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Initial loss to follow up among tuberculosis patients: the role of Ward-Based Outreach Teams and short message service (SMS) technology

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INITIAL LOSS TO FOLLOW UP AMONG TUBERCULOSIS PATIENTS: THE ROLE OF WARD-BASED OUTREACH TEAMS (WBOTs) AND SHORT MESSAGE SERVICE (SMS) TECHNOLOGY

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, in fulfilment of the requirement for the degree of Doctor of Philosophy

Johannesburg, 2023

Candidate declaration

I declare that this thesis is my own work and has not been submitted before for any degree or examination at any other university.

All materials adopted from previously published work have been appropriately cited in this thesis.

This thesis is submitted in the optional format, approved by the faculty, of published work with a supporting introduction, as a literature review, and discussion.



March 2023

_____ _____

Judith Reegan Mulubwa Mwansa-Kambafwile **Date**

Dedication

This work is dedicated to the loving memory of my mother, Angela Jean Mercy Chabu. May your gentle soul continue to rest in peace.

Abstract

Introduction: In South Africa, tuberculosis (TB) is still a serious public health problem with rates of initial loss to follow up (initial LTFU) varying between 14.9% and 22.5%. Poor clinician-patient communication resulting in lack of clarity on next steps, patients not prioritizing their healthcare and patients not knowing that their results are ready at the clinic are some reasons for initial LTFU. This PhD aimed to assess the effectiveness of Ward-based Outreach Teams (WBOTs) or Short Message Service (SMS) technology in reducing TB initial LTFU in Johannesburg, South Africa between 2018 and 2020.

Methods: A mixed methods approach comprising two phases (formative and intervention) was employed. In the formative phase, secondary data were analyzed for frequency distributions to determine the rates of initial LTFU in the study area. In addition, in-depth interviews with WBOT Managers and with TB Program Managers were conducted to determine their perceived reasons for TB initial LTFU. In the intervention phase, two interventions (WBOTs/SMS technology) were tested using a 3 arm randomized controlled trial (RCT) comparing each of the interventions to standard of care (SOC). The WBOTs delivered paper slip reminders while SMS intervention entailed sending reminder SMS messages to patients as soon as TB results were available. Chi square statistics, Poisson regression and Kaplan-Meier estimates were used to analyze the data. The RCT was followed by in-depth interviews with WBOT members and with some of the trial participants who had tested TB positive and had received reminder messages. To identify themes in the qualitative studies, both inductive and deductive coding were used in the hybrid analytic approach.

Results: From the formative phase, the TB initial LTFU among the 271 patients was found to be 22.5% and the overall time to treatment initiation was 9 days. Interviews with managers revealed that relocation and “shopping around” were the main patient related factors found as the reasons for initial LTFU. Health system related factors for initial LTFU were

communication and staff rotations. In terms of TB related work, WBOTs screened household members for TB and referred them for TB testing. The services of the WBOT/TB programs which were found to be integrated were: referral of symptomatic patients for TB testing and adherence monitoring in patients already on TB treatment. There was minimal involvement of the WBOTs in the treatment initiation of patients diagnosed with TB. Findings from the trial were that 11% (314/2850) of the participants tested positive for TB. The 314 TB patients were assigned to one of the 3 arms (SOC=104, WBOTs=105, and SMS=105). Overall, 255 patients (81.2%) were initiated treatment across all study arms. More patients in the SMS arm were initiated TB treatment than in the SOC arm (92/105; 88% and 81/104; 78% respectively; P=0.062). Patients in the SMS arm also had a shorter time to treatment initiation than those in the SOC arm (4 days versus 8 days; P<0.001). A comparison of the WBOTs arm and the SOC arm showed similar proportions initiated on treatment (45/62; 73% and 44/61; 72% respectively) as well as similar times to treatment initiation. Findings from the post-trial interviews showed that delivery of the reminder paper slips by the WBOTs during the trial was something new, but possible to incorporate into their daily schedule. The patient interviews revealed that various emotions (happiness, fear, worry etc.) were experienced upon receipt of the reminder messages. Participants also reported that receiving the reminder message did influence their decision to go back to collect the results.

Conclusion: Reminder messages to patients are beneficial in TB treatment initiation. National TB programs can use SMS messaging because it is an affordable and feasible method. Although implementation of the WBOTs intervention was suboptimal, findings show that with proper integration of TB and WBOT programs, WBOTs have the potential to contribute to improved treatment initiation.

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List of Outputs

Manuscript Publications:

1. **Mwansa-Kambafwile J,** Maitshotlo B, Black A. Microbiologically Confirmed Tuberculosis: Factors Associated with Pre-Treatment Loss to Follow-Up, and Time to Treatment Initiation. PLoS One. 2017 Jan 9;12(1):e0168659.
2. **Mwansa-Kambafwile JRM,** Chasela C, Ismail N, Menezes C. Initial loss to follow up among tuberculosis patients: The role of Ward-Based Outreach Teams and short message service (SMS) technology (research proposal). BMC Res Notes. 2019;12(1).
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List of Abbreviations

AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
CARTA	Consortium for Advanced Research Training in Africa
CHVs	Community Health Volunteers
CHW	Community Healthcare Workers
CI	Confidence Interval
COJ	City of Johannesburg
DOI	Diffusion of Innovations
DOTS	Directly Observed Therapy Short-Course
DRC	District Research Committee
DTDs	Demonstration and Training Districts
EHP	Environmental Health Officer
FGD	Focus Group Discussion
GDP	Gross Domestic Product
HAST	HIV, AIDS and STIs
HBM	Health Belief Model
HCW	Healthcare Workers
HIV	Human Immunodeficiency Virus
HP	Health Promoter
IDIs	In depth interviews
LTFU	Loss to Follow Up
NDOH	National Department of Health
NHRD	National Health Research Database
NTCP	National Tuberculosis Control Program
OR	Odds Ratio
PHC	Primary Healthcare

PMTCT	Prevention of Mother to Child Transmission
RCT	Randomized Controlled Trial
SEM	Social Ecological Model
SMS	Short Message Service
SOC	Standard of Care
STIs	Sexually Transmitted Infections
TB	Tuberculosis
WBOTs	Ward-Based Outreach Teams
WHO	World Health Organization
WITS	University of the Witwatersrand
Xpert	Xpert Mtb/Rif

Preface

This doctoral thesis is presented in a block format and organized into 8 chapters:

Chapter 1 outlines the background information regarding tuberculosis initial loss to follow up (TB initial LTFU), the research gap, and the justification for conducting the study. This chapter also explores and elaborates on the existing literature on TB initial LTFU. It discusses the magnitude and reasons for TB patients not initiating treatment. Also discussed in this chapter are concepts and theories underpinning the understanding of the study topic the conceptual framework which was used as a guide for the study is presented. Theories around provider-patient communication, patients' understanding/knowledge of their disease, and social/environmental factors' impact on patient behavior are discussed. Interventions to improve linkage to care in the TB program and programs other than TB are highlighted. The chapter further details literature on SMS technology and WBOTs in healthcare service delivery with a focus on the TB program. **Chapter 2** explains the different methodological approaches which were used to obtain the data. The analysis of the data collected are highlighted.**Chapters 3 to 6** are the results of the research answering each specific objective and presented as journal manuscripts. Chapters 3, 4 and 5 are published manuscripts and each of them follows the format of the respective journal which is published with the presentation of background, methods, findings, and discussion/conclusion of the findings. My PhD supervisors were co-authors and the contribution of all co-authors is acknowledged at the end of each manuscript. Chapter 3 gives the rate of initial LTFU in the study area while in Chapter 4, the results of the interviews with the TB program managers and the WBOT managers regarding TB initial LTFU are presented. The results of the RCT (SMS/WBOTs) are presented in Chapter 5. The results of the post trial interviews with WBOT members and with trial participants are presented in Chapter 6. The manuscript is yet to be submitted to a journal for publication. **Chapter 7**

discusses the results of the PhD work in relation to existing literature. It also speaks to the challenges and limitations of the PhD work and gives a conclusion based on results and discussion. Recommendations for the TB program and policy implications based on findings from this study as well as the overall conclusion of the PhD thesis are also presented in this chapter. **Chapter 8** comprises the appendices of the thesis.

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Introduction

1.1. Background

Tuberculosis (TB) remains a serious public health problem in South Africa. While it is preventable, there were approximately 1.4 million deaths globally and 10 million people who had TB in 2019. The TB incidence and the HIV co-infection rates among incident cases in South Africa are currently 615/100000 population and 58% respectively (1). In spite of a decline in TB mortality, it was the country's number one leading cause of death between 2015 and 2017 (2). TB is preventable and curable. It is important that TB patients take their treatment to ensure they are cured and it prevents them from spreading the disease. Patients with positive TB results who do not start treatment are known as initial loss to follow up (LTFU) patients (3).

In South Africa, initial LTFU rates in TB patients have been found to range between 14.9% and 17.9% (4,5) but can reach 22.5% in densely populated economic hubs like the inner-city Johannesburg (6). South African estimates derived from the electronic TB register data, the TB laboratory data, and some studies revealed that patients are lost from the TB care pathway at various stages of the care cascade (test access, diagnosis, treatment initiation, and successful treatment completion), with 12% being lost at treatment initiation (7). These rates are much higher than the South African National TB Control Program (NTCP) target of "less than 5%" (3). Delaying initiation of treatment or the lack of treatment altogether in patients with bacteriologically confirmed TB contributes to ongoing TB transmission in communities and poor patient outcomes. In addition, delays in starting TB treatment in TB/HIV co-infected patients impact negatively on their HIV status as TB is an opportunistic infection which can further deteriorate one's immunity. Timely treatment initiation reduces infectivity of TB in patients on treatment (8–10).

The South African national targets for TB treatment success rate and TB initial LTFU rate are "more than 90%" and "less than 5%" respectively (3). According to the national TB guidelines, the former is the proportion of new positive TB patients cured plus the number who completed treatment but not meeting the definition of "cure" or "failure". The denominator for this is the total number of new positive pulmonary TB patients registered (3). However, the number of patients started on treatment is only a proportion of those eligible. (11,12). Therefore, the

success rate may be overestimated due to the assumption that the initial LTFU rate is negligible and therefore not factored in.

There are various reasons for patients missing clinic or hospital appointments for treatment initiation or follow up visits. Being unaware or unsure of appointment dates were found as some of the reasons for patients not turning up for appointments in a South African study conducted in a regional hospital (13). Other studies on TB conducted in India and Pakistan also showed this finding, suggesting poor provider-patient communication on subsequent steps after testing (14–16). Sometimes patients may lack motivation for a subsequent visit or may have other competing priorities and therefore fail to return to the clinic or hospital (15,17).

It is important to ensure that patients testing for TB receive their results so that treatment can be initiated if needed. Over the past decade, the use of mobile cellular phones has been on the increase globally and in 2015 there were over 7 billion mobile cellular subscriptions (18). Short message service (SMS) reminders to patients has helped patients adhere to various chronic medications such as HIV/AIDS, hypertension, and diabetes (19–22). It has also shown an increased chance of adherence to antiretroviral therapy among HIV-infected individuals (OR:1.55; 95% CI: 1.01–2.39) (23). SMS technology is acceptable among patients who use it (24,25). In a study conducted in South Africa, more patients were returning for results after testing for TB in the group that received SMS notification that results were ready than in the group that did not receive any notification (64.2% versus 51.5%; p value=0.03) (26).

Brazil has benefitted from the model of taking healthcare services to the communities through the use of Community Healthcare Workers (CHWs). There has been a decline in infant mortality (27) and the model has also resulted in improved access to healthcare (28). In South Africa, Ward-Based Outreach Teams (WBOTs) are a cadre of healthcare staff that are part of the re-engineered primary healthcare (PHC) model. They offer services at household and community levels in catchment areas of respective PHC facilities. Each team is led by a Professional Nurse and comprises 6 CHWs, a Health Promoter (HP), and an Environmental Health Officer (EHP). For TB services, the teams identify, support and follow up already diagnosed TB patients and their contacts with a minor or no role in treatment initiation (29).

Adherence support to TB treatment in patients already initiated on treatment is covered in the scope of work of the WBOTs. However, following up of patients diagnosed with TB but not

initiated on treatment is not in their scope of work. Initiating treatment in TB patients is important for TB control because they become less infectious and as such transmission is reduced (9,30). Not initiating treatment leads to poor outcomes for the patients and to continuous spread among community members.

There is need to have strategies in place which ensure that TB patients initiate treatment in order to reduce community transmissions. Healthcare services can be delivered at the family and community levels using WBOTs. There is evidence that community level healthcare reduces infant mortality rate (27). WBOTs also monitor treatment adherence to chronic medication such as TB and HIV treatment (25). However, their scope of work does not include TB treatment initiation although it is a potential way initial LTFU among TB patients can be reduced. Various programs have benefitted from the use of SMS technology (31). Therefore, sending SMS messages to newly diagnosed TB patients is another way of reducing TB initial LTFU.

Health system structural barriers cause long pathways to diagnosis and this consequently causes initial LTFU (32). Using SMS or paper slip reminder messages to TB patients and asking them to go to the clinic to collect their test result could increase the number of patients initiated on treatment and potentially reduce TB initial LTFU.

1.2. Literature Review

To achieve the WHO End TB Strategy by 2035, monitoring of the TB patient care cascade is very important, particularly treatment initiation among those diagnosed with TB. Initial LTFU is an important measure of success for a TB program as it will give insight into the possible proportion of transmission risk in the communities.

Between 1997 and 2013, the South African NTCP achieved high treatment success rates and several milestones ranging from “Phased implementation of Directly Observed Therapy Short-Course (DOTS), the establishment of demonstration and training districts (DTDs)” to “Guidelines for managing TB/HIV in prisons” (33). Despite this achievement and although there is room for improvement with regards to the current 58% TB treatment coverage rate in South Africa (1), there is a greater need to have all newly diagnosed TB patients initiated on treatment within the shortest possible time. It is recommended that treatment gets initiated

within 2-5 days of diagnosis (34). However, not all that are eligible for treatment actually initiate treatment (11,12).

1.3. Research Gap

NTCPs in many countries have focused on TB patients already on treatment i.e. ensuring that they take their treatment. The implementation of Directly Observed Therapy Short-Course (DOTS) is evidence for this (35). In South Africa, the scope of work for the WBOTs in the re-engineered PHC model includes adherence support to TB patients on treatment (29). However, the scope does not cover work related to ensuring that the patients who test positive for TB get initiated on treatment.

It is important to follow up on untreated TB patients because they are highly infectious. The NTCP in South Africa uses the number of TB patients started on treatment as the denominator to measure the success of the program. Patients diagnosed with TB but not started on treatment are not considered. These patients continue to transmit infection and therefore contribute to the burden of TB in communities. Treatment initiation is a way of controlling TB infection because patients are no longer a source of the infection by about 2 weeks of starting treatment (9,36,37). Therefore, active TB case finding and treatment initiation can help reduce the TB burden (38). Various interventions including telephone prompts and assistance by lay health workers to improve TB treatment adherence are beneficial (39). However, there is a paucity of data on interventions to ensure that all patients diagnosed with TB initiate treatment. In HIV programs, interventions tailored towards supporting the self-management of patients have been shown to improve linkage to care (40).

1.4. Magnitude of the Problem

Evidence shows that not every patient diagnosed with TB is started on treatment (11,41,42). The proportion of initial LTFU has been reported to vary between 4% and 38% in TB patients with values of 13% and 18% for Asian and African studies respectively (12). Initial LTFU rates in South Africa range between 14.9% and 18% (4,5). Although the latter is similar to the rate previously found in African studies (12), higher rates of 22.5% and 25% have been found in urban city areas with dense populations and in some rural locations of the country respectively

(6,43). These rates reported above are much higher than the national target of "less than 5%" for the South African NTCP (3).

1.5. Reasons for "No-Return"

Generally, there are different reasons why patients with different conditions do not honor their respective appointments at healthcare facilities. The patient-related factors for the non-attendance are several. A study conducted at a Massachusetts community healthcare center serving a predominantly low income population found that forgetfulness and miscommunication accounted for 66% of the reasons for patients not showing up for clinic appointments (44). These reasons probably apply to the TB program in the South African context since TB is primarily managed at the primary/community healthcare centers. A study conducted in India found "being busy with other work" as the main reason for no return (45). Other reasons for TB patients not initiating treatment that have been found are: lack of motivation for a second visit and having other competing priorities (17,46), lack of education, poverty, having to go to the clinic alone, seeking traditional healer services, social stigma and religious beliefs (32,47,48). Poor healthcare worker (HCW) attitude, re-treatment, changing residence, feeling ashamed, poor counseling, and alcohol (49–51) have also been found as reasons for TB initial LTFU. A short duration to the next appointment date has also been shown to be a factor in missing the appointment (17). Stigma related to TB and its association with HIV has been found to contribute to reasons for not initiating treatment among TB patients (16,52).

Patients traveling between towns for various reasons is another factor contributing to non-adherence to clinic appointments. An example of an area in South Africa that is resident of a migrant population emanating from other parts of the country as well as from other countries is the inner-city Johannesburg (53). The rate of failure to initiate TB treatment in this area was found to be as high as 22.5% (6). In a study conducted in Western Cape Province South Africa, which is similar to Johannesburg in terms of being an economic hub, the most common reasons for missed appointments among patients on chronic medication were mobility and temporary migration due to travel during the festive season or on other planned holidays (54). Many of those in this highly mobile population may test for TB in the economic hub, but return to their rural homes before they get the results and are not initiated on treatment.

Apart from the patient-related factors highlighted above, reasons related to the quality of the healthcare services rendered to patients are also a frequent cause of initial LTFU (32,42,55). Other healthcare system-related factors for failure to initiate TB treatment are poor communication between patient and healthcare provider (16). This was found in two studies conducted in India and Pakistan which revealed that patients were unaware of their results being ready at the facilities (14,46). Both studies reported on lack of awareness around TB in patients who had sought healthcare services and were actually diagnosed with TB. This indicates poor communication from the healthcare provider side. This could have been as a result of next steps not being discussed during their last clinic consultation.

The reasons explained above have not only been noted in countries with low Gross Domestic Product (GDP) per capita but also in those countries with a high GDP such as Qatar and Portugal (56,57). Analysis of data from upper-middle income countries in a systematic review revealed an average 10-day delay in TB diagnosis and treatment initiation associated with patient related factors such as poor TB knowledge and stigma (58). This explains that the problem of initial LTFU is not unique to poor people.

From the magnitude of the problem of TB initial LTFU and the reasons highlighted above, one can deduce that patients have other competing priorities and may tend to overlook their health. Therefore, an intervention that can be explored to reduce initial LTFU among TB patients is sending reminder messages to them informing them that their results are ready. This can be done through SMS messaging to the patient or through WBOTs delivering a paper slip advising the patient to collect their test.

1.6. Theories around TB Initial LTFU

There are over ten different concepts and theories explaining why patients would not start treatment after seeking healthcare services for a particular condition (59). Below are three concepts that offer possible explanations for TB patients not initiating treatment.

1.6.1. Patients' perception and understanding/knowledge of their disease

To understand why patients do not return for TB test results as well as to plan for targeted interventions, one needs to consider individual patient behavior. Patient behavior can be explained using a type of Behavioral Change Theory known as the Health Belief Model

(HBM). This model "addresses the individual's perceptions of the threat posed by a health problem (susceptibility, severity), the benefits of avoiding the threat, and factors influencing the decision to act (barriers, cues to action, and self-efficacy)" (60). It was first developed in 1966 by Irwin Rosenstock as a result of inspiration from a study that looked at why patients agreed or disagreed to have a chest x-ray for TB investigation done on them (61). There were 4 constructs under this model. These were patients' perception of their risk of getting the disease; patients' perception of the seriousness and complications of the disease; patients' perception of barriers such as medication side effects; and patients' perception of the cost. The model was later modified by Becker and colleagues in the 1970s and 1980s to include illness behavior, preventive health and health screening (59). In the HBM, positive health behaviour is more likely to be influenced by cost-effective strategies and those that achieve the desired outcome, rather than expensive strategies (61,62).

In the case of patients testing for TB, this model would explain their failure to return for results. It could be that they are thinking they cannot be at risk of getting TB or they are not seeing the disease as serious/deadly if they do have it. A cross sectional study conducted in India showed that 32% of patients who did not initiate treatment were busy with other jobs while 21% were not busy but decided to stay home doing nothing in particular (45). This is an example of the patients not viewing their condition as serious as explained in the HBM. The limitations of this model are the following: It focuses on individual factors rather than socioeconomic and environmental factors, leading to victim-blaming. In addition, it addresses more negative factors than positive factors which prompt healthy behaviors. Lastly, it lacks concepts associated with strategies for change.

1.6.2. Social and environmental factors impact on patient behavior

The impact of social and environmental factors on patient behavior is important in understanding why patients would opt not to return for their TB test results and take TB treatment if the test is positive. This can be explained using the Social Ecological Model (SEM). The model "addresses the importance of interventions directed at changing interpersonal, organizational, community, and public policy, factors which support and maintain unhealthy behaviors" (63). Based on this model, the efforts that patients make towards their wellbeing are likely to be successful in an environment where there is adequate support from the family or community around them. This support can be in form of patients being

reminded of clinic appointment visits. Patients testing for TB are asked to return for their results after 2 days. Reminder messages through SMS or paper slips delivered by the WBOTs are a way that these patients can get support from the environment around them.

The SEM has evolved over time. The original one of 1979 which was authored by Urie Bronfenbrenner was the Ecological Systems Theory. This theory looks at the fact that the individual, the organization, the community, and culture are nested spheres. Therefore, what happens in one sphere influences what happens in the next sphere (64). Environmental theories have the advantage of benefiting a large number of people not only an individual. If sending SMS or paper slip reminders to patients to go and get their TB test results becomes policy, it would not require extra effort on the part of the patient to receive the SMS. This is different from Behavioral Change Models like the HBM which require patients' active participation for change to occur (65). Therefore, such passive policy interventions are likely to work under such a model. However, it is important to consider potential barriers to successful implementation such as income and geographical mobility to enable patients to attend clinic appointments as was shown in an adherence study conducted in Tanzania (66).

1.6.3. Provider-patient communication

The Diffusion of Innovations (DOI) Theory is "a type of communication theory which is relevant to health promotion and describes the stages involved in adopting technological advances such as informatics and electronic media" (59). The use of electronic media in the health sector for health promotion has been increasing over the years. According to the DOI theory, the relevant stages of change are knowledge, persuasion, decision, implementation, and confirmation.

In the case of sending reminder messages to patients (SMS or paper slips by WBOTs) for them to go and collect their test results from the clinic, the stages above also apply. The message gives the patient the information that the TB test result is ready (knowledge). It also says that the patient should go and collect his/her TB test result (persuasion). The patient then makes a decision to go or not to go to the clinic. The DOI model explains that an innovation or health promotion program should be easy to understand, to use, and to be adopted with minimal investment of time (67,68). The reminder message intervention through SMS or paper slip by WBOTs is a form of communication to patients which conforms to the above named

characteristics of the DOI Theory. The intervention is advantageous compared to passively waiting for patients to come for their TB test results.

Using reminders to change patient behavior incorporates all 3 concepts explained above. Patients testing for TB can return for their test results and get initiated on treatment if the test is positive. This could be through them seeing their disease as serious, the environment being supportive by sending reminders as well as through communication (SMS or paper slip by ward-based outreach teams) to give knowledge that the result is ready.

1.7. Conceptual Framework

The conceptual framework for this study is based on a combination of the HBM , the SEM and the DOI (59). Concepts of health behavior are explained in the HBM of the 1950s which was later modified by Rosenstock and colleagues (69). The model by Krishnan and colleagues (a variation of the Health Belief Model) looks at delays to TB diagnosis and treatment (individual and provider/system barriers) at various time points along the continuum of TB care (70).

Some patients will not go back to the health facility for their results because they are forgetful or lazy and want to stay home (45) or they are not willing to do so (71). The framework in **Error! Reference source not found.** shows that both patient and health system factors (specifically lack of a reminder system) are barriers to treatment initiation. SMS and paper slip reminders are methods to minimize these barriers. Through these methods, patients are reminded to collect their test results at the clinic. During routine home visit schedules, WBOTs can distribute the paper slip reminder messages to patients and this is one way to address health system barriers, i.e. having a reminder system at the facility."

The Diffusion of Theory model looks at the concept of provider-patient communication. A patient gets to have the knowledge that his/her TB test result is ready at the facility. This can be through either SMS communication or through paper slip delivered by WBOTs. The message advises the patient to go to the clinic to collect results (a component of persuasion).

Reminder messages to say results are ready for collection is a way of having support from the environment. The patient does not have to go actively to get a message. It comes to him/her either through SMS or through delivery of a paper slip by the WBOTs.

Patients' failure to return for results can also be explained using the HBM and using the SEM (59). Patients may not view their disease as serious and therefore find no need to collect the results. If the healthcare system does not emphasize to patients the need for them to get their results (sending reminders) and does not warn them of the possible serious risks to their health, there is a possibility that they will not return for results.

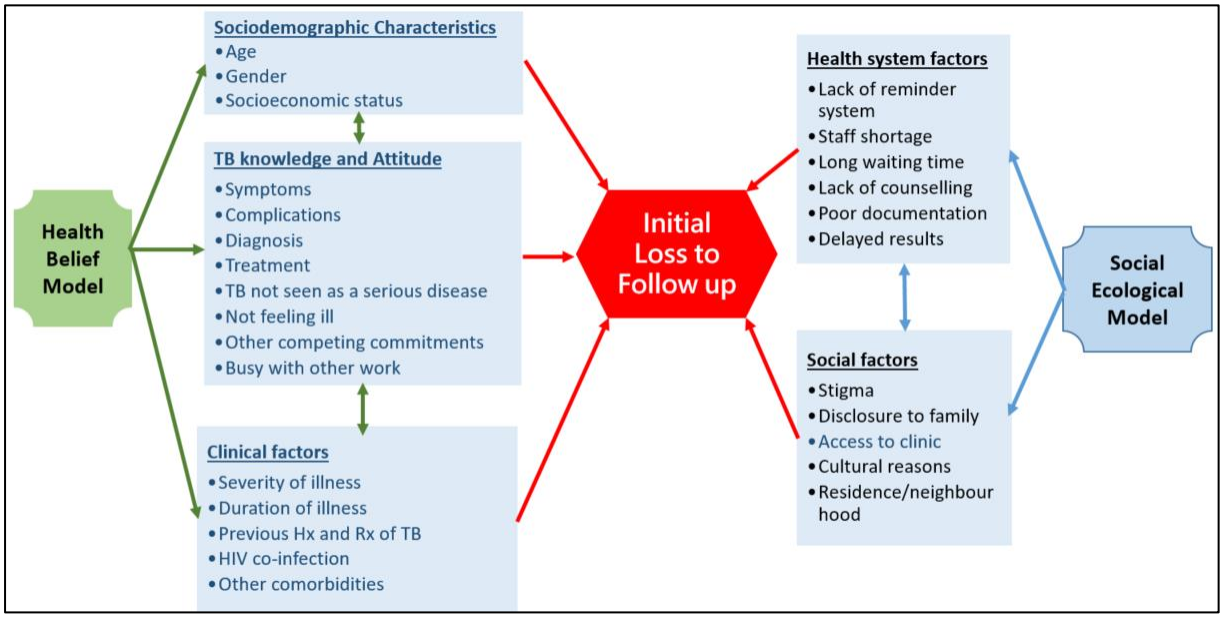


Figure 1.1: Conceptual Framework

1.8. Interventions

With the high rates of initial LTFU among TB patients in South Africa, there is a need for the NTCP to put strategies in place which aim to reduce the time from diagnosis to treatment initiation. The number of TB patients initiating treatment may be increased by sending reminder messages to patients for them to return to the clinic for their results. The reminders could be sent via SMS messages or through paper slips messages delivered by the WBOTs. Paper slip messages have been shown to work in influencing health seeking behavior among contacts of TB patients (72,73) and contacts of patients with sexually transmitted infections (74). In the former, TB contact tracing rates of 26% and 22.3% were found in the Johannesburg study and the eThekwini study respectively (72,73). This shows that getting a message advising one to go to the clinic can make him/her go to the clinic. This reminder system has been known to work in TB adherence programs (75).

1.8.1. SMS Technology

A number of studies have shown that SMS messaging can improve clinic attendance and return for follow up. SMS technology is a potential method that healthcare facilities could use to relay health promotion messages to patients. Over the past decade, the use of mobile cellular phones has been on the increase globally and in 2015 there were over 7 billion mobile cellular subscriptions (18). The use of SMS technology has shown to increase attendance at healthcare appointments among patients (76–79) and is cost-effective (80,81). The intervention is acceptable (24,25) and has shown to improve linkage to care in different healthcare programs such as ophthalmology (82), family planning (83), and HIV (84,85). It has resulted in improved adherence to medication of different chronic medical conditions (19–22,86–88). A systematic review found a 65% increased chance of adherence to ART (OR = 1.65; 95% CI: 1.25-2.18) when SMS messages were used compared to no SMS (23). SMS messages have shown benefit in serving as treatment reminders to TB patients and in increasing TB knowledge (89).

SMS messaging is important in ensuring good clinic attendance and return for follow up. A multicenter three-arm randomized controlled trial at 7 primary healthcare clinics in Malaysia was conducted to determine if SMS messages are effective in improving clinic attendance (90). The trial enrolled patients (or their caregivers) who would need to be followed up at the clinic for the subsequent 3 months. The 3 study arms were SMS message reminders, phone reminders, and a control arm which had neither SMS nor phone reminders. Reminders were sent to patients or caregivers in the intervention groups 48 hours before the appointment date. The attendance rate of the SMS messaging reminder group was significantly higher compared with that of the control group (OR=1.59, 95% CI: 1.17-2.17). A comparison of the attendance rate between the SMS messaging reminder group and the phone reminders group showed no difference (OR=0.98, 95% CI: 0.72 - 1.33). This trial had 2 main limitations: Firstly, only those who came on actual appointment dates (not before or after) were counted as attendees. So there is a chance that some were missed. Also, because there was no need for a reply to the SMS, it was not easy to tell if all messages sent out were received and read.

Evidence from chronic disease programs also supports SMS technology. Through SMS messaging ensuring regular clinic attendance, this technology improves the lifestyle of patients with chronic conditions such as diabetes and HIV as shown in the following two studies. Haddad and colleagues conducted a study in Iraq to evaluate the feasibility and utility of SMS

among adults with newly diagnosed type 2 diabetes in their first year of diagnosis. At baseline, patients completed a knowledge questionnaire and the scores were compared to those after a 6 months' intervention phase. During the intervention, SMS messages on self-management and appointment reminders to assess acceptability were sent weekly. The findings were that patients were happy with the messages and wished for more. In addition, knowledge was better after the intervention. (24).

In another study conducted in Uganda, a combination of SMS intervention and transportation reimbursement was used to improve linkage to care among HIV-positive patients (84). This quantitative study, which was conducted at a publicly operated HIV clinic, enrolled HIV-positive patients undergoing CD4 count test who had access to a mobile phone. Pre-intervention interviews with patients and staff revealed that lack of communication and lack of transport were the main barriers to patients returning for clinic appointments. In the intervention period, participants with abnormal CD4 count readings received one of three SMS messages (a direct one which stated results were abnormal, a PIN protected one or a coded message) in addition to a transport incentive if they returned for results within 7 days of testing.

The researchers found that participants in the intervention period returned earlier for results than those in the pre-intervention period (6 days versus 33 days; p-value <0.001). The time to ART initiation was 12 days in the intervention period while in the pre-intervention period it was 47 days. Although this methodological approach matched the research question, the study had some limitations. Firstly, it was conducted within a research setting and not on a real world scale. This makes it difficult to generalize results. Also, there is no guarantee that transport reimbursement is a sustainable intervention. Lastly, the study used a combined intervention, and therefore it is difficult to say if the impact was due to either method or due to both.

These 2 studies above (24,84) show that patients receiving SMS messages were happy with the health service, returned early for appointments, and were more knowledgeable about their condition.

Although the use of SMS intervention in healthcare has been advantageous in terms of linkage to care, unresponsiveness to SMS messages has been the down side. Irons and colleagues (83) conducted a study to understand the factors which influence adolescents' non-responsiveness

to text messaging. This was a sub-study of a trial on feasibility, acceptability, and effectiveness of a text messaging reminder system to improve clinic attendance at family planning appointments among young women using Depo-Provera contraception. The main cause of non-responsiveness they found was personal conflicts such as school or work. However, findings from this study cannot be generalized due to the small sample size. In addition, further stratification of the sample to identify differences between non-responders may be limited due to the small sample size (83).

In TB programs, the SMS intervention has been tested to evaluate adherence to treatment (31,91). There are techniques to improve adherence to TB treatment. The SIMpill is a technique where TB drugs are packed in a special bottle that has a sim card in it. When bottle is opened, a message is sent to a central server where unique information for that medication bottle is stored. The information is linked to the name and contact details of the patient. This SIMpill was piloted in Cape Town, South Africa between July 2006 and April 2007 among 155 TB patients at three clinics. The findings showed an improvement in treatment success rate from 71% in 2005 to 94% after the pilot. The drug adherence ranged between 86% and 92% after 10 months of using the SIMpill. Whether or not this was an improvement cannot be ascertained as no baseline adherence information or control group information was provided by the researchers (31).

In another study conducted in Cape Town, South Africa, SMS messages were sent to patients testing for TB to assess whether or not they returned to the clinic for their results and the time to return. This 3 arm randomized controlled trial had 2 arms with SMS intervention. The participants in one intervention arm received a plain and simple message asking them to collect their results. The message to patients in the other intervention arm was longer with details of national TB mortality rates in addition to the reminder. The researchers found a higher return rate among patients who had received the intervention than among those who had not (62% and 64.2% in the intention to treat analysis and in the per protocol analysis respectively versus the 51.5% in the control arm). A limitation of this study is that return for result does not necessarily mean treatment initiation and therefore further data collection on treatment initiation would have been beneficial. Also, patients who started treatment were not followed up to completion of their treatment course, an estimate of the health gain cannot be ascertained (26).

In terms of TB treatment initiation, a study conducted in Cambodia that looked at active TB case finding in communities sent SMS messages with positive test results from the laboratory to TB workers (92). This was a quantitative study which entailed door-to-door community based active TB case finding. Household members were screened for TB and if found positive on symptomatic screening, they were tested for TB. After receiving SMS with positive TB test results from the laboratory, the TB workers would either phone the patients to inform of the results or they would inform them through Community Health Volunteers (CHVs) who conducted home visits. The researchers found that a 94.6% (741/783) treatment initiation rate with 3 days (IQR 1–6) median time to treatment initiation among the patients diagnosed with TB (92). The TB notification rate also improved by 12%. Among the limitations of this study was that about 50% of household members were not home when the CHVs reached their homes for either TB screening or to deliver results to those who TB workers failed to reach telephonically. In such cases, symptom screening was done through a proxy and therefore no further tests could be conducted. As such, underestimation of presumptive or real TB was possible.

A South African study also showed improved TB treatment initiation among patients who had received reminder messages when results were ready. In their mHealth study conducted in Johannesburg South Africa, Maraba and colleagues (93) sent text messages of results to patients testing for TB as well as to the healthcare workers. The automated messages were sent out directly from the central laboratory system as soon as the results were ready. The messages to the patients entailed a reply where entry of a pin number was required before accessing the result. They found a 15.2% initial LTFU rate after implementation of the mHealth intervention compared to the 31.8% rate before the implementation. One limitation of this study was that it was a pilot study in 2 facilities and therefore generalizability of the results is questionable. Another limitation was the fact that some participants lacked understanding of the retrieval process for the results using the secret pin sent to them and therefore did not receive their results (93).

Despite some limitations highlighted above, SMS technology has a role in healthcare. Research has shown that patient return rates for clinic appointments are better and patients are more adherent to a medication when they receive reminders via SMS. Furthermore, the benefits of

SMS technology have been seen in linkage to HIV care. It is envisaged that this intervention would work in linkage to care among patients who test positive for TB.

1.8.2. Ward-based Outreach Teams (WBOTs)

In Brazil, the community level healthcare model has been shown to work since its inception in the late 1980s (94,95). People had more access to healthcare services and this resulted in healthier communities (28,96). Also, during the evaluation of Brazil's Family Health Program, it was found that there was a decline in infant mortality rate from 49.7/1000 live births in 1990 to 28.9/1000 live births in 2002 (27). Promoting primary care, providing education, encouraging testing and facilitating engagement in care are some of the roles of CHWs in Kenya (97). A systematic review showed that CHW performance would be better if they used mobile technology (98).

WBOTs are part of the re-engineered PHC model in South Africa. They work within catchment areas of PHC facilities. A WBOT comprises the following: a Team Leader (often a Professional Nurse) and 6 CHWs including a Health Promoter (HP) and sometimes an Environmental Health Officer (EHP) (99). Their work focuses on health promotion and prevention of disease. They link patients to healthcare by refering them to appropriate PHC facilities when necessary. A qualitative study on perceptions of the role of WBOTs with key informants conducted in Kwa Zulu Natal, South Africa revealed that although WBOTs deliver chronic medication, their work schedule was unclear (100). For TB services, they ensure that TB patients adhere to treatment once initiated by identifying, supporting, and following them up and their contacts (99). Their role is to ensure that TB patients adhere to treatment once initiated (99,101–104). The scope of work speaks much to contact tracing and treatment adherence, and less to initial LTFU and treatment initiation.

The scope of work of the WBOTs seems to lack adequate content on TB and more specifically TB treatment initiation as seen in **Error! Reference source not found.** (99). Implementation of WBOTs is limited by inadequate training and skill of CHWs who in most cases are overburdened with complex tasks beyond their capacity (105). It is therefore not surprising that their TB knowledge is low. Research conducted in both urban and rural parts of the Free State Province of South Africa showed that about a third of the CHWs had not received TB training

and over half of them had no formal training in HIV counselling and testing (106). The work of this cadre of staff can be further appreciated with training and supervision (107,108).

Problems with community-based models have been described elsewhere. In a previous study conducted in Papua New Guinea, CHWs who were assessed on clinical competency obtained low scores which worsened the further away the assessment was from the last training. For optimal healthcare service delivery, closer on-site supervision and semi-annual training were recommended (109). Findings from a Malawian study showed that CHWs could not function as TB adherence supporters due to a lack of knowledge on TB (106). Two other Brazilian studies also found a lack of TB knowledge as a limitation to CHW work performance (110–112). In Honduras, CHWs were able to manage 80% of local health problems after they were capacitated with knowledge and skills (113,114). CHWs would need some training on TB for them to be supporting treatment adherence (115). With proper guidance and training support, this cadre of staff could deliver reminder paper slips to patients who test for TB thereby enhancing their current role of taking healthcare to the community.

Table 1.1: Scope of Work for the WBOTs

Improve the quality of life of community members by mobilizing for improved access to and delivery of Primary Health Care at local level within the context of an inter-sectoral environment. 1. Promote health and prevent illness 2. Conduct community assessments and mobilize around community needs 3. Conduct structured household assessment to identify their health needs 4. Provide psychosocial support to community members 5. Identify and manage minor health problems 6. Support screening and health promotion programmes in schools and Early Childhood Development (ECD) centers 7. Promote and work with other sectors and undertake collaborative community based interventions 8. Support continuum of care through service coordination with other relevant service providers

Provincial Guidelines for the Implementation of the three streams of PHC re –engineering (99)

The WBOTs have not been used for linkage to TB care. It is possible that in addition to ensuring adherence to chronic medication, WBOTs can be utilized to deliver reminders to patients testing for TB to collect their results from the facilities. A study conducted in Kwa Zulu Natal Province in South Africa, on training CHWs to provide comprehensive TB/HIV/PMTCT integrated care, showed that after CHW training, there was an increase in the uptake of TB services and linkage to care (116).

The WBOTs are frontline staff who can contribute to the success of TB programs. During their routine household visits and through symptom screening, they assist with identification of who needs to be tested for TB. They also check adherence to TB treatment as part of their chronic disease patient follow up. With the inclusion of reminding patients to collect test results so that TB treatment can be initiated if necessary, the WBOT work can cut across the entire care TB cascade.

This chapter has discussed existing literature on the magnitude of and reasons for TB initial LTFU. It has also explored what is known about the proposed interventions (reminder messages through SMS messaging and through the delivery of paper slips by WBOTs) for reducing initial LTFU among TB patients. SMS messages have been shown to work in other health programs. WBOTs bring healthcare services to the community level and have been shown to improve accessibility to services such as immunization and TB screening as well as adherence support to those on chronic medication. If implemented, both interventions have the potential to contribute tremendously to the success of the national TB program in South Africa.
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1.9. Aim and Objectives

Aim

The main aim was to assess the effectiveness of WBOTs or SMS technology in reducing initial LTFU among TB patients.

Objectives

1. To determine the initial LTFU rate and the time to treatment initiation among TB patients at PHC facilities in inner-city Johannesburg
2. To determine reasons for initial LTFU from the perspective of TB Program Managers and WBOT Managers
3. To assess the effectiveness of WBOTs in reducing initial LTFU among TB patients.
4. To assess the effectiveness of SMS technology in reducing initial LTFU among TB patients.
5. To explore the experiences of TB patients and of WBOTs during the implementation of the SMS and paper slip reminders to TB patients.

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Methodology

This chapter details the methods that were undertaken to achieve the stipulated objectives. A mixed methods approach was used. The first step was to establish the TB initial LTFU rate in the study area. This entailed a retrospective study using secondary data from a roll-out of point of care Xpert Mtb/Rif (Xpert) machines. The next step was to conduct in-depth interviews with managers from the WBOT and TB programs. This was to understand what they thought were the reasons for TB initial loss to follow up. The quantitative data were collected through a 3 arm randomized controlled trial (standard of care and two interventions). The interventions were SMS technology and WBOTs. The trial tested the effectiveness of the two interventions in reducing initial LTFU among TB patients. The WBOTs delivered paper slip reminders while SMS reminder messages were sent to participants' mobile phones. The messages informed the participants that their TB results were ready at the facility where they had been tested. To complete the PhD project, another piece of the qualitative data was collected at the end of the trial from participants of the trial and from the WBOT members. The aim was to explore their experiences of the trial.

2.1. Study Setting

The inner-city Johannesburg is found in Region F sub-district in the City of Johannesburg in the Gauteng Province of South Africa. It occupies an area of 1645km^2 and has a population of 4.4 million (1). This region is densely populated with mostly economic migrants from other parts of the country as well as from across the South African borders.

2.2. Care Cascade of Patients Testing for TB

In South Africa, a patient presenting to a PHC facility is screened for TB symptoms using the four symptom WHO check list (cough, fever, weight loss and night sweats). If any one of these four symptoms is present, the patient is asked to submit a sputum on the spot. The sputum is couriered to the laboratory where it is tested using the Xpert machine. Smear microscopy is used if the Xpert machine is not available. Xpert testing turnaround time is 2 hours. However, taking transportation time and delivery into consideration, patients are asked to return for results after 2 days. Treatment is initiated within 5 days. The patient is required to submit another sputum sample for smear microscopy if Xpert was the diagnostic method. Smear

microscopy is used to monitor the response to treatment and assist in determining whether treatment can be switched from intensive to continuation treatment phase (2).

2.3. Ethical Considerations

The protocol for the PhD study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Reference number: M170651) and permission to conduct the study at the different PHC facilities study was granted by the City of Johannesburg District and the Gauteng Provincial Department of Health (DRC Ref: 2017-08-001 AND NHRD Ref #: GP_201708_024 respectively).

This PhD work utilized a mixed methods approach with an initial secondary data analysis of the data from a study that had previously been conducted in the study area. This was to give an idea of the TB initial LTFU rates in this area. Interviews were conducted with key informants from the TB and WBOT programs to understand their perceived reasons for TB initial LTFU. The RCT tested the effectiveness of the sending reminder messages to patients to reduce initial LTFU. Post-intervention interviews with the study participants and with the WBOT members were conducted to explore their experiences during the RCT. The methods undertaken for each of the objectives are described in detail below and in the published papers.

2.4. Study Procedures

2.4.1. Activity 1: Determining the initial LTFU rate and the time to treatment initiation among TB patients at PHC facilities in inner-city Johannesburg

Study Design: This retrospective cohort research entailed use of secondary data from a project called the "Region F TB Blitz". The latter assessed the feasibility of point of care use of Xpert for TB testing. Data had been collected from seven PHC facilities in inner-city Johannesburg which had implemented Xpert at the point of care. At the time of this implementation, sputum smear microscopy for acid-fast bacilli (AFB) test was the routine TB investigation although a national roll-out of centralized TB testing using Xpert was also underway. Patients who tested positive with Xpert were also asked to submit another sputum sample for AFB testing. This second sample was used as a baseline for monitoring progress on treatment as per National Department of Health (NDOH) guidelines for South Africa. The data from the "Region F TB Blitz" project had been captured into an electronic TB register.

Participants of the main study had given written consent for their data to be used for research. The University of the Witwatersrand, Human Research Ethics Committee granted approval for the study to be conducted (M110233).

Study setting: The Region F TB Blitz project, from which the data for this objective was analyzed, had been conducted at 7 PHC facilities in inner-city Johannesburg, South Africa.

Study Population: Patients suspected to have TB based on symptoms they presented with (TB suspects/patients with presumptive TB) and whose sputum has been tested for TB using Xpert and/or smear microscopy.
Inclusion criteria for TB suspects: Patients 18 years old and older with no TB diagnosis who had a productive cough of more than 24 hours as one of the symptoms.
Exclusion criteria for TB suspects Less than 18 years old patients, already on treatment, those too ill to give consent for participation or those with psychiatric conditions.

Sample Size: The Region F TB Blitz project enrolled 2286 patients between October 2011 and September 2012. These were patients that were tested for TB using the point of care Xpert and/or smear microscopy. Of these, 305 were already on TB treatment. The 1981 TB suspects were taken as the sample for this objective. It was assumed that in the context of point of care testing, the TB LTFU would drop by 2% from 18%, and using a level of significance of 5%, the study with this sample size was powered at 76%.

Data Collection: All data were stored in the Electronic TB (eTB) Register. This database had a unique identifier for each patient and this allowed information specific to a patient to be extracted. Data on the 1981 TB suspects were accessed from the eTB register for analysis. This register was password protected and therefore access was limited to research team members. The variables of interest from the Region F TB Blitz project were the following: demographics, HIV status, duration of cough, the turnaround time to TB diagnosis result, Xpert result, smear result, number of clinical consultations for cough at the time being investigated, date of study enrolment, and treatment start date.
Statistical Methods and Analysis: The outcomes of interest were the initial LTFU rate and the time to treatment initiation in patients diagnosed with TB using a point of care Xpert MTB/Rif and/or smear microscopy. The national TB guidelines had no standard definition for initial

LTFU in TB patients. Initial LTFU patients were patients diagnosed with TB and documented as either LTFU before treatment initiation in the TB register or those diagnosed with TB but not evaluated (no outcome indicated in the TB identification register and never entered in the TB treatment register). In this research, initial LTFU was defined as failure to initiate TB treatment within 4 weeks of testing for TB. There were two cut off points for "delayed treatment" that were used (30 days and 3 months). Descriptive analysis of the sample, regression analysis, and survival analysis were run using STATA® version 12 software (3). Being secondary data, one limitation was missing data. However, the proportion of missing data was less than 10% and therefore did not warrant any further data cleaning action before the analysis.

2.4.2. Activity 2: Determining reasons for initial LTFU from the perspective of TB Program Managers and WBOT Managers

Study Design: In depth interviews (IDIs) with key informants were conducted between August 2018 and February 2019. Names and contact details of managers in the study area were obtained from the District office. The managers working in the WBOT and TB programs were invited to participate. A maximum of four attempts (three telephonic and one email) over five days were made to arrange an appointment before declaring a potential participant "unable to reach." A logbook was used to record the process when administering the interviews. During the interviews, probing of questions was done to ensure the interviewee responded accordingly and efforts to finalize respective topic areas were made before moving unto subsequent questions.

Study setting: Inner-city of Johannesburg in the respective offices of the participants.

Study Population: TB Program Managers and WBOT Managers as key informants.

Sample Size and Data Collection: The participants were selected depending on their availability. Seven of the twenty managers selected were not reachable. One manager was reached by email but unfortunately he had moved to live outside the country. The remaining twelve managers were approached telephonically for participation and nine accepted the invitation. Annual leave, illness and other commitments were the reasons given for non-availability of the three who did not participate.

The IDIs were audio-recorded once participants gave verbal permission, and each IDI lasted about 35 minutes. An interview guide was developed for standardization of topics for discussion. The following topic areas were included: TB communication, WBOT functions, and reasons for loss to follow up. The interview guide was piloted with two managers working outside the TB/WBOT programs and this helped to refine and finalize the instrument. The sample finally interviewed was considered sufficient when data saturation was reached.

The audio recordings were transcribed verbatim and the transcripts were systematically coded using NVivo 11 software (4). A codebook framework consisting of the topic areas was created. Four of the transcripts were recoded as a way of checking the reliability of the coding framework. A hybrid approach (5), comprising an inductive phase and then according to deductive codes was used to code each transcript. After this, the codes were put into themes aligned with the different concepts/topic areas.

An understanding of the problem and reasons for the initial LTFU of TB patients from the perspective of managers was the outcome of interest.

2.4.3. Activity 3: Assessing the effectiveness of SMS messaging or WBOTs on initial LTFU among TB patients.

This activity covered objectives 3 and 4. To answer these objectives, treatment initiation was taken as the outcome of interest (as a proxy for initial LTFU).

Study Design: This was a 3-arm randomized controlled trial conducted between 10 September 2018 and 25 March 2020, with 22 April 2020 being the last date for follow up of the participants. Two interventions (WBOTs/SMS) were tested using the same population. The intervention "WBOTs" referred to WBOTs delivering paper slip reminders to patients whose test results were ready. SMS intervention entailed sending reminder SMS messages to TB patients to inform them that the results were ready. The third arm was the standard of care.

The reminder message, which was both on the paper slips delivered by the WBOTs and in the SMS message sent, read as follows:

"Good day, your results are ready at the clinic for your collection. You are advised to collect your results as soon as possible".

Study setting: The study sites were two public sector primary level non-fee paying clinics. They offer holistic primary level healthcare services such as family planning, maternity and well-baby services to the low income population they serve.

Study Population: Patients with presumptive TB accessing healthcare services from the PHC facilities.

Inclusion criteria for TB suspects: Patients aged 18 years old and above not yet diagnosed with TB who present with a productive cough of more than 24 hours
Exclusion criteria for TB suspects: Children less than 18 years old; patients already on TB treatment.

Data Collection Tool: A questionnaire was used to collect participant information on demographics, TB risk factors, and clinical information. The administration of this tool was interviewer administered. The development of the questionnaire entailed a pilot phase where 10 random people from one of the facilities were asked to co9mplete the questionnaire. They gave feedback on an understanding of the questions, on any ambiguity noted, and on the duration to complete the questions. The tool was then revised accordingly.

Sampling and Sample Size Calculation: Using data from the 2017 NTCP report, 8 clinics with the highest TB notification in the area were selected. The study was implemented in only two of these clinics because of the effects of the COVID 19 pandemic and also due to some financial challenges faced. Patients were enrolled if they met the inclusion criteria at the selected facilities and if they consented to participation.
As the results of the study participants were received at the respective facilities, the patients with positive test results were allocated to any of the 3 arms. Randomization was done after the TB result was available rather than at the point of enrolment because the outcome of interest was the treatment initiation and not the positivity of test results. A Stata generated pre-run block randomization sequence (block sizes ranging between 6 and 15 for the 3 arms – SMS, WBOTs, