Examples:
The patient visited a facility sooner but was not tested for TB because:
Test not offered
The wait at the clinic was too long
Health care worker not available
Other…

The patient put off visiting the facility because he/she was:
Afraid that health care workers would be rude (may have previously defaulted)
Afraid of being diagnosed with TB (may have been previously treated for TB)
Unable to get time off work or find a caregiver for children
Too ill to travel to the facility
Other…

4) After being diagnosed with DR-TB what were you told to do by the health care worker that diagnosed you?

Examples:
Was the patient told to he/she would need to be hospitalised to start treatment
Was the patient told he/she could start treatment from home with daily visits to the clinic
Was the patient told he/she could start treatment immediately or was there a waiting list

5) How were you treated by health care workers after you were diagnosed with DR-TB?

6) Were you informed that you would need to be hospitalised to start treatment or that you could take treatment from home if you visited a facility daily?

Follow up: Did this impact on why you did not start treatment?

7) Did the facility that diagnosed you provide you with any educational materials or counselling sessions explaining DR-TB and the importance of treatment?

Follow up: If yes, please describe

8) How did you feel after finding out you had DR-TB?

9) What did you do after finding out you had DR-TB?

Ask the interviewee to describe anything that they can recall - there are no wrong answers.

10) Why did you not start treatment after finding out that you had DR-TB?

Try to clarify if this was a personal choice or if it was due to problems at the facility, such as lack of beds or rude health care workers.

11) Has your DR-TB diagnosis affected your personal life in any way?

Examples:
Housing
Employment
Relationships
Personal responsibilities i.e. care giving
Substance abuse

Follow up: If yes, how

12) At any point after learning your diagnosis did you seek out care from a private provider, traditional healer, alternative practitioner or faith healer?

Follow up: If yes, from where?

13) Has anyone from the diagnosing facility or elsewhere contacted you – either via telephone or home visit – to follow up regarding your health condition and why you have not started treatment?

Follow up: If yes, by whom and what was the purpose of this contact?

14) Have you returned to the facility since your diagnosis?

Follow up: If yes, was your DR-TB discussed?
Follow up: Why or why not?

15) Why have you still not initiated treatment?

16) Like yourself, many other people that have been diagnosed with DR-TB never started treatment. According to government estimates about half of the people diagnosed with DR-TB in 2013 did not start treatment.

Do you have any recommendations for how the Department of Health could make it easier for people with DR-TB to start treatment?

INTERVIEW GUIDE 6

This guide should be used to interview family members of patients that started treatment

INSTRUCTIONS:

1) **XXX appears throughout the document. Wherever XXX appears, insert the patient's first name**

2) **PROBES AND EXAMPLES ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN** *blue, italicised text*

3) **IF THE PARTICIPANT'S RESPONSES ARE UNCLEAR, USE FOLLOW UP QUESTIONS TO FIND OUT MORE**

   Examples:
   - Why?
   - Can you tell me more?

4) **WHEN DOING JOINT INTERVIEWS ASK THE PARTICIPANTS TO STATE THEIR FIRST NAME BEFORE EACH ANSWER THEY GIVE. THIS IS NECESSARY FOR TRANSCRIBING THE INTERVIEW.**

   WHEN DOING JOINT INTERVIEWS, ASK FOLLOW UP AND PROBING QUESTIONS IN ORDER TO FIND OUT BOTH PARTICIPANTS' PERSPECTIVES

   Examples:
   - Would you like to add anything?
   - Do you agree that…?
   - Can you tell me more?

   WHEN DOING JOINT INTERVIEWS, OPEN UP QUESTIONS TO BOTH INTERVIEWEES WHENEVER APPROPRIATE

   Examples:
   - Change: Do you have recommendations…
   - To: Do either of you have recommendations…

INTERVIEW GUIDE 6 QUESTIONS:

1) What is/was your relationship with XXX?

2) When did you find out that XXX had Drug Resistant Tuberculosis (DR-TB)?

3) How did you find out that XXX had DR-TB?

4) Did XXX experience any symptoms of TB before being diagnosed with DR-TB?

Examples:
Bad cough
Coughing up blood or sputum/ phlegm
Pain in chest
Fever and/or chills
Night sweats
Weakness and fatigue (tired)
Weight loss
Other…

Follow up: If yes, for how long did XXX experience these symptoms?

Follow up: If XXX experienced symptoms for more than a couple of weeks, ask why they were not tested for TB sooner

Examples:
The patient visited a facility sooner but was not tested for TB because:
Test not offered
The wait at the clinic was too long
The health care worker was not available
Other…

The patient put off visiting the facility because he/she was:
Afraid that health care workers would be rude (may have previously defaulted)
Afraid of being diagnosed with TB (may have been previously treated for TB)
Unable to get time off work or find a caregiver for children
Too ill to travel to the facility
Other….

5) How did XXX react to the news that he/she had DR-TB?

6) What did XXX do after learning that he/she had DR-TB?

Ask the interviewee to describe anything that they can recall - there are no wrong answers.

7) Can you describe what happened to XXX between finding out that he/she had DR-TB and starting treatment?

Ask the interviewee to describe anything that they can recall - there are no wrong answers.

8) Do you know whether XXX received any educational materials or counselling sessions explaining DR-TB and the importance of treatment?

Follow up: If yes, please describe

9) How was XXX treated by health care workers after he/she was diagnosed with DR-TB?

10) Do you know whether XXX experienced any challenges in starting treatment?

Examples:
Lack of transport
No beds available for patients requiring hospitalisation

Delays in receiving diagnostic results, records unavailable
Doctor unavailable when visiting treatment site
Medicine shortages
No one to take care of children
Unable to take time of work to visit the facility
Other…

Follow up: If yes, did any of these challenges impact on when XXX started treatment?

Follow up: How?

11) Was there anything that helped XXX to start treatment?

Examples:
Started treatment close to home
Unemployed or able to take time off
Transport available
Received social grant
Had a good understanding of DR-TB, received counselling and education
Good social and emotional support system
Doctor available
Other…

Follow up: Did any of these factors impact on when XXX started treatment?

Follow up: How?

12) At any point after finding out his/her diagnosis, did XXX choose to delay starting treatment?

Examples:
Dependants (new caregiver needed)
Employment (quit or lost job)
Place and location of residence (moved)
Substance abuse
Use of traditional or alternative medicines
Other…

Follow up: If yes, why?

13) At any point between learning his/her diagnosis and starting treatment did XXX seek out care from a private provider, traditional healer, alternative practitioner or faith healer?

Follow up: If yes, from where?

14) Did XXX start his/her treatment for DR-TB from a hospital, or from home with daily visits to the facility?

Follow up: From where would XXX preferred to have started treatment?

Follow up: Did this impact on when XXX started treatment?

15) How far from his/her home was the facility where XXX started taking treatment for DR-TB?

(Time according to mode of transport used, i.e. 30 minutes by foot)

16) Did XXX face any challenges in reaching the facility where he/she started treatment?

Follow up: If yes, did these challenges impact on when he/she started treatment?

Follow up: If yes, please describe

17) Was XXX given any assistance in reaching the facility where he/she started treatment? (I.e. ambulance)

18) Overall, what were the biggest challenges that XXX faced in starting treatment?

19) What were the biggest challenges that your family faced as a result of XXX's diagnosis?

20) Do you have any suggestions for how facilities could make it easier for patients to start DR-TB treatment?

21) Is XXX still on DR-TB treatment today?

Follow up: If not, why not?

INTERVIEW GUIDE 7

This guide should be used to interview family members of patients that never started treatment

INSTRUCTIONS:

5) **XXX appears throughout the document. Wherever XXX appears, insert the patient's first name**

6) **SKIP INSTRUCTIONS ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN** *red, italicised text*

7) **PROBES AND EXAMPLES ARE PROVIDED THROUGHOUT THE INTERVIEW GUIDE IN** *blue, italicised text*

8) **IF THE PARTICIPANT RESPONSES ARE UNCLEAR, USE FOLLOW UP QUESTIONS TO FIND OUT MORE**

   Examples:
   - Why?
   - Can you tell me more?

