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SCHOOL OF PUBLIC HEALTH

THE EFFECT OF DECENTRALIZED SERVICES ON MULTIDRUG-RESISTANT TUBERCULOSIS CARE IN SUB-SAHARAN AFRICA: A SYSTEMATIC REVIEW

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology in the field of Implementation Science

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November, 2021

Declaration

I **Meckie P. Achayo** declare that this research report is my own, unaided work. I am submitting this work for the degree of MSc in Epidemiology in Implementation Science at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

I declare this on the _17th day of November, 2021____ in Johannesburg, South Africa.

Dedication

I dedicate this work to God Almighty whose never-failing providence has always prevailed.

Abstract

Introduction

MDR-TB is tuberculosis caused by *Mycobacterium tuberculosis* strains which are resistant to the main anti-TB drugs, rifampicin and isoniazid. Potential approaches for MDR-TB care exist, i.e. centralized and decentralized approaches. A centralized approach is one whereby, MDR-TB patients are treated as inpatients (i.e. remaining over night or more than one night in hospitals) in designated, specialized DR-TB treatment facilities. Decentralized MDR-TB care, on the other hand, is defined as management (treatment and care) of MDR-TB provided at the community where the patient resides. The two approaches allow different levels of accessibility to MDR-TB services by patients. However, there are few data available examining the levels of accessibility between the two approaches. Accessibility of services can be measured in terms of utilization and cost of these services. This study aims to examine the effect of decentralizing MDR-TB care on the accessibility (utilization and cost) of services and patient treatment outcomes in sub-Saharan Africa through a systematic synthesis of literature.

Methodology

A systematic review of published studies conducted within sub-Saharan Africa (SSA) where nine out of thirty high MDR-TB burdened countries are located was conducted. Inclusion criteria were observational studies (cohort, case-control and cross-sectional) or interrupted time series conducted between 2011 and 2021. These studies had to compare the utilization and/or cost of MDR-TB services and/or treatment outcomes (treatment success, loss to follow up, death and treatment failure) between decentralized and centralized approaches to MDR-TB care. Five databases (PubMed, Cochrane library, Global health, Scopus and Global Index Medicus (WHO)) were searched using keywords to identify studies for inclusion. Quality assessment of included studies was conducted using the Effective Public Health Practice Project (EPHPP) tool for observational studies and the CHEERS checklist for economic evaluation studies. Study selection and quality assessment was conducted by two reviewers (Principal Investigator and a second reviewer).

Results

Twelve studies met the eligibility criteria for inclusion. Four studies were cohort studies, five were cost-analyses, two were interrupted time series and one was a cross-sectional study. Findings from this study have demonstrated that decentralization of MDR-TB care in SSA

has improved accessibility of patients to the services through increase in utilization of MDR-TB services. The volume of patients utilizing both diagnostic and treatment services has increased in all countries represented by the studies. Decentralizing MDR-TB services has also improved accessibility of MDR-TB services through the reduction of MDR-TB treatment cost. Increased successful treatment as well as reduction in patients who are lost to follow up have also been shown to be outcomes of decentralizing MDR-TB treatment services within sub-Saharan Africa.

Conclusion

Decentralizing MDR-TB services enables more MDR-TB patients to utilize diagnostic and treatment services. This approach is also related to lower service delivery costs than a centralized approach, which is beneficial in resource limited settings such as those in SSA. Countries in SSA can achieve and maintain high MDR-TB treatment success when using decentralized approaches than centralized approaches. This is also true to the retention of MDR-TB patients in care.

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List of Abbreviations

DALY	Disability Adjusted Life Years
DOT	Direct Observed Therapy
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
LMIC	Low- and Middle-Income Countries
LTFU	Lost to follow up
MDR	Multidrug-resistance
MDR-TB	Multidrug-resistant tuberculosis
NGO	Non-Governmental Organization
RR-TB	Rifampicin-resistant tuberculosis
SSA	Sub-Saharan Africa
WHO	World Health Organization
XDR-TB	Extensive drug-resistant tuberculosis

Definition of Terms

Terminology	Definition
Access to MDR-TB services	The opportunity of MDR-TB patients to utilize MDR-TB services(1,2).
Centralized MDR-TB care	Care that is provided at designated facilities specialized for MDR-TB treatment by specialized providers(3).
Cured	Treatment completed without failure and having negative culture results in three or more consecutive tests taken after the intensive phase at least 30 days apart(4).
Decentralized MDR-TB care	Treatment and care provided at the community where the patient resides, for example, a peripheral health center, a community center or the patient's home(5).
Died	Death occurring in the course of treatment due to any reason(4).
Drug susceptible tuberculosis	Tuberculosis caused by *Mycobacterium tuberculosis* strains that can be treated by the four anti-TB drugs (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol)(6).
Extensive drug-resistant tuberculosis (XDR)	Tuberculosis caused by *Mycobacterium tuberculosis* strains resistant to any fluoroquinolone, and at least one second-line injectable drug (capreomycin, kanamycin and amikacin), in addition to multidrug resistance(4).
Lost to follow-up	Interruption of treatment by a patient for two or more consecutive months(4).
Multidrug-resistant tuberculosis (MDR-TB)	Tuberculosis caused by *Mycobacterium tuberculosis* strains that exhibit resistance to both rifampicin and isoniazid(3).

New cases/patients	Patients who have never received TB treatment or have taken anti-TB drugs for less than one month(7).
Not evaluated	This is a patient for whom a treatment outcome is not assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown)(4).
Previously treated cases/patients	Patients who have received anti-TB drugs for one month or more in the past(7).
Rifampicin-resistant tuberculosis (RR-TB)	Tuberculosis caused by *Mycobacterium tuberculosis* strains that are resistant to rifampicin(4).
Treatment completed	Treatment completed with no evidence of treatment failure but no record of negative culture results from three or more consecutive tests taken after the intensive phase at least 30 days apart(4).
Treatment failed	Treatment that was discontinued or needed an irreversible change of at least two anti-tuberculosis drugs in the regimen(4).
Treatment success	The sum of cured and treatment completed(4).
Tuberculosis	An airborne bacterial infection caused by *Mycobacterium tuberculosis* which affects any part of the body, most commonly the lungs(8).

1 CHAPTER ONE: INTRODUCTION

1.1 Introduction

This chapter provides; a brief history and overview of multidrug-resistant tuberculosis (MDR-TB), global, regional and prevalence estimates of MDR-TB in sub-Sahara Africa as well as a synopsis of treatment approaches including centralised and decentralised approaches. A problem statement, research question, objectives and justification for the study are also stated.

Furthermore, a literature review which presents various studies that have been conducted to assess the effect of the two MDR-TB treatment approaches on the accessibility (utilization and cost) of MDR-TB services and MDR-TB treatment outcomes is presented. The literature review points towards gaps in the current field that this study will address.

1.2 Background

1.2.1 Brief history and overview of TB and MDR-TB

Tuberculosis (TB), an airborne disease caused by *Mycobacterium tuberculosis* bacteria, has been a global health concern for many decades (9). Historical literature suggests presence of the *Mycobacterium* from more than 150 million years ago and as early as 1720 the infectious nature of the bacteria was conjectured(9). For a number of years TB has been found to be associated with social conditions of over-crowding, poverty and poor nutrition(9,10).

General symptoms of the disease, whether pulmonary or extra-pulmonary, can be debilitating and include fever, weight loss, night sweats and loss of appetite(11). More organ specific symptoms depend on the location of the TB infection in the body(11). When TB affects the lungs for example, coughing, chest pain and coughing up blood are likely to present as symptoms(11). When TB affects the spine, individual patients could experience localized pain. When TB affects the neck localized swelling could be present(12). Being an airborne disease, TB is highly infectious and affects over 10 million people each year(9,13).

In the early 1990's, outbreaks of TB which were found to be resistant to existing first line drugs (including rifampicin and isoniazid) as well as other anti-TB drugs were detected across Europe and the United States of America(14–17). This became known as multidrug-resistant tuberculosis (MDR-TB)(9) and was observed to be associated with high mortality in

HIV positive patients(15–17) presenting a challenge to TB control programmes(18). As a result, DR-TB began to be perceived as a threat to public health(19).

MDR-TB has been found to be related to various factors including health care provider and patient factors(20). These include several inter-related factors such as inappropriate treatment regimens or dosages, frequent stockouts in anti-TB drugs, poor quality of available drugs, poor patient adherence to anti-TB medication and poor access to care(20,21).

1.2.2 Global burden of MDR-TB

Globally, the incidence of MDR-TB has been estimated at 3.5%, 3.4% and 3.3% by the World Health Organization (WHO) in the years 2017, 2018 and 2019, respectively(22–24). In these three years, it was estimated from global data that 18% of TB cases receiving treatment developed MDR-TB(22,23,25).

The prevalence of MDR-TB however, varies across regions and countries around the world. For example, a systematic review and meta-analysis pooling data from the Latin America and Caribbean regions in 2019 suggested that, 7% and 26% of new and previously treated cases, respectively, had developed MDR-TB(26). Meanwhile, in the South East Asian region 2.5% of new cases and 14% of previously treated cases were estimated by the WHO to have developed MDR-TB in 2019(24).

In mainland China, a systematic review and meta-analysis conducted in 2015 reported a prevalence of 4.8% among new cases and 26.3% among cases who had received TB treatment before(27). Through similar studies, higher prevalence estimates have been observed in India (42.6%) in 2017(28) and Russia (19% – 26% among new TB patients and 60% - 70% among previously treated TB patients) in 2020(29). MDR-TB related death estimates of between 12.6% and 15% have been reported globally(24,30,31).

1.2.3 Burden of MDR-TB in Sub-Saharan Africa

Nine out the thirty high MDR-TB burdened countries are located in sub-Saharan Africa (SSA). These countries are Angola, Democratic Republic of Congo, Ethiopia, Kenya, Mozambique, Nigeria, Somalia, South Africa and Zimbabwe. The prevalence of MDR-TB in SSA also varies across regions and countries, reflective of the global patterns(24).

For example, drug resistance surveillance studies conducted between 2005 – 2011 in East Africa, reported multidrug-resistance (MDR) estimates to range from 0.4% in Tanzania to 4.4% in Uganda among new cases and 3.9% in Tanzania to 17.7% in Uganda among cases previously treated for TB (32). In West Africa, a pooled prevalence of 6% in new cases and 34% in previously treated cases was observed across eight countries in 2016(33). In the Southern African region, countries have reported MDR-TB prevalence estimates ranging from 1.3% to 8% in 2019, among new cases in Botswana and Angola, respectively(34,35). Among previously treated cases, the prevalence estimates reported were respectively, 7.7% and 71.1% in Botswana and Angola(34,35). A systematic review and meta-analysis conducted in 2017 by Musa and colleagues, found a pooled prevalence of 2.0% for MDR-TB in the sub-Saharan African region(36). When examining regional prevalence estimates of MDR TB, the prevalence was found to be 1.7% in East Africa, 1.9% in West Africa, 2.1% in Central Africa and 3.1% in the Southern African region(36).

1.2.4 Models of care for MDR-TB

Two models of care exist for the management of MDR-TB. The first is a centralized model of care and the second a decentralized model of care(3,37). These are described in further detail below.

1.2.4.1 Centralized MDR-TB Care

A centralized approach is one whereby, MDR-TB patients are treated as inpatients (i.e. remaining over night or more than one night in hospitals) in designated, specialized DR-TB treatment facilities(3). The patients are likely to be treated by specialized provider(s) throughout the intensive phase of treatment or until negative diagnostic results (through culture or smear conversion)(3).

Centralized MDR-TB care can be advantageous in low MDR-TB prevalence settings. This is because the low number of patients in a larger region can be transferred to the facilities thereby controlling infection and preventing the spread of drug-resistant strains in the community(38). This approach also allows easier monitoring of patients' adherence to medication and adverse events such as skin rash, hearing disturbances, kidney failure and others(4,5). However, among the limitations to this approach are delays in treatment initiation due to insufficient bed capacities, limited human resources to deliver care and increased socioeconomic costs associated with hospitalization(38). Also, centralized facilities are

sometimes located far from the patients' homes necessitating patients to travel long distances to access services(39).

In the sub-Saharan African region, resource limitations in centralized facilities such as limited bed capacities, is related to a backlog of patients who wait for several months before being initiated on treatment(39,40). Often, MDR TB patients also have to travel long distances to be monitored closely while on treatment, resulting in high default rates(39).

1.2.4.2 Decentralized MDR-TB Care

Decentralized MDR-TB care is defined as management (treatment and care) of MDR-TB provided at the community where the patient resides. These include a peripheral health center, a community center or the patient's home(5). This approach was recommended by the WHO, in 2011, in response to the challenges of a centralized approach as presented above (25). The decision followed evidence from studies conducted in Peru, the Philippines and Russia which suggested that a decentralized approach was more efficient and cost-effective than a centralized approach(41–43). Findings of these studies are further expanded in the literature review.

Decentralized care mainly incorporates ambulatory modes of care which can be defined as care provided on an outpatient basis(3). Ambulatory care can include clinic-based where patients attend a peripheral clinic or community-based, which is also referred to as home-based model of care(25). Community-based care involves a community-based directly observed therapy (DOT) approach, which utilizes local health care workers (HCWs), former patients, coworkers, neighbors or family members to directly observe treatment rather than requiring hospitalizations or frequent visits to a health care facility(40). Decentralized care for MDR-TB has been reported to improve accessibility to MDR-TB diagnostic and treatment services(38).

1.2.5 Accessibility of MDR-TB services

Access to health care services is a broad and complex concept whose definition has been the subject of debate for many years(44). It has been suggested that access has three dimensions namely: availability, affordability and acceptability of the services within a setting(2,45–47). Donabedian suggested that proof of access is the use of the services(1). Some researchers

have therefore, added service utilization as another dimension of access(1,46,48). In the present study, focus is given to utilization and affordability of services as these areas fall short from the target set at the United Nations high-level meeting on TB in 2018. In this meeting, a global target of treating 1.5 million people by 2022 was set. By 2019, only 333,000 people (22% of target) had received treatment for MDR-TB globally(24).

Service affordability is the ability to pay for services without facing financial hardship(2). It is an integral component to achieving universal access to health services. It accounts for direct and indirect (e.g. transportation to health facilities) costs of health services, including MDR-TB services(2). The present study looks at these costs as experienced by MDR-TB service providers (health system) and recipients of MDR-TB services (patients) in sub-Saharan Africa.

Service utilization in healthcare can be defined as the use of healthcare services by patients when they(patients) interact with healthcare providers(44). This can be assessed from two perspectives i.e. the patient or physicians'/providers' perspective(44). The providers' perspective may be more objective as it hinges on the volume of services provided to patients and documented in databases(44). Indicators used to measure service utilization from the provider's perspective include number of visits, number of medical acts, number of hospitalizations per year and number of patients(44). This study uses the indicator "number of patients" to measure utilization of MDR-TB services as a dimension of access. In this review therefore, accessibility to services focuses on the utilization, by patients, and costs of MDR-TB services.

1.3 Problem statement

Since the WHO recommended treatment of MDR-TB via decentralized approaches, several countries have adopted the approach. Many of these countries are in high MDR-TB burdened areas including countries in the sub-Saharan African region such as South Africa and Ethiopia(49,50). This has allowed studies to be conducted in respective countries assessing the effectiveness of decentralized approaches.

In 2013, Bassili and colleagues published a systematic review and meta-analysis which aimed to compare the effectiveness of the ambulatory and hospital-based approach to MDR-TB treatment. The study included 35 studies from 22 countries, South Africa being the only sub-Saharan African country. Another systematic review and meta-analysis comparing MDR-TB

treatment outcomes between community-based and hospital-based approaches was published in 2016 by Williams and colleagues (38). The review included 16 studies from nine high MDR-TB burdened countries, only three of which were conducted in sub-Saharan Africa (Kenya, South Africa and Ethiopia)(38). Similarly, published in 2017, is a systematic review and meta-analysis which aimed to compare MDR-TB treatment outcomes between decentralized and centralized approaches(5). This review included eight studies from which South Africa and Swaziland were the only sub-Saharan countries(5). These studies had a narrow scope of the effect of decentralization across the sub-Sahara African region as they included only a maximum of 3 countries from a region with over 45 countries. There is also a limited summary of evidence of the effect of decentralization on the accessibility of MDR-TB services since its recommendation.

A lack of systematic reviews and/or meta-analyses on the subject for the sub-Sahara African region as evidenced from the literature review below, limits evidence on how the decentralized approach has affected the utilization, cost and treatment outcomes of MDR-TB in the region.

1.4 Research question

What is the effect of decentralizing MDR-TB care on the accessibility (utilization and cost) of services and patient treatment outcomes in sub-Saharan Africa?

1.5 Research aim

To examine the effect of decentralization of MDR-TB care on the accessibility (utilization and cost) of services and patient treatment outcomes in sub-Saharan Africa.

1.6 Research objectives

- To examine the effect of decentralization of MDR-TB care on the accessibility of services, in terms of utilization and cost, in sub-Saharan Africa.
- To examine the effect of decentralization of MDR-TB care on patient treatment outcomes in sub-Saharan Africa.

1.7 Justification of the study

Examining the effect of decentralizing MDR-TB services will provide evidence of the extent to which decentralization has influenced utilization and cost of MDR-TB services within SSA region. Also, examining the effect of decentralization of MDR-TB services will provide evidence of its effect on MDR-TB treatment outcomes across the wider SSA region. This evidence will help to ascertain the effectiveness of decentralized approaches in MDR-TB care within the SSA context. Consequently, this evidence will help to enhance decision making processes to the adoption of decentralized approaches across the SSA region.

1.8 Literature review

A body of literature exists examining the effect of decentralizing MDR-TB services in various settings. This literature review presented below synthesizes findings of the effect of decentralizing MDR-TB services from available literature. The literature review examines studies that focus on measurable MDR TB treatment outcomes and access to MDR-TB services. As mentioned above in the introduction chapter access is measured by service utilization and cost of MDR-TB treatment in line with existing literature. The literature review below is presented under the umbrella of two major themes: access to MDR-TB services by patients and MDR-TB treatment outcomes.

1.8.1 Accessibility of MDR-TB services by patients

1.8.1.1 Utilization of MDR-TB diagnostic services

Literature suggests that decentralization of MDR-TB services is associated with increased access to laboratory services such as testing for drug susceptibility. This was observed in a study conducted in Kenya between 2012 and 2013, that aimed to investigate the effect of decentralized laboratory services in MDR-TB diagnosis(51). The study examined the proportion of retreatment cases tested for drug resistance comparing between central and decentralized regional laboratories (51). Over 400 cases were registered at hospitals referring to a decentralized laboratory while over 300 (about 70 less cases than the hospitals referring to the decentralized laboratory) were registered at hospitals referring to a centralized laboratory(51). The authors noted that 55% of cases registered at hospitals referring to the regional laboratory were tested for drug susceptibility while only 25% of cases registered at hospitals referring to the central laboratory were tested(51). Despite no analyses conducted to

determine statistically significant differences, the absolute numbers yielded by the study suggest that the decentralized laboratory had capacity to test more cases. In Peru another comparable low and middle income country context, Shin and colleagues also noted an increase in demand for Drug Susceptibility Testing (DST) when decentralization of laboratory services for MDR-TB diagnosis was introduced(52). For second line drugs, DST increased from 0 to over 2000 tests conducted per year(52).

1.8.1.2 Utilization of MDR-TB treatment services

The WHO reported a large gap in utilization of treatment services observed in 2019. Only 177,099 (38%) of the estimated 465,000 MDR/RR-TB patients were enrolled into care(24). Among the reasons thought to contribute to this gap is reliance on centralized, hospital-based treatment models(24). Based on this observation, recommendation is given for greater decentralization and use of ambulatory models of care which has been further explored in subsequent literature(24).

Literature suggests that decentralization of MDR-TB services in low- and middle-income countries is associated with more patients having access to treatment services similar to the diagnostic services described above. In Bangladesh, Daru and colleagues were motivated by observations that centralized treatment could result in avoidable hospitalization and use of already limited hospital beds(37). They collected secondary data from diagnostic laboratories, hospitals that treat TB and extensive patient records(37). They found that initiation of treatment increased from 77% prior to intervention (community-based approach) to 100% when the community-based approach was used(37). Furthermore, they found that a median number of days between diagnosis and the start of treatment decreased substantially (37). Another study conducted in South Africa reported improved access to MDR-TB treatment services when the decentralized approach was initiated. This study observed that, across a 3year period prior to decentralization of MDR-TB services, 158 patients were initiated on treatment(53). After decentralization, 257 patients were initiated in the first two years and 938 patients in total after a 5year period(53).

1.8.1.3 Cost of MDR-TB care

Studies have suggested that managing MDR-TB patients by hospitalization is costlier when compared to managing MDR-TB patients by an outpatient approach(41,54). This was evident in a study conducted in Estonia and in another study conducted in Tomsk, a city in Russia. The two studies followed up hospitalized MDR-TB patients to estimate the cost and cost-effectiveness of MDR-TB treatment(54). The cost per patient was found to be $8,974 and $10,088 in Estonia and Tomsk, respectively(54). Also, the cost per Disability Adjusted Life Years (DALY) averted was found to be $579 and $429 in Estonia and Tomsk, respectively(54). These figures were higher in comparison to findings from a study conducted in Peru(41,54), which assessed the feasibility and cost-effectiveness of managing MDR-TB via the ambulatory model(41). For those who completed treatment, the observed cost per patient was $2,381 and the cost per DALY gained was $211(41).

A systematic review by Fitzpatrick and Floyd conducted in 2010 corroborated the findings presented above that a decentralized model is less costly and more cost-effective than a centralized model(55). The review involved studies from four low to middle income countries (Estonia, Russia, Peru and Philippines)(55). Treatment was provided using an outpatient model in Philippines and Peru and as inpatients in Estonia and Russia(55). The authors found that an out-patient approach cost an average of $13,259 per patient while an inpatient approach costed 2.6 times more ($34,599 per patient)(55). The cost-effectiveness for the outpatient model was found to be on average $725 for each DALY averted while that of an inpatient model was $1,812 for each DALY averted(55).

1.8.2 MDR-TB treatment outcomes

Treatment completion

Studies have suggested increased treatment completion rates when MDR-TB patients are treated on an outpatient basis in the community or at clinics. For example, a retrospective cohort study conducted in Iran found that 23.3% of MDR-TB patients completed treatment(56). This study assessed treatment outcomes of hospitalized MDR-TB patients between the years 2002 and 2006(56). Another retrospective study conducted between 2010 and 2015 in north-west Ethiopia by Alene and colleagues, which investigated treatment outcomes for admitted MDR-TB patients at a specialized MDR-TB facility, found that 10% of the patients completed treatment(57). In comparison, a study in which patients were

treated as outpatients reported up to 88% of patients completing treatment(58). This study was conducted in Lima, Peru(58).

A contrasting finding has been noted by some researchers. For example, Narita and colleagues, in Florida, USA, conducted a cohort study in 2001 to investigate patient treatment experiences(59). They compared treatment outcomes for patients treated under a community-based model against outcomes of those who attended specialized, hospital-based care(59). They found that community-based care had lower completion rates (48%) than hospital-based care (79%)(59). This was attributed partly to lack of expertise for MDR-TB management amongst providers in the community care arm(59).

Cure

A decentralized approach for MDR-TB has been associated with higher cure estimates when compared to a centralized, hospital-based approach. In Estonia, a study conducted by Floyd and colleagues reported treatment outcomes before and after the introduction of outpatient management of MDR-TB(54). This study followed up a cohort of patients to observe their treatment outcomes(54). The results of the study revealed a rise in the estimates of patients cured from 43% when inpatient treatment was predominant to 54% when outpatient treatment was introduced(54). In the same study, a cohort of MDR-TB patients were followed up in Tomsk, Oblast in Russia to identify their treatment outcomes(54). The findings showed that 14.6% patients were cured before the introduction of outpatient treatment(54). This figure rose to 76% after outpatient treatment of MDR-TB was introduced(54). Another prospective cohort study which was conducted in the Philippines between 1999 and 2002 also showed similar findings(42). In this study, MDR-TB patients were mainly treated as outpatients(42). The observed estimates of cured patients for the entire cohort was 60% which is higher than estimates of cure for inpatient treatment observed in Estonia and Tomsk(42,54).

Treatment success

Treatment success (i.e. sum of cured and treatment completed) has been observed to be higher in some studies when MDR-TB treatment services were decentralized. For example, a study conducted in Bangladesh by Daru and colleagues between 2011 and 2015 found increased treatment success when services were decentralized(37). In this pre- and post-intervention study, treatment success increased from 70% to 76% after MDR-TB care shifted from centralized to community-based(37). Similarly, Morris and colleagues, observed an increase in treatment success from 70% to 82% in a retrospective cohort study conducted

between 2014 and 2017(60). This study was conducted in a district island of the Western province of Papua New Guinea where treatment was decentralized to health centres during the study period(60).

Other studies have, however, observed similar treatment success estimates between centralized and decentralized approaches. A systematic review assessing the effectiveness of managing MDR-TB using a hospital and ambulatory-based approach reported pooled treatment success estimates of 65.5% and 66.7% respectively, for the ambulatory and hospital-based approaches(61). This review, however, involved studies from 22 countries, South Africa being the only country from Sub-Saharan Africa(61).

Despite these differences, authors from the studies agree on the use of a decentralized model over a centralized model for the management of MDR-TB, except in particular situations such as when patients are severely ill(37,60,61).

Lost to follow-up (LTFU)

Studies have suggested that there are differences in estimates of lost to follow-up (i.e. where patients do not remain in care)(62) between decentralized and centralized approaches to MDR-TB treatment. One study conducted in 2018 in Indonesia found that, lower estimates of patients lost to follow-up are associated with a decentralized treatment approach than with a centralized approach(63). This retrospective cohort study aimed to examine the influence of decentralization on the incidence of LTFU among MDR-TB patients(63). The authors found that the proportion of patients categorized as LTFU receiving decentralized care (community-based) was significantly lower than those categorized as LTFU receiving non-decentralized care (24.43% vs 47.06%; p-value = <0.0001)(63). However, missing data for some variables (HIV status, adverse events, and culture conversion status) limited the analysis of their relationship to the outcomes(63). Another study conducted in the Philippines by Gler and colleagues noted similar observations. The findings from this retrospective study suggested that patients receiving decentralized care were less likely to be lost to follow up than those receiving treatment at centralized facilities(64).

A systematic review and meta-analysis conducted by Ho *et al*, 2017, included six studies reporting on treatment outcomes(5). These studies were from five economically diverse countries including two countries from sub-Saharan Africa (South Africa and Swaziland)(5). A pooled prevalence estimate of 18% of patients receiving care under a centralized model were LTFU while 11.9% of patients receiving care under a decentralized model were

LTFU(5). Another systematic review that involved studies from 22 countries, South Africa being the only Sub-Saharan African country, reported similar findings(61). The findings from the review show that 14.7% of patients receiving hospital-based treatment were LTFU while 13.3% of those receiving ambulatory care were LTFU(61). However, these differences were not significant statistically(5,61).

Among the reasons for the observed findings (reduced LTFU in decentralized care) is delivery of treatment close to or at the patient's home(63,64). For this reason, the authors posited that patients are likely to remain in care when treatment is offered in their local setting(5,61,63,64).

Treatment failure

Treatment failure (i.e. discontinued treatment or irreversible change of two or more drugs in a regimen) estimates among those treated with an ambulatory approach compared to those who were hospitalized have been found to be similar by some studies. For instance, a study conducted under programmatic conditions in a district of southern India between 2006 and 2007, reported a failure estimate of 13% in patients treated by an ambulatory approach(65). A similar finding (failure estimate of 14.1%) was noted in a retrospective cohort study conducted in Israel(66). The study assessed treatment outcomes in MDR-TB patients hospitalized at a specialized TB treatment facility between 2000 and 2005(66).

Differences in estimates of treatment failure have also been reported. A systematic review comparing failure estimates between treating MDR-TB in a community setting and a hospitalized setting, showed lower estimates when a community-based approach was used than when a hospital-based approach was used(38). This study, conducted in 2015, included 16 studies from nine MDR-TB high burdened countries, three being SSA countries(38). The authors found that the probability of a patient failing treatment whilst on community-based approach was 6.5% while that of failing when hospitalized was 18.8%(38).

Death

Some studies have shown that, both centralized and decentralized treatment approaches have similar death estimates. A study conducted in Myanmar by Wai and colleagues, 2017, found that, 12.7% of patients who did not receive community-based care died while, 12.3% of those who received community-based care died(38). A systematic review of eight studies, comparing treatment outcomes between decentralized and centralized models showed no

difference between the two approaches(5). Six of the eight studies which reported patient treatment outcomes were from five countries, two (South Africa and Swaziland) of which are located in sub-Saharan Africa(5). The pooled estimates of death related to decentralized and centralized care were 17.8% and 18.6% respectively(5).

A retrospective cohort study conducted in Florida, USA, examining treatment experiences of MDR-TB patients diagnosed from 1994 to 1997 found a difference in death estimates between the two treatment approaches(59). The authors found that, 26% among those treated as out-patients (community care group) died while 18% among those treated as in-patients (specialized care group) died(59). Among the reasons for this observation was minimal technical knowledge in MDR-TB management amongst providers in the community care group(59).

2 CHAPTER TWO: METHODOLOGY

2.1 Introduction

This chapter details the methods that were used to undertake this research project. The chapter provides a description of the study design, the study setting, the criteria used in selecting studies to be included in the review and the strategy used for searching literature. The chapter also provides details on how eligible studies were selected, the data extracted from these studies and how the quality of these studies was assessed.

2.2 Study setting

Sub-Saharan Africa is home to over 1.1 billion people living in the 48 countries of the region(67,68). The region spans from the southern border of the Saharan Desert to the southern tip of the African continent (Figure 1). The region is among the poorest in the world with 42.3% of its inhabitants living in extreme poverty(67,69). As a result of poverty, weak health systems with inadequate diagnostic services and human resource capacities pose hindrances to the deployment and sustainability of MDR-TB interventions(70).

Nearly half (47%) of the urban residents in sub-Saharan Africa live in unimproved houses, that is, houses with poor sanitation, poor water supply, uncompleted buildings and/or crowded houses with more than three people living in a single room(71,72). These conditions have been shown to influence MDR-TB transmission and consequently increase the disease burden(73). Agriculture provides a livelihood for many people in the rural areas of sub-Saharan Africa and employs over half of the total labor force in the region(74).



Figure 2.1: Map of Africa showing sub-Sahara African region ***(countries below the grey area). (Source: https://www.librarything.com/topic/183039)***

2.3 Study design

This study is a systematic review of studies conducted in sub-Saharan Africa. It was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines which is a 27-item guideline developed to guide the reporting of systematic reviews and meta-analyses(75).

2.4 Eligibility criteria

Table 2.1 presents the criteria used to select eligible studies for inclusion in the review.

Table 0.1: Eligibility criteria for study selection

Criteria	Description
Location	The study had to have been conducted in a country or in countries that are within the sub-Saharan African region. All studies conducted in countries outside SSA, including northern African countries (Egypt, Libya, Algeria, Morocco, Tunisia and Western Sahara) were excluded from the review.
Study design	Interrupted time series, observational studies (prospective and retrospective cohort studies, case control studies and cross-sectional studies) and cost evaluation studies were included in the review. These were included because they were the only study designs available. Studies with a qualitative design were excluded from the review.
Comparison groups	The study should be comparing patients receiving **decentralized** (ambulatory or community-based) mode of care and those receiving a **centralized** mode of care for MDR-TB treatment. *Decentralized MDR-TB care was considered to be one which is purely provided on an outpatient basis, from treatment initiation to completion. Also, for diagnostic services (e.g. laboratory services), decentralized care was one where diagnosis is done at facilities other than the central laboratory.* *Centralized MDR-TB care was considered to be care which is provided on an in-patient basis at designated specialized facilities by specialized providers.*
Outcomes	The study should have reported at least one treatment outcome as per WHO standards, including, cure, completion, success, death, failure, default/lost to follow-up. Studies reporting the number of patients accessing MDR-TB services, and/or cost of MDR-TB services were also included.

	All studies **solely** reporting treatment outcomes and/or cost for RR-TB, pre-XDR and XDR-TB, and not for MDR-TB, were excluded from the review.
Data source	Peer reviewed studies published in peer reviewed journals.
Year of publication	Between 2011 and 2021. This time period was selected because 2011 was the year when WHO recommended the decentralized approach and 2021 the year the study was conducted.
Language of published study	English. No other languages were included as none of the reviewers were proficient in either French, Portuguese or Arabic. Also, there was limited time for translation services.

2.5 Search strategy

Studies conducted within sub-Saharan Africa focusing on decentralized and centralized treatment approaches for MDR-TB were searched from five scientific databases. These databases are PubMed, Global health, Cochrane library, Scopus and Global Index Medicus (WHO). The search was limited to studies published from 2011 to 2021. The last search was conducted on January 28, 2021. Language was restricted to English.

Keywords that were used to facilitate the literature search included multidrug-resistant tuberculosis, decentralized, decentralization, centralized, hospital-based, mdr-tb, "mdr-tb AND decentralization", "mdr-tb AND community-based", "mdr-tb AND ambulatory", "mdr-tb AND sub-Saharan Africa", "(mdr-tb AND decentralization) AND *sub-Saharan country name*", "(mdr-tb AND community-based) AND *sub-Saharan country name*", "(mdr-tb AND ambulatory) AND *sub-Saharan country name*"

A manual search of literature was also conducted using the reference lists of studies that had been identified.

2.6 Study selection

Mendeley referencing manager (version 1.19.8) was used to manage the retrieved studies. These studies, obtained from databases, were stored in a folder within Mendeley. This was followed by searching for duplicates and their removal using the software.

A total of 1,013 titles and abstracts of retrieved studies were then screened to determine their eligibility for inclusion in the review. Those which were found to be ineligible (n = 925) were excluded. Despite being related to the study question of this review, twenty-two studies were excluded based on their study design (n = 9) and location of study (n = 13). Those excluded because of their study design were either a systematic review or systematic review and meta-analyses, qualitative studies or a protocol of a cluster randomized trial in line with the exclusion criteria originally set. Studies excluded based on location were conducted outside the sub-Saharan African region. The remaining 66 studies were fully read. After full text reading, fifty-four studies were excluded and a justified reason for their exclusion was noted for reporting purposes. Finally, twelve studies were found eligible for inclusion in the review. Figure 2.2 illustrates the study selection process.

Study selection was conducted by two reviewers, the principal investigator and a second reviewer (both MSc in Epidemiology candidates). The principal investigator trained the second reviewer on the eligibility criteria for study inclusion, documentation of reason(s) for exclusion of ineligible studies and quality assessment of eligible studies. The two reviewers worked independently during study selection and met to compare their inclusions. Differences on the inclusion/exclusion of a study between the two reviewers were resolved by a consensus.

Flow diagram showing the selection of studies on centralized and decentralized management of MDR-TB

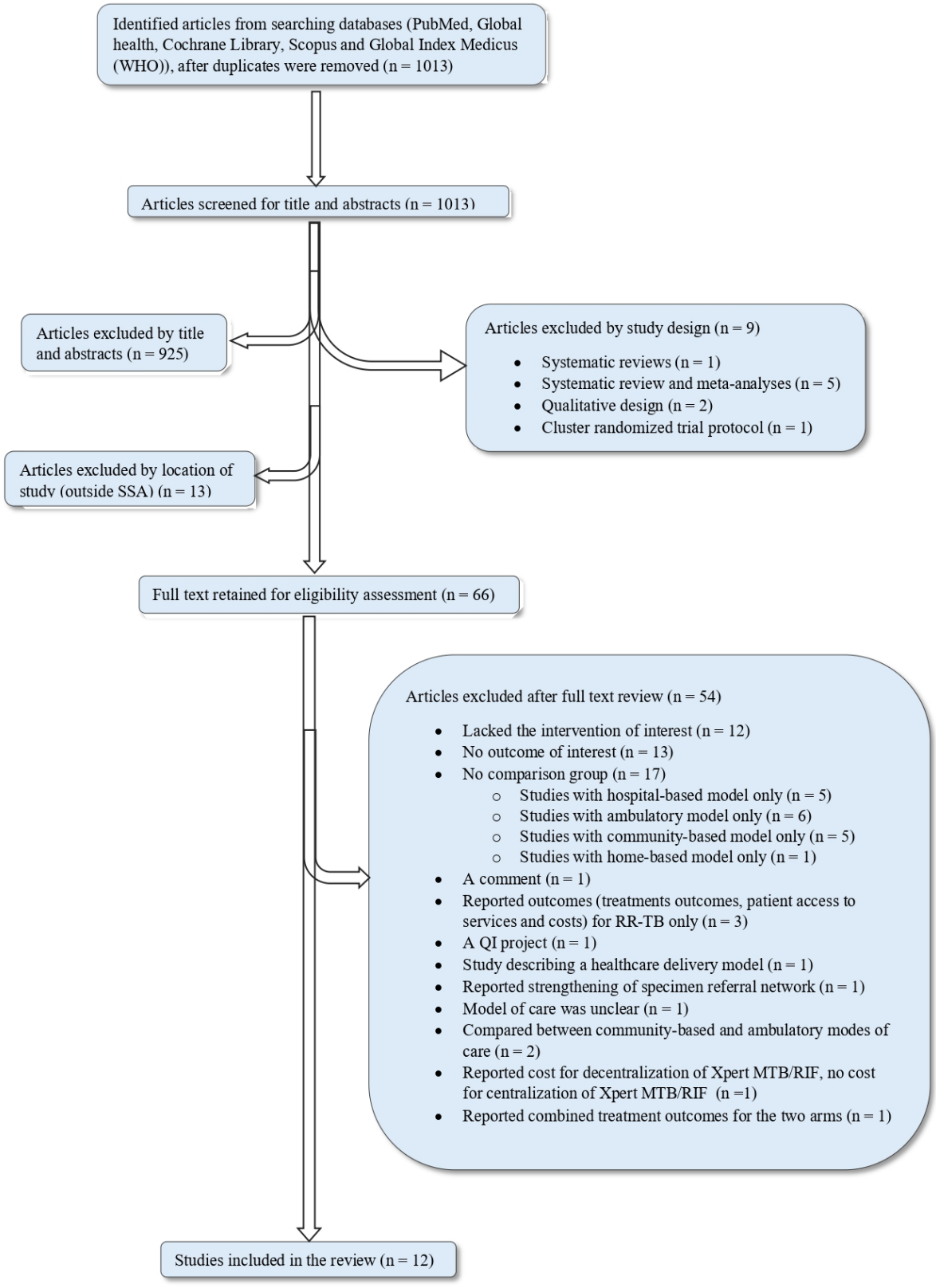

Figure 0.1: Flow diagram showing study selection

2.7 Data extraction

The following information was extracted from each eligible study; first author's name, year of publication, study design, study setting and description of centralized and decentralized models of care. When available, the following information was also extracted from eligible studies; number of patients utilizing MDR-TB services and/or number of samples tested for MDR-TB, cost of MDR-TB care and prevalence estimates of patient treatment outcomes such as death, loss to follow up, treatment failure and treatment success. Data was extracted by the principal investigator and re-checked by the second reviewer.

2.8 Quality assessment

2.8.1 Observational studies and interrupted time series designs

The Effective Public Health Practice Project (EPHPP) tool was modified and used to assess the quality of the seven studies that fall under this heading – i.e. the observational studies (n=5) and interrupted time series designs (n=2). This tool has been useful for observational studies, before and after studies and randomized control trials (RCTs)(76). The EPHPP is attached in Appendix B.

The tool assesses six domains to establish the quality of a study. However, one domain (blinding) was removed because it is a feature of experimental studies (eg RCTs) which were excluded from this study. Five domains, therefore, were used to establish the quality of these studies. Each domain received a rating of being either weak (1 point), moderate (2 points) or strong (3 points). The five domains are

- *Participant selection bias*

  This domain assessed if the study participants were representative of the target population and the proportion of the participants who agreed to participate.

  For representativeness; this was achieved by identifying the method of selecting participants in the study. For studies which randomly selected their participants, a response of "very likely" was documented. If study participants were referred from a source (eg clinic) in a systematic manner, then a response of "somewhat likely" would be documented. And studies in which participants were self-referred a response of "not likely" was noted.

  For those who agreed to participate; this was the percentage of participants in both the control and intervention groups who agreed to participate in the study before being

assigned into the two groups, control and intervention. Responses fall into either one of the following five categories; 1) 80 – 100% agreement, 2) 60 – 79% agreement, 3) less than 60% agreement, 4) Not applicable and 5) Can't tell.

Based on the responses for the two questions, the study was then assigned to be either weak, moderate or strong in this domain. Weak studies were those with individuals not likely to be representative of the target population or with less than 60% participation or lacking a description of participant selection process and/or level of participation. Moderate studies were those with a somewhat likely representative population and a 60 – 79% participation rate. Strong studies were those with individuals who were very likely to be representative of the target population and more than 80% participation rate.

In this review, five studies were rated strong as their sample population was very likely to be representative of the target population and had more than 80% participation(49,50,77–79). Two studies were rated moderate despite having more than 80% participation(39,80). This is because their sample population was somewhat likely to be representative of the target population.

- *Design of study*

  This domain assessed the type of study design for the included studies. While the EPHPP incorporates RCTs, it was still useful for observational studies. The EPHPP tool considers RCTs to be strong studies. Cohort studies, case-control studies and interrupted time series are considered to be of moderate strength and any other study design is considered to be weak. Four studies in this review were cohort studies and two were interrupted time series(39,49,50,78–80). These were scored as moderate. One study was a cross-sectional study and this was scored as weak(77).

- *Confounding*

  This section assessed if confounding variables existed in the study and if they (confounders) were controlled for. Scoring was based on the percentage of confounders controlled for. To determine this percentage, the number of confounding variables listed in a study was counted and the percentage of confounders that were controlled for estimated. A score of being strong was assigned to studies which

controlled for at least 80% of confounders and a moderate score was assigned for those which controlled for 60 – 79% of the confounders. A weak score was assigned for studies which controlled for less than 60% of confounders or did not describe the controlling of confounders.

Four of the included studies received a score of being strong as they controlled for more than 80% of the confounders(39,49,79,80). Three studies received a score of being weak as they did not state whether confounders were accounted for or not(50,77,78).

- *Data collection methods*

  In this domain, the validity and reliability of the data sources were assessed. A study was scored as strong if the data source was shown to have undergone a validation and reliability testing process. A moderate score was assigned to studies using a valid but unreliable data source or did not report the reliability of the data source. Studies which did not report the validity and reliability of the data source were scored as weak.

  All studies included in this review used routinely collected programmatic data. Several challenges have been documented with this type of data source in resource poor countries, including sub-Saharan African countries. Documented challenges are data incompleteness, errors in reporting and untimely reporting(81–83). For this reason, the data source was considered to be valid but not reliable. As a result, all seven studies received a score of moderate.

- *Withdrawals/dropouts*

  In this section, presence of participant withdrawal is assessed as well as the proportion of participants completing a study. Studies which reported presence of participant withdrawal and 80% or more of the participants completing the study were classified as strong. Studies which had 60 – 79% of its participants completing a study were classified as moderate and a weak classification was given to studies with less than 60% of its participants completing the study. For one-time studies such as surveys and cross-sectional studies, a “not applicable” response was assigned. This was classified as moderate.

In this study, three of the seven studies had more than 80% of their participants completing the study and were scored as strong(50,78,79). Three studies had 60 – 79% of their participants completing the study and were scored as moderate(39,49,80). One was a cross-sectional study; therefore, it received a score of moderate(77).

The scores from the domains were then added to derive a total score. From the total score, an average score was calculated to get the global rating for a study. The minimum and maximum attainable global rating score per study was 1.00 and 3.00, respectively.

Individual studies were then classified into either weak, moderate or strong categories depending on their global rating scores. Weak studies had a global rating score ranging between 1.00 – 1.50, moderate studies scored between 1.51 – 2.50 and strong studies obtained a score between 2.51 – 3.00(76).

The quality of six studies was classified as moderate and one study was classified as strong. No study was classified as weak.

2.8.2 Economic evaluation studies

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline was used for the five studies that fall into this category. CHEERS is a 24-item checklist aimed at optimizing the reporting of health economic evaluations(84). The checklist is attached in Appendix C.

For each item of the checklist, the page number and line to which the item is reported in each study were documented. Items which were not reported by studies and those which were not applicable to studies were documented.

Generally, the quality of reporting was good with three of the studies reporting all items that were applicable(85–87), one study reported all applicable items except two(88) and the last study reported all but one applicable item(89).

2.9 Ethics

Approval to conduct this study was granted by the University of Witwatersrand ethics committee (Medical), reference number, W–CBP–210219-01. A copy of the ethics certificate is attached in Appendix D.

3 CHAPTER THREE: RESULTS

3.1 Introduction

This chapter reports the study characteristics, synthesized results for the accessibility (utilization and cost) of MDR-TB services and synthesized results of the treatment outcomes. It also provides tables that summarize: the main characteristics of the studies (Table 3.1), the results for utilization of services (Table 3.2), cost of services (Table 3.3) and treatment outcomes (Table 3.4).

3.2 Study Characteristics

3.2.1 General characteristics

Twelve studies were found eligible and included in this review (Figure 2.2). Five of the studies were from the southern region of sub-Saharan Africa (South Africa), two from the west African region (Nigeria) and five from the east African region (Ethiopia (2), Tanzania (1), Uganda (1) and Kenya (1)). Four of the included studies were cohort studies, 5 were cost analyses, 2 were interrupted time series and one was a cross sectional study (Table 3.1).

3.2.2 Study characteristics on MDR-TB care models

Table 3.1 summarizes the characteristics of the MDR-TB care models reported by the studies. For the centralized model, 10 studies reported MDR-TB diagnosis and treatment at centralized hospitals, one study reported specimen diagnosis at a central laboratory and one study reported limited access (35% access) to diagnostic services during a scale-up project. For the decentralized model, 9 studies reported on MDR-TB treatment. The studies involved various treatment models such as ambulatory clinic-based model, home-based treatment and community-based treatment by mobile healthcare providers. One study reported specimen diagnosis at regional laboratories, one reported expanded access (>90% access) to diagnostic services during a scale-up project and one reported expansion of diagnostic services to peripheral facilities.

3.2.3 Study characteristics on accessibility (utilization and cost) of services and MDR-TB treatment outcomes.

Utilization of MDR-TB services was reported by four studies. Two of these reported utilization of diagnostic services, one reported utilization of treatment services and one reported utilization of both diagnostic and treatment services. Five studies reported costs for MDR-TB care. Of the five studies that reported treatment outcomes, all but one reported on treatment success. Lost to follow up, death and treatment failure were reported by all five studies (Table 3.1).

Table 3.1: Characteristics of studies included in the systematic review of decentralized versus centralized care of MDR-TB in Sub-Saharan Africa

Author and year of publication	Country	Study design	Year of intervention	Sample size		Description of models of care		Timing of intervention	Outcome(s) measured
				Control	Intervention	Centralized (Control)	Decentralized (Intervention)		
Loveday et al, 2015	South Africa	Prospective cohort	2008 - 2010	813	736	Treatment at a specialized central hospital	Treatment at a rural hospital followed by outpatient clinic or home-based care	Concurrent	Treatment outcomes (cure, completion, success, failure, default, death, unsuccessful, transferred out)
Sharma et al, 2015	Kenya	Cross-sectional	2012 - 2013	355	432	Hospitals referring specimens to a central laboratory	Hospitals referring specimens to a regional laboratory	Concurrent	Number and proportion of retreatment cases tested; event time when testing retreatment cases in reference laboratory
Loveday et al, 2012	South Africa	Prospective cohort	2008 - 2009	441	419	Treatment at a centralized specialist hospital followed by outpatient visits at the same facility	Treatment at district hospitals followed by outpatient follow-ups by healthcare workers	Concurrent	Proportion of patients who culture converted; time-to-conversion, treatment-initiation-delay, survival
Molla et al, 2017	Ethiopia	Interrupted time series	2012 - 2015	56	790	Hospital-based care	Ambulatory-based care	Consecutive	MDR-TB service accessibility (number of TICs established, number of MDR-TB patients enrolled to treatment); treatment outcomes (cured, completed, failed, lost to follow up, died)
				662	14,361	Diagnosis at centralized MDR-TB diagnostic centres (two culture centres, no GeneXpert centre)	Diagnosis at decentralized MDR-TB diagnrostic centres (5 culture and DST centres, 49 GeneXpert centres	Consecutive	MDR-TB service accessibility (number of samples tested)
Kasozi et al, 2020	Uganda	Interrupted time series	2013 - 2017	41	1311	Treatment at specialized facilities	Treatment initiated at specialized facilities followed by long periods of ambulatory care	Consecutive	Number of treatment initiation sites; number of patients enrolled to treatment; treatment outcomes (cured, completed, lost to follow up, died, failed)

Evans et al, 2018	South Africa	Retrospective cohort	2011 - 2014	594	713	Early/limited access to Xpert MTB/RIF (i.e 35% decentralization of Xpert MTB/RIF)	Expanded/full access to Xpert MTB/RIF (i.e >90% access to Xpert MTB/RIF)	Consecutive	Proportion of patients initiated on treatment; time to treatment initiation; treatment outcomes (cured, completed, failure, lost to follow up, death)
Mollel et al, 2019	Tanzania	Retrospective cohort	2009 - 2013	14	90	Diagnosis by Xpert MTB/RIF and treatment at a single specialized hospital	Diagnosis by Xpert MTB/RIF at 10 peripheral health facilities	Consecutive	Number of patients initiated to treatment; time to treatment initiation; treatment outcomes (cured, completed, lost to follow up, failure, death)
Ramma et al, 2015	South Africa	Cost analysis	2013	82	52	Hospital-based care	Ambulatory-based care	Concurrent	Patient costs
Alemayehu et al, 2020	Ethiopia	Cost-effectiveness analysis	NR	128	115	Hospital-based care	Ambulatory-based care	NR	Health system costs
Loveday et al, 2018	South Africa	Cost-effectiveness analysis	2008 - 2010	582	70	Treatment at a specialized central hospital	Treatment at community-based clinic or by mobile healthcare provider team	Concurrent	Health system costs; treatment outcomes (cured, completed, success, died, failed, defaulted, transferred out)
Bada et al, 2019	Nigeria	Cost analysis	2013 - 2014	NR		Hospital-based care	Community-based DOT by trained provider	Concurrent	Health system costs
Bada et al, 2020	Nigeria	Cost analysis	N/A	N/A		Hospitalization followed by outpatient visits for DOT	Ambulatory-mode of care through home-based DOT or clinic-based DOT	N/A	Health system costs

NR – Not reported N/A – Not applicable

3.3 Accessibility of MDR-TB services by patients

The following section describes results for the accessibility of MDR-TB services in terms of utilization and cost of the services. Results for the utilization of services are provided for both diagnostic and treatment services.

3.3.1 Utilization of MDR-TB diagnostic services

Three studies assessed the effect of decentralizing diagnostic services for MDR-TB (50,51,79). Two out of the three studies noted increases in the number of samples tested when diagnostic services were decentralized. In western Kenya, a cross-sectional study conducted by Sharma *et al* between 2012 and 2013, found that a higher number of patients (238) registered in hospitals referring to the regional laboratory underwent DST compared to those registered in hospitals referring to the central laboratory (88)(51) (Table 3.2).

Again, in two regions of Ethiopia, an increase in number of patients tested for MDR-TB was noted by Molla and colleagues between 2012 and 2015(50). At baseline, in 2012, only two centres that could perform culture for MDR-TB existed and no GeneXpert machines (machines used to diagnose TB and detect drug-resistance) were available(50). At the end of the program, 2015, five laboratories were equipped for liquid culture and DST and 49 GeneXpert centres existed(50). The effect of this achievement was an increase in the number of samples tested per year, from 662 in 2012 to 14,361 in 2015(50) (Table 3.2).

One study conducted in Tanzania by Mollel *et al*, 2019, reported an increase in the number of patients enrolled into care when diagnostic services (Xpert MTB/RIF machines) were decentralized(79). Prior to decentralization, patient enrollment into care relied on DST results from the Central Tuberculosis Reference Laboratory(79). Patient enrollment into MDR-TB care increased from 14 patients, prior to decentralization in 2009, to 90 patients in 2013 after 10 peripheral facilities were equipped with Xpert MTB/RIF technology(79) (Table 3.2).

3.3.2 Utilization of MDR-TB treatment services

Two studies examined the effect of decentralizing MDR-TB treatment services on the utilization of these services(50,78). Both studies reported an increase in patients enrolled into MDR-TB treatment. Under programmatic conditions in Uganda, Kasozi and colleagues reported the effect of expanding MDR-TB treatment initiating facilities and allowing

outpatient DOT(78). Before intervention, in 2012, treatment could be initiated at only three sites in the country. At the end of the intervention, in 2017, treatment could be initiated at 15 sites(78). This increased the number of patients enrolled into care from 41 at baseline (2012) to over 200 patients every year, amounting to a cumulative total of 1311 patients enrolled into care in 2017(78) (Table 3.2).

Also, between 2012 and 2015, Molla and colleagues observed an increase in patient enrollment in two regions of Ethiopia when treatment facilities were scaled-up(50). At baseline, in 2012, one MDR-TB treatment initiating facility was available, which enrolled 56 patients(50). At the end of the program in 2015, 23 treatment initiating facilities had been established(50). As a result, a cumulative total of 790 patients were enrolled to treatment at the end of the program with, 155, 254 and 325 patients enrolled in the years 2013, 2014 and 2015 respectively(50).

Table 3.2: Utilization of MDR-TB services in centralized and decentralized models

Study	Study design	Country	Utilization of services	
			Centralized (n)	Decentralized (n)
Utilization of diagnostic services (number of samples tested for MDR-TB)				
Sharma et al, 2015	Cross-sectional	Kenya	88	238
Molla et al, 2017	Interrupted time series	Ethiopia	662	14361
Utilization of treatment services (number of patients enrolled into MDR-TB care)				
Kasozi et al, 2020	Interrupted time series	Uganda	41	1311
Mollel et al, 2019	Retrospective cohort	Tanzania	14	90
Molla et al, 2017	Interrupted time series	Ethiopia	56	790

n = number of samples tested for MDR-TB or number of patients enrolled into MDR-TB care.

3.3.3 Cost of MDR-TB care

Costs related to decentralized services were found to be less than costs related to centralized services. Three studies from Ethiopia, Nigeria and South Africa reported costs for MDR-TB treatment when using hospital-based and ambulatory-based models(85,88,90). Treatment costs per patient treated was lower by 24.9%, 48.8% and 54.6% in the three countries, respectively, when ambulatory care was compared to hospital-based care (Table 3.3).

Two studies reported treatment costs using hospital-based and community-based approaches. These studies were conducted in KwaZulu-Natal, South Africa and in Nigeria by Loveday *et al* and Bada *et al*, respectively(86,89). In South Africa, 77.7% less cost was incurred when treatment was offered using community-based models compared to using centralized models(89). In Nigeria, the cost for treating a patient using a community-based approach was 49.1% lower than treating a patient using a centralized, hospital-based approach(86) (Table 3.3).

The study from Ethiopia also compared the cost-effectiveness between hospital-based and ambulatory-based models of care. Alemayehu and colleagues, 2020, reported that the average cost per DALY averted was $671 for an ambulatory treatment approach while for a hospital-based approach it was $1,417 per DALY averted(88).

Table 3.3: Costs for MDR-TB care in decentralized and centralized models

Study	Study design	Country	Centralized care		Decentralized care		Difference in cost per-patient (centralized vs decentralized care)*
			Description	Cost (US$/patient)	Description	Cost (US$/patient)	
Ramma et al, 2015	Cost analysis from a patient's perspective	South Africa	Hospital-based care	269.2	Ambulatory-based care	122.1	-54.6%
Alemayehu et al, 2020	Cost-effectiveness analysis from a	Ethiopia	Hospital-based care (HIV positive)	1922	Ambulatory-based care (HIV positive)	1443	-24.9%

	provider's perspective		Hospital-based care (HIV negative)	1798	Ambulatory-based care (HIV negative)	1391	-22.6%
Loveday et al, 2018	Cost-effectiveness analysis from a provider's perspective	South Africa	Treatment at a specialized central hospital	30185	Treatment at community-based clinic	6739	-77.7%
					Treatment at community-by mobile healthcare provider team	9394	-68.9%
Bada et al, 2019	Cost analysis from a provider's perspective	Nigeria	Hospital-based care	18528	Community-based DOT by trained provider	9424	-49.1%
Bada et al, 2020	Cost analysis from a provider's perspective	Nigeria	8month hospitalization followed by 12 months of outpatient care	14781	A fully ambulatory model for 20 months	7572	-48.8%
			4months hospitalization followed by 5 - 8 months of outpatient care	7705	A fully ambulatory model for 9 - 12 months	4334	-43.8%

∗ - Difference = (Cost in decentralized – Cost in centralized model) / Cost in centralized model

3.4 MDR-TB treatment outcomes

The prevalence estimates for each treatment outcome are shown separately for the centralized and decentralized models in Table 3.4.

Treatment success

Two of the included studies reported higher estimates of treatment success for the decentralized model of care compared to the centralized model of care. This is reported by Loveday and colleagues in prospective cohort studies conducted in KwaZulu-Natal, South Africa in 2015 and 2018(39,89). In these studies, treatment success for the centralized model were estimated to be 54% and 54.1%, respectively(39,89). Treatment success for the decentralized model were estimated to be 58% in 2015 and 64.3% in 2018(39,89).

Two studies, however, found reduced treatment success estimates with decentralized models compared to centralized models. A retrospective cohort study by Evans *et al*, 2018, found that 32.9% of those treated by a centralized model were successfully treated while 29.6% of those treated by a decentralized model were successfully treated(49). An interrupted time series conducted in Uganda reported that 78% of patients were successfully treated at baseline in 2012(78). During the decentralization program, the overall estimate of treatment success was reported to be 72.6% in 2015(78). However, the proportions from Uganda are from a population of 41 patients at baseline (2012) and 649 patients enrolled to treatment during decentralization (2013 – 2015)(78). In the three years of decentralization, the program consistently noted high success rates (73.9%, 2013; 74.1%, 2014; and 70.1%, 2015) even with increasing population sizes(78).

Lost to follow-up (LTFU)

Three studies reported reduced estimates of LTFU for decentralized treatment approaches compared to a centralized approach. All three studies were reported by Loveday *et al*, in 2012, 2015 and 2018(39,89,91). All three studies were cohort studies conducted in KwaZulu-Natal, South Africa(39,89,91). In two studies, the prevalence estimates of patients treated in decentralized facilities who were LTFU was nearly half of those treated in a centralized hospital and were lost to follow-up (14.5% vs 28.3%, 2015 and 12.9% vs 24.9%, 2018)(37,82). In the 2012 study, the percentage of patients treated in decentralized facilities and were lost to follow-up was 18.9% while those treated in a centralized hospital and were lost to follow-up was 30.2%(91).

Kasozi *et al* and Evans *et al*, reported similar estimates of LTFU in their studies. Kasozi *et al*, reported that 9.8% and 10.9% of patients were LTFU before decentralization and after three years of decentralizing MDR-TB services, respectively(78). Evans *et al*, reported that 55.3% of patients utilizing the centralized model were LTFU while 55.9% of patients under the decentralized model were LTFU(49).

Death

Two studies reported large discrepancies in death estimates between the two treatment models, with estimates being higher in the decentralized model. Loveday *et al*, in 2012, reported that 6.8% of patients under centralized care died while 16% of patients under decentralized care died(91). Kasozi *et al*, 2020, reported that 5% of patients receiving

treatment using the centralized model died while 15% of those receiving treatment using the decentralized model died(78).

While Loveday *et al* and Evans *et al* also reported higher death estimates among patients treated using a decentralized model, these differences were not shown to be statistically significant(39,49). According to Loveday *et al* in 2015, fourteen percent of patients using the centralized model died while eighteen percent of those using the decentralized model died(39). Also, twelve percent of patients receiving centralized care died while fourteen percent of those receiving decentralized care died, as reported in 2020 by Evans *et al*(49). Being HIV positive with MDR-TB and not on antiretroviral therapy (ART) was associated with these high estimates of deaths(39,49).

Treatment failure

Two studies reported similar treatment failure estimates for the two treatment models (centralized and decentralized). Evans *et al* and Kasozi *et al* reported no treatment failure before decentralization and 0.3% and 1.1% failure rates after decentralization, respectively(49,78).

Three studies reported increased treatment failure estimates for the decentralized model compared to centralized model. In one study, Loveday and colleagues, 2012, noted no patient (0.0%) failing treatment in the centralized group while 15 (3.6%) patients failed treatment in the deacentralized group(91). Also, in 2015, Loveday and colleagues noted that 3.6% of patients failed treatment in the centralized group while 6.7% of patients in the decentralized group failed treatment(39). Although, increased estimates of failing treatment were also reported in 2018 by Loveday *et al* (3.3% in centralized group vs 7.1% in decentralized group), the sample size of the two groups differed significantly (582 vs 70 respectively)(89).

Table 3.4: Prevalence estimates of treatment outcomes for patients treated with decentralized and centralized models

Study	Centralized care						Decentralized care					
	Total patients	Number of patients (%)					Total patients	Number of patients (%)				
		Treatment success	Lost to follow up	Death	Treatment failure	Others		Treatment success	Lost to follow up	Death	Treatment failure	Others
Loveday et al, 2015	813	439 (54)	230 (28.3)	113 (13.9)	29 (3.6)	2 (0.2)[a]	736	427 (58.0)	107 (14.5)	133 (18.1)	49 (6.7)	20 (2.7)[a]
Loveday et al, 2012	441	ONA	133 (30.2)	30 (6.8)	0 (0.0)	278 (63.0)[b]	419	ONA	79 (18.9)	67 (16)	15 (3.6)	258 (61.6)[b]
Kasozi et al, 2020*	41	32 (78.0)	4 (9.8)	2 (4.9)	0 (0.0)	3 (7.3)[c]	649	471 (72.6)	71 (10.9)	100 (15.4)	7 (1.1)	0 (0.0)[c]
Evans et al, 2018	161	53 (32.9)	89 (55.3)	19 (11.8)	0 (0.0)		365	108 (29.6)	204 (55.9)	52 (14.2)	1 (0.3)	
Loveday et al, 2018	582	315 (54.1)	145 (24.9)	101 (17.4)	19 (3.3)	2 (0.3)[a]	70	45 (64.3)	9 (12.9)	8 (11.4)	5 (7.1)	3 (4.3)[a]

*Outcomes up until 2015 only, study ended in 2017 ONA - Outcome Not Assessed [a] – Transferred out [b] – Still on treatment [c] – Not evaluated

4 CHAPTER FOUR: DISCUSSION

4.1 Introduction

This chapter provides an overview of findings and discusses the results of the systematic review. The results are discussed under the themes: accessibility to MDR-TB services, cost of MDR-TB services and MDR-TB treatment outcomes. Lastly, the chapter states the study strengths and limitations, conclusion and recommendation of the study.

4.2 Overview of findings

The current review aimed to examine the effect, across studies, of decentralizing MDR-TB services on the accessibility of services and patient treatment outcomes in sub-Saharan Africa. Findings from this study have shown that decentralization of MDR-TB care in SSA has improved accessibility of patients to the services through increase in utilization of MDR-TB services and reduction of MDR-TB treatment cost. Increased successful treatment and retention to care have also been shown to be outcomes of decentralizing MDR-TB services within sub-Saharan Africa.

4.3 Accessibility (utilization and cost) of MDR-TB services by patients

4.3.1 Utilization of diagnostic and treatment services

This systematic review has demonstrated that decentralizing MDR-TB services has increased the utilization of MDR-TB services in sub-Saharan Africa. The included studies reported higher numbers of patients accessing and utilizing decentralized MDR-TB diagnostic and treatment services compared to accessing and utilizing centralized services. Similar findings are reported by studies conducted in other low- and middle-income countries (LMICs) such as Peru, Bangladesh and Myanmar. In Peru, the demand for DST doubled after diagnostic services were decentralized(52). In Bangladesh and Myanmar, significant expansions in the volume of patients enrolled into care after decentralization were noted(37,92). Daru *et al* observed, in Bangladesh, a rise from 77% to 100% of patients being enrolled into MDR-TB care after decentralization of MDR-TB services(37). A doubling of the number of patients treated for MDR-TB was observed after decentralization of MDR-TB services in Myanmar(92). Thus, in resource limited settings such as those in sub-Saharan African countries, decentralized models of care are vital to ensure service accessibility by MDR-TB patients.

4.3.2 Cost of MDR-TB treatment

All cost studies included in this review suggested that MDR-TB care using decentralized approaches is less costly than using centralized approaches. Alemayehu *et al*, 2020, the only study which reported cost-effectiveness using economic models, also suggested that decentralized care is more cost-effective than centralized care(88). These findings are consistent with findings from a systematic review conducted by Fitzpatrick C. and Floyd K who compared costs between decentralized and centralized approaches. The findings in their study indicated that decentralized (outpatient) treatment models are more affordable and cost-effective than centralized (inpatient) treatment models(55). Likewise, a systematic review by Ho *et al*, which compared treatment outcomes and costs between the two approaches reported lower costs associated with decentralized treatment approaches(5). Therefore, findings from the current review imply that decentralization of MDR-TB services can be operationalized at affordable costs in the sub-Saharan setting.

4.4 MDR-TB treatment outcomes

Treatment success

Success rates in some studies were found to be higher for decentralized model of care than for the centralized model(39,89). These results were similar to results from previous studies reporting treatment outcomes for decentralized models(58,60). While these studies received support from external organizations (eg international donors), studies included in this review reported no external support for the decentralization program(39,58,60). This implies that decentralization of MDR-TB services can successfully be implemented in resource limited settings such as those of sub-Sahara African nations.

While Kasozi *et al* reported, in their interrupted time series, a reduction in treatment success estimates during a decentralization program, the program was able to maintain high levels of treatment success amidst the large expansion in patient volumes(78). This suggests that governments within sub-Saharan Africa can maintain high treatment success rates even with increase in patient numbers. This can be achieved by means of implementing continuous quality improvement strategies such as peer-to-peer mentorships and holding learning sessions as applied in Uganda(78).

Lost to follow up

Decentralized MDR-TB care was related to lower estimates of loss to follow up in most studies conducted in South Africa(39,89,91). Contrastingly, a study in Uganda reported that estimates of loss to follow up between centralized and decentralized models of care were similar(78). This difference could be attributed to low capacity and lack of experience in MDR-TB management of selected sites during decentralization in Uganda(78). Similar estimates of lost to follow up between the two treatment approaches were also reported by Evans *et al* in South Africa(49). In agreement with these findings are systematic reviews and meta-analyses conducted by Bassili *et al* and Ho *et al*, who both compared MDR-TB treatment outcomes between decentralized and centralized models of care. In their studies, Bassili *et al* and Ho *et al* found no statistical difference in loss to follow up estimates between decentralized and centralized treatment models(5,61). In sub-Saharan Africa, therefore, decentralization of MDR-TB has potential to reduce estimates of loss to follow-up when treatment sites are adequately capacitated.

Death

While some studies in this review reported higher estimates of death among patients in decentralized sites than in centralized sites(78,91), only one study, however, reported statistically significant differences(91). The difference noted in this study is reported to have been probably due to missing data in the registers from which data was extracted at centralized sites(91). This may have led to the underestimation of death estimates at the centralized site. Another study, by Kasozi *et al*, 2020, showed estimates of death to be three times higher in decentralized than centralized models of care(78). However, a large difference exists between the sample sizes of the two arms (centralized arm; 41 patients vs decentralized arm; 649 patients), from which the estimates were calculated(78).

Other studies found no significant differences in the death estimates between decentralized and centralized models of care(39,49). These findings are in agreement with systematic reviews conducted by Ho *et al* and Bassili *et al* who also found no significant differences in the death estimates between decentralized and centralized models of care(5,61).

Treatment failure

The estimates of MDR-TB treatment failure for decentralized and centralized care was found to be similar in some studies included in this review(49,78). These findings are consistent with findings from a cohort and a systematic review conducted by Sam *et al* and Ho *et al,* respectively, comparing treatment outcomes between decentralized and centralized care(5,93). However, other studies included in this review reported higher estimates of treatment failure in decentralized settings than in centralized settings(39,89,91). These results were contrary to results from other studies such as one conducted in Bangladesh by Daru *et al* and a systematic review conducted by Williams *et al*, which reported lower estimates of treatment failure in decentralized settings than in centralized settings(37,38).

4.5 Study strengths and limitations

The strengths of this review include, a comprehensive literature search from scientific databases and using strict eligibility criteria to limit the review to studies with patients receiving a decentralized and centralized care. This allowed studies to be selected without bias and comparisons to be made from same population groups in similar settings.

This review also had several limitations. Literature search was limited to studies that were published in the English language alone. This prevented acquiring studies published in French, Portuguese and Arabic which are official languages used by several SSA countries. Therefore, findings from these countries were not examined. Grey literature and organizational reports were not included in the review as it focused only on literature published in scientific journals. This limited the analysis of evidence from reports documented by governments and NGOs dealing with management of TB within the region. Despite searching for literature using country names of sub-Saharan Africa, numerous countries within the region had no studies published on the subject. This led to evidence of the effect of decentralization of MDR-TB services be gathered from some regions within sub-Saharan Africa. While none of the included studies received a weak rating on the EPHPP tool, most studies were of moderate quality because they were observational studies. This limits the generalizability of findings from this systematic review and underpins the importance of further research on the effects of decentralization of MDR-TB care in various settings.

4.6 Conclusion

In conclusion, studies have suggested that decentralization of MDR-TB services in sub-Saharan Africa has increased access to MDR-TB services. There is an increase in the number of patients tested and diagnosed with MDR-TB in the region due to decentralization programs. Also, the number of MDR-TB patients enrolled into treatment has increased because of decentralization. Managing MDR-TB using decentralized models is also suggested to be less costly and more cost-effective than using centralized models. This is pertinent to sub-Saharan Africa due to resource-constraints in many countries in the region.

Included studies have also suggested that, through decentralization of MDR-TB services, countries in SSA can achieve and maintain high treatment success rates. The studies have also suggested that more patients can be retained in care when decentralized models are used. MDR-TB treatment failure, on the other hand, was found to be higher in most studies in this review, a finding which warrants further studies.

4.7 Recommendations

Based on findings from this study, countries in sub-Saharan Africa should manage MDR-TB using more decentralized models than centralized models. Decentralized facilities should be well capacitated to ensure quality care is provided to MDR-TB patients. Efficient data recording systems should also be established at decentralized facilities as well as centralized facilities. This will enable effective monitoring and evaluation of various components of MDR-TB management such as patient treatment outcomes.

Furthermore, a meta-analysis should be conducted to estimate the pooled estimates of treatment outcomes for the two treatment approaches in sub-Saharan Africa. Studies examining the effect of decentralization of MDR-TB care on other dimensions of accessibility, such as acceptability, are also recommended.

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6 APPENDICES

Appendix A: Plagiarism Declaration – University of the Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Meck P. Nyanda (Student number: 2372092) am a student registered for the degree of MSc Epidemiology (Implementation Science) in the academic year 2021.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: June 29, 2021

Appendix B: Quality Assessment Tool For Quantitative Studies (EPHPP Tool)

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES



COMPONENT RATINGS

A. SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

1 Very likely
2 Somewhat likely
3 Not likely
4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

1 80 - 100% agreement
2 60 – 79% agreement
3 less than 60% agreement
4 Not applicable
5 Can't tell

RATE THIS SECTION	WEAK	MODERATE	STRONG
See dictionary	1	2	3

B. STUDY DESIGN

Indicate the study design

1 Randomized controlled trial
2 Controlled clinical trial
3 Cohort analytic (two group pre + post)
4 Case-control
5 Cohort (one group pre + post (before and after))
6 Interrupted time series
7 Other specify _____
8 Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)
No Yes

RATE THIS SECTION	WEAK	MODERATE	STRONG
See dictionary	1	2	3

C. CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?

1 Yes
2 No
3 Can't tell

The following are examples of confounders:

1 Race
2 Sex
3 Marital status/family
4 Age
5 SES (income or class)
6 Education
7 Health status
8 Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g.stratification, matching) or analysis)?

1 80 - 100% (most)

2 60 - 79% (some)

3 Less than 60% (few or none)
4 Can't Tell

RATE THIS SECTION	WEAK	MODERATE	STRONG
See dictionary	1	2	3

D. DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?

1 Yes
2 No
3 Can't tell

(Q2) Were data collection tools shown to be reliable?

1 Yes
2 No
3 Can't tell

RATE THIS SECTION	WEAK	MODERATE	STRONG
See dictionary	1	2	3

E. WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1 Yes
2 No
3 Can't tell
4 Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record thelowest).

1 80 -100%
2 60 - 79%
3 less than 60%
4 Can't tell
5 Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	WEAK	MODERATE	STRONG	
See dictionary	1	2	3	Not Applicable

F. INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

1 80 -100%
2 60 - 79%
3 less than 60%
4 Can't tell

(Q2) Was the consistency of the intervention measured?

1 Yes
2 No
3 Can't tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that mayinfluence the results?

4 Yes
5 No
6 Can't tell

G. ANALYSES

(Q1) Indicate the unit of allocation (circle one)

community organization/institution practice/office individual

(Q2) Indicate the unit of analysis (circle one)

community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?

1 Yes
2 No
3 Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actualintervention received?

1 Yes
2 No
3 Can't tell

GLOBAL RATING

COMPONENT RATINGS
Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	**SELECTION BIAS**	**WEAK**	**MODERATE**	**STRONG**	
		1	2	3	
B	**STUDY DESIGN**	**WEAK**	**MODERATE**	**STRONG**	
		1	2	3	
C	**CONFOUNDERS**	**WEAK**	**MODERATE**	**STRONG**	
		1	2	3	
D	**DATA COLLECTION METHOD**	**WEAK**	**MODERATE**	**STRONG**	
		1	2	3	
E	**WITHDRAWALS AND DROPOUTS**	**WEAK**	**MODERATE**	**STRONG**	
		1	2	3	Not Applicable

GLOBAL RATING FOR THIS PAPER (circle one):

1	STRONG	(no WEAK ratings)
2	MODERATE	(one WEAK rating)
3	WEAK	(two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-E) ratings?

No Yes

If yes, indicate the reason for the discrepancy

1	Oversight
2	Differences in interpretation of criteria
3	Differences in interpretation of study

Final decision of both reviewers (circle one):

1	**STRONG**
2	**MODERATE**
3	**WEAK**

Appendix C: CHEERS Checklist

CHEERS checklist—Items to include when reporting economic evaluations of health interventions.

Section / Item	Item no.	Recommendation	Reported on page no./line no.
Title and abstract			
Title	1	Identify the study as an economic evaluation, or use more specific terms such as ‘‘cost-effectiveness analysis’’ and describe the interventions compared.	_____
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions.	_____
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	_____
Methods			
Target population and subgroups	4	Describe characteristics of the base-case population and subgroups analysed including why they were chosen.	_____
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	_____
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	_____
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	_____

Section / Item	Item no.	Recommendation	Reported on page no./line no.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	_____
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	_____
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	_____
Measurement of effectiveness	11a	*Single study–based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	_____
	11b	*Synthesis-based estimates:* Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.	_____
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	_____
Estimating resources and costs	13a	*Single study–based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	_____
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	_____

Section / Item	Item no.	Recommendation	Reported on page no./line no.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	_____
Choice of model	15	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.	_____
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytic model.	_____
Analytic methods	17	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g., half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	_____
Results			
Study parameters	18	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	_____
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	_____
Characterizing uncertainty	20a	*Single study–based economic evaluation:* Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective).	_____

Section / Item	Item no.	Recommendation	Reported on page no./line no.
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	_____
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	_____
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	_____
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.	_____
Conflicts of interest	24	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations.	_____

Note. For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist.

Appendix D: Ethics Waiver Certificate – University of the Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

19/02/2021

Ref: W-CBP-210219-01

TO WHOM IT MAY CONCERN

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)

Investigator: Dr M Nyanda
Student No. (if appropriate): 2372092
Staff No. (if appropriate):

Supervisor: Dr S Mall

School: Public Health
Department: Epidemiology and Biostatistics
Medical School
University

Project title: *The effect of decentralised services on multidrug-resistant tuberculosis care in Sub-Saharan Africa: a systematic review*

Reason: Review of information in the public domain
No human participants will be involved in the study

CB Penny

Dr CB Penny
Chairperson: Human Research Ethics Committee (Medical)

Research Office Secretariat:
Third Floor, Phillip Tobias Building, corner of St Andrews and York Roads, Parktown, Johannesburg 2193
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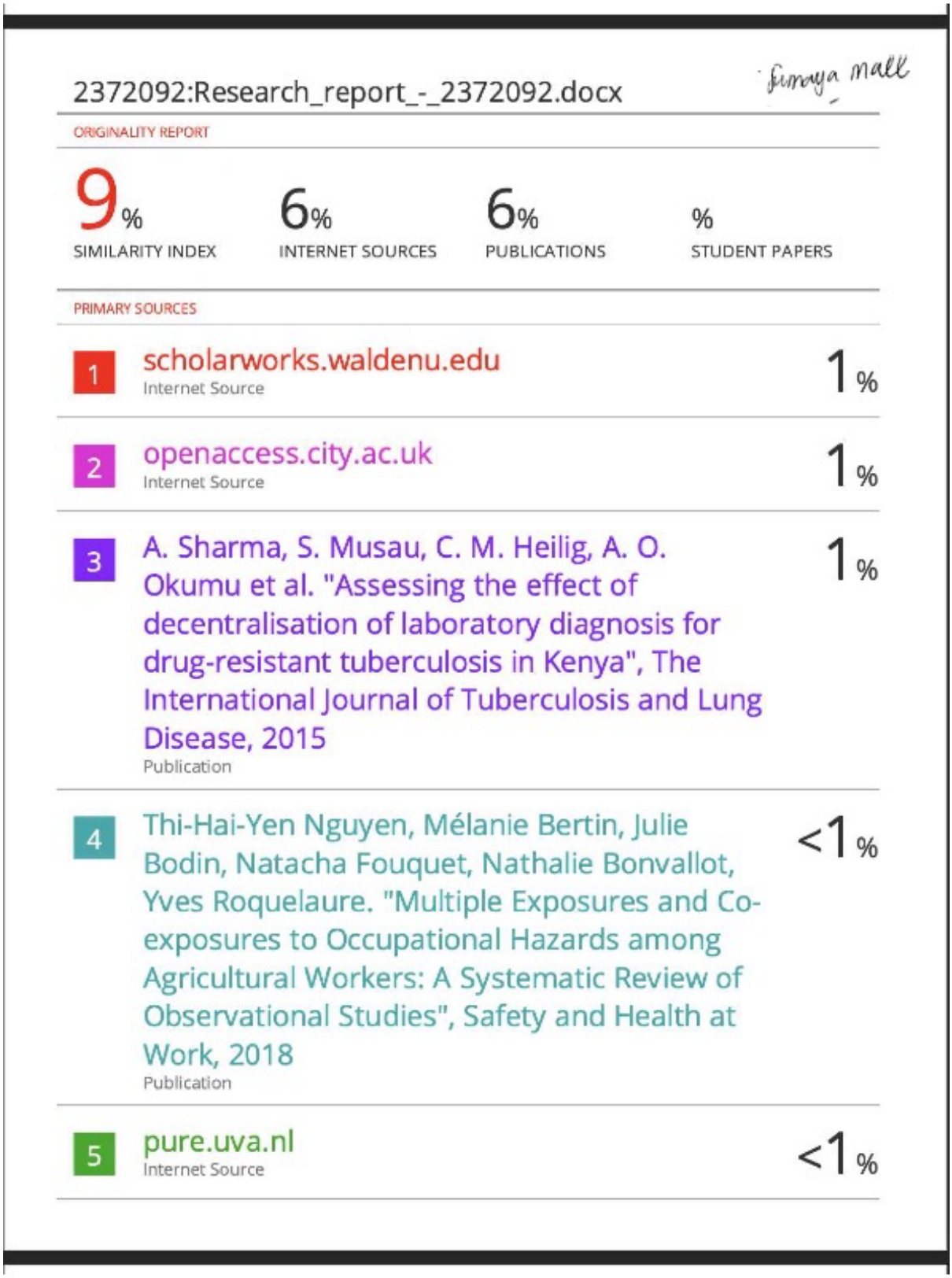
Tel Nos: +27 (0)11 717 1234/1252/2656/2700
Office E-mail: HREC-Medical.ResearchOffice@wits.ac.za
Website:
https://www.wits.ac.za/research/researcher-support/research-ethics/ethics-committees/

Appendix E: Turnitin report



2372092:Research_report_-_2372092.docx

Sunaya Mall

ORIGINALITY REPORT

9%	6%	6%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	scholarworks.waldenu.edu Internet Source	1%
2	openaccess.city.ac.uk Internet Source	1%
3	A. Sharma, S. Musau, C. M. Heilig, A. O. Okumu et al. "Assessing the effect of decentralisation of laboratory diagnosis for drug-resistant tuberculosis in Kenya", The International Journal of Tuberculosis and Lung Disease, 2015 Publication	1%
4	Thi-Hai-Yen Nguyen, Mélanie Bertin, Julie Bodin, Natacha Fouquet, Nathalie Bonvallot, Yves Roquelaure. "Multiple Exposures and Co-exposures to Occupational Hazards among Agricultural Workers: A Systematic Review of Observational Studies", Safety and Health at Work, 2018 Publication	<1%
5	pure.uva.nl Internet Source	<1%

Appendix F: Search Strings for Databases

PubMed

"mdr-tb AND decentralization", "mdr-tb AND community-based", "mdr-tb AND ambulatory", "mdr-tb AND sub-Saharan Africa", "(mdr-tb AND decentralization) AND *sub-Saharan country name*", "(mdr-tb AND community-based) AND *sub-Saharan country name*", "(mdr-tb AND ambulatory) AND *sub-Saharan country name*"

Global Health

"mdr-tb AND decentralization", "mdr-tb AND community-based", "mdr-tb AND ambulatory", "mdr-tb AND sub-Saharan Africa", "(mdr-tb AND decentralization) AND *sub-Saharan country name*", "(mdr-tb AND community-based) AND *sub-Saharan country name*", "(mdr-tb AND ambulatory) AND *sub-Saharan country name*"

Scopus

"mdr-tb AND decentralization", "mdr-tb AND community-based", "mdr-tb AND ambulatory", "mdr-tb AND sub-Saharan Africa", "(mdr-tb AND decentralization) AND *sub-Saharan country name*", "(mdr-tb AND community-based) AND *sub-Saharan country name*", "(mdr-tb AND ambulatory) AND *sub-Saharan country name*"

The Cochrane Library

"mdr-tb AND decentralization", "mdr-tb AND community-based", "mdr-tb AND ambulatory", "mdr-tb AND sub-Saharan Africa", "(mdr-tb AND decentralization) AND *sub-Saharan country name*", "(mdr-tb AND community-based) AND *sub-Saharan country name*", "(mdr-tb AND ambulatory) AND *sub-Saharan country name*"

Global Index Medicus (WHO)

"mdr-tb AND decentralization", "mdr-tb AND community-based", "mdr-tb AND ambulatory", "mdr-tb AND sub-Saharan Africa", "(mdr-tb AND decentralization) AND *sub-Saharan country name*", "(mdr-tb AND community-based) AND *sub-Saharan country name*", "(mdr-tb AND ambulatory) AND *sub-Saharan country name*"