9) **WHEN DOING JOINT INTERVIEWS ASK THE PARTICIPANTS TO STATE THEIR FIRST NAME BEFORE EACH ANSWER THEY GIVE. THIS IS NECESSARY FOR TRANSCRIBING THE INTERVIEW.**

   WHEN DOING JOINT INTERVIEWS, ASK FOLLOW UP AND PROBING QUESTIONS IN ORDER TO FIND OUT BOTH PARTICIPANTS PERSPECTIVES

   Examples:
   - Would you like to add anything?
   - Do you agree that…?
   - Can you tell me more?

   WHEN DOING JOINT INTERVIEWS, OPEN UP QUESTIONS TO BOTH INTERVIEWEES WHENEVER APPROPRIATE

   Examples:
   - Change: Do you have recommendations…
   - To: Do either of you have recommendations…

INTERVIEW GUIDE 7 QUESTIONS:

22) What is/was your relationship with XXX?

23) When did you find out that XXX had Drug Resistant Tuberculosis (DR-TB)?

24) How did you find out that XXX had DR-TB?

25) Did XXX experience any symptoms of TB before being diagnosed with DR-TB?

Examples:
Bad cough
Coughing up blood or sputum/ phlegm
Pain in chest
Fever and/or chills
Night sweats
Weakness and fatigue (tired)
Weight loss
Other…

Follow up: If yes, for how long did XXX experience these symptoms?

Follow up: If XXX experienced symptoms for more than a couple of weeks, ask why they were not tested for TB sooner

Examples:
The patient visited a facility sooner but was not tested for TB because:
Test not offered
The wait at the clinic was too long
Health care worker not available
Other…
The patient put off visiting the facility because:
Afraid that health care workers would be rude (may have previously defaulted)
Afraid of being diagnosed with TB (may have been previously treated for TB)
Unable to get time off work or find a caregiver for children
Too ill to travel to the facility
Other….

26) How did XXX react to the news that he/she had DR-TB?

27) What did XXX do after learning he/she had DR-TB?

Ask the interviewee to describe anything that they can recall - there are no wrong answers.

28) Did finding out that he/she had DR-TB affect XXX's personal life?

Follow up: If yes, how?

Examples:
Housing
Employment
Relationships
Personal i.e. care giving
Substance abuse
Other…

29) Do you know whether XXX received any educational materials or counselling sessions explaining DR-TB and the importance of treatment?

Follow up: If yes, please describe

30) Do you know what XXX was told to do by the facility in order to start treatment after his/her diagnosis?

Examples:
Was the patient told to he/she would need to be hospitalised to start treatment
Was the patient told he/she could start treatment from home with daily visits to the clinic
Was the patient told he/she could start treatment immediately or was there a waiting list
Other…

31) How was XXX treated by health care workers after he/she was diagnosed with DR-TB?

32) Was XXX given instructions regarding where he/she should start treatment?

    Follow up: If not, was it explained to XXX why he/she was not referred to treatment (i.e. bed shortages or other issues)?

INSTRUCTIONS: Ask family members that reported that patients were referred to care (informed where they should start treatment) questions 12 through 14. For patients that were not referred to care, skip to question 15.

33) Was XXX told that he/she would need to be hospitalised to start treatment or that he/she could be treated from home with daily visits to the facility?

    Follow up: Did this impact on why XXX did not start treatment?

34) How far away from XXX's home was the facility where he/she was instructed to start treatment?

    (Time according to mode of transport used, i.e. 30 minutes by foot)

    Follow up: Did this impact on why XXX did not start treatment?

35) Did XXX ever arrive at the facility where he/she was referred to start treatment?

    Follow up: If not, why not?

    Follow up: If yes, can you describe what happened and why XXX was not initiated onto treatment after arriving at the facility?

INSTRUCTIONS: Ask all family members the following questions

36) In your opinion, why did XXX never start treatment?

37) Did anyone from the diagnosing facility or elsewhere contact XXX – either via telephone or home visit – to follow up regarding his/her health condition and why he/she has not started treatment?

    Follow up: If yes, by whom and what was the purpose of this contact?

38) At any point after learning his/her diagnosis did XXX seek out care from a private provider, traditional healer, alternative practitioner or faith healer?

` *Follow up:* If yes, from where?

39) What were the biggest challenges that your family faced as a result of XXX's diagnosis?

40) Do you have any suggestions for how facilities could make it easier for patients to start DR-TB treatment?

Patient record data extraction form

Date:	
Patient linkage ID:	
Facility name:	
District:	
Province:	
Researcher name (who extracted clinical notes):	

Patients contact number: **Emergency contact number:** **Emergency contact name:**

Current treatment status (select one)	Did not start treatment	
	On treatment	
	Defaulted treatment	
	Dead	
	Unknown	

Location where currently receiving treatment (if currently on treatment): _____

Most recent culture test results

Date _____ Result (positive/ negative) _____

Any previous culture test results

Date _____ Result (positive/negative) _____

Date _____ Result (positive/negative) _____

Any additional resistance detected (INH, AMK, ETH, PAS, OFL, MOX, CAP, other)

_____

Most recent sputum microscopy result

Date _____ Result _____

Any previous sputum microscopy test results

Date _____ Result _____

Date _____ Result _____

Clinical notes

DRUG RESISTANT TB INFORMATION:

Understanding drug resistant tuberculosis

This pamphlet provides guidance for people diagnosed with drug resistant tuberculosis (DR TB), as well for their family members and friends. This pamphlet explains what DR TB is and how it is treated. It provides advice on dealing with the side effects of DR TB treatment and explains the importance of completing treatment. The pamphlet also explains steps that people with DR TB and their contacts can take to reduce the risk of DR TB transmission between people.

What is tuberculosis (TB)?

TB is very common illness and the leading cause of death in South Africa. People that are HIV positive and HIV negative can get TB – although people that are HIV positive are more vulnerable to developing active TB illness.

TB can be treated. Treatment for TB involves a combination of four medicines that are taken every day for six months. The four medicines used to treat TB are rifampicin, isoniazid, ethambutol and pyrazinamide. Often the four medicines are combined into a single tablet or pill.

What is DR TB?

DR TB is a disease caused by TB germs, but the germs are **resistant** to the normal medicines used to treat TB. What this means is that regular TB medicines cannot be used to treat TB and different medicines must be used to treat DR TB.

The medicines that a DR TB patient is given will depend on his/her level of resistance. In other words, in selecting a medicine regimen health care workers must consider what medicines a patient is resistant to. The more resistance a patient develops, the more difficult TB is to treat. Treatment for DR TB usually lasts between 18 and 24 months.

How does one become infected with DR TB?

A person may become infected with DR TB in two ways:

1) If a patient with regular TB is not able to take their medication every day for six months, then he/she may develop resistance to some of the medicines used to treat TB. Patients that develop resistance to both rifampicin and isoniazid must be switched to DR TB treatment.

2) DR TB may also be transmitted directly from people with DR TB to others in their close contact. Many DR TB patients in South Africa contracted DR TB from other patients, rather than because of medicine interruptions.

How are TB and DR TB spread between people?

TB and DR TB are spread in the same way. When a person infected with TB or DR TB coughs, spits, sneezes, laughs, or sings, they produce small drops into the air that can carry TB germs. These drops

can be inhaled by people in close contact with someone who has TB, and can cause them to get infected and possibly sick as well.

Who is most at risk of getting DR TB?

Close contacts

People who spend a lot of time in close contact with DR TB patients often face a risk of infection. But this risk can be reduced by improving ventilation in shared spaces.

The risk of contracting DR TB is highest when in poorly ventilated spaces indoors as TB germs may linger in droplets in the air. When spending time together indoors, DR TB patients and their family members and friends should open doors and windows to allow air to move through the room. As much as possible, DR TB patients and their close contacts should spend time together outdoors where the risk of contracting DR TB is very low.

People with HIV

People living with HIV face a higher risk of becoming sick with TB or DR TB than people who are HIV negative. People with HIV can reduce their risk of becoming ill with TB or DR TB by monitoring their CD4 count and starting antiretroviral treatment as soon as they become eligible

People with HIV that are in close contact with DR TB patients must inform their health care workers to discuss additional strategies to protect their health. It is also advisable that everyone know their HIV status and anyone in the household who is not sure of their status should consider having a HIV test.

Children under 5 years

Children under 5 years old and especially those under a year old face the greatest risk of developing TB or DR TB. All children under 5 that are in close contact with DR TB patients should be taken to the clinic to be screened for TB and to discuss taking treatment that may prevent them from getting infected or sick from DR TB.

How can people with DR TB protect the health of their friends and family?

If you have DR TB, there are additional steps that you can take to protect the health of your friends and family

- The most important way to avoid spreading TB is to take your treatment on time every day and complete the full course of treatment. You are still infectious to others until your culture is negative. With proper treatment adherence your sputum culture test should convert from positive to negative. Once your culture has converted to negative it is important to continue taking your medicines until you have completed the full course of treatment. If you stop taking medicines before you have completed your full treatment course then your culture may convert back to positive, which exposes your family and friends to DR TB infection.

- Avoid close contact with others, especially children under 5, until your sputum culture test is negative. If possible, sleep in a bedroom on your own. Or at least try not to share a bed with others.
- Open the doors and windows in your home to allow air to move through the rooms. Whenever possible, spend time with other people outside. Try wearing a mask when you are sharing indoor spaces with poor ventilation.
- Wear a mask or cover your mouth with a disposable tissue when you cough. Make sure to properly dispose of tissues and masks you have coughed in. If you do not have a tissue or mask, cover your mouth with your sleeve or elbow when you cough. Do not spit on the ground. Spit in a tissue and throw it away.

Why is starting treatment as early as possible important for DR TB patients?

Without proper treatment, DR TB is usually a fatal illness. Therefore it is important for people diagnosed with DR TB to start treatment as early as possible in order to protect their health.

What does DR TB treatment entail?

DR TB can be cured with proper treatment, although the treatment is often physically and emotionally difficult on patients. DR TB treatment involves a combination of medicines that are taken for 18 to 24 months. Many patients are also given injections for the first six months or longer. Some patients are hospitalised at the start of treatment.

Patients have to see their doctor monthly for a check-up. Patients must produce sputum every month around the same date, this sputum will be taken to the lab and the results will tell your doctor if your treatment is working speedily or not.

What are some of the challenges you might experience with the treatment?

There are lots of pills to swallow and most patients have to be given injections every Monday to Friday for at least 6 months. It will not be easy to continue your treatment but your TB nurse and doctor are there to help you get through this.

Do you need to eat before taking your medicines?

It is not necessary to eat before taking your medicines. It is safe to take your TB treatment on an empty stomach.

What are the side effects of DR TB treatment?

DR TB treatment is often associated with difficult side effects. Minor side effects include nausea, vomiting, stomach pains, diarrhoea, dizziness, ringing in the ears, rashes, aching joints and painful or burning feet. Serious side effects may include vision loss, hearing loss, seizures or fits, depression, anxiety, confusion and peeling of skin.

Tell your doctor or nurse if you experience any of these side effects as the may be able to change your medicines or give you additional medicines to reduce or stop the side effects. If you experience vision loss, report this immediately to your doctor as it may lead to blindness if not dealt with. It is also important that you have regular hearing screening tests so that changes in hearing may be picked up early as hearing loss may be permanent.

What happens if I take my treatment well?

- You should start feeling better and healthier
- You should start gaining weight
- Your sputum tests should come back negative
- You will prevent any further damage to your lungs or infected organ
- You will stop being infectious to others

What happens to you if you stop your treatment?

- Every time you do not take your DR TB treatment, you give the germs a chance to grow again and you will eventually become sick again.
- Every time the germs grow again there is a chance that further resistance will develop. The more resistance a patient develops, the more difficult TB becomes to treat as fewer medicines are available with even more difficult side effects.
- You may become infectious again and spread DR TB germs to other people, including your children, family, friends and others in the community.

Your best chance to beat DR TB is to complete your treatment!

If you are having difficulty with side effects or adherence, do not stop treatment, rather seek out support

- Tell your health care worker if you are experiencing side effects as there may be ways to reduce or manage the side effects.
- Find out if there is a support group for DR TB patients at your clinic. If there is no support group, talk to other patients or the community health worker/ nurse at your clinic about starting one.
- Call a free counselling support line

Can DR TB be treated with faith healing, alternative or traditional medicine?

Being on DR TB treatment is quite difficult and it is normal to seek alternative treatment and spiritual support. Please discuss you this with your doctor as some traditional medicines may interfere with the DR TB treatment and could be quite dangerous to use together. Alternative or traditional medicines that cause diarrhoea or vomiting should be avoided as they will prevent your DR TB medicines from being properly absorbed and working in your body. Leaning on your faith at this time is quite important but remember to keep using your treatment. If you are feeling unsure about continuing treatment talk to your doctor first and invite you pastor or spiritual healer to accompany you to your doctor to discuss your treatment.

Who can I contact for support and counselling?

The Depression and Mental Health Helpline	0800 567 567
Lifeline	0861 322 322
The National AIDS Helpline (also provides TB assistance)	0800 012 322
The National HIV & TB Health Care Workers Hotline	0800 212 506
The Social Grants Helpline	0800 601 011

<u>You may also contact one of the following NGOs for information and support</u>

TB/HIV Care	021 425 0050
Treatment Action Campaign	021 422 1700

BMC Health Services: Instructions for authors

Research articles

Criteria | Submission process | Preparing main manuscript text | Preparing illustrations and figures |Preparing tables | Preparing additional files | Style and language

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Manuscripts for Research articles submitted to *BMC Public Health* should be divided into the following sections (in this order):

- Title page
- Abstract
- Keywords
- Background
- Methods
- Results and discussion
- Conclusions
- List of abbreviations used (if any)
- Competing interests
- Authors' contributions
- Authors' information
- Acknowledgements
- Endnotes
- References
- Illustrations and figures (if any)
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The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

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The title page should:

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- indicate the corresponding author

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Acknowledgements

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OnlineFirst chapter in a series (without a volume designation but with a DOI)
Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.
Complete book, authored
Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.
Online document
Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.
Online database
Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.
Supplementary material/private homepage
Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.
University site
Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.
FTP site
Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.
Organization site
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Tim Albert has produced for BioMed Central a list of tips for writing a scientific manuscript. American Scientist also provides a list of resources for science writing. For more detailed guidance on preparing a manuscript and writing in English, please visit the BioMed Central author academy.

Abbreviations

Abbreviations should be used as sparingly as possible. They should be defined when first used and a list of abbreviations can be provided following the main manuscript text.

Typography

- Please use double line spacing.
- Type the text unjustified, without hyphenating words at line breaks.
- Use hard returns only to end headings and paragraphs, not to rearrange lines.
- Capitalize only the first word, and proper nouns, in the title.

- All lines and pages should be numbered. Authors are asked to ensure that line numbering is included in the main text file of their manuscript at the time of submission to facilitate peer-review. Once a manuscript has been accepted, line numbering should be removed from the manuscript before publication. For authors submitting their manuscript in Microsoft Word please do not insert page breaks in your manuscript to ensure page numbering is consistent between your text file and the PDF generated from your submission and used in the review process.
- Use the *BMC Public Health* reference format.
- Footnotes are not allowed, but endnotes are permitted.
- Please do not format the text in multiple columns.
- Greek and other special characters may be included. If you are unable to reproduce a particular special character, please type out the name of the symbol in full. **Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF.**

Units

SI units should be used throughout (liter and molar are permitted, however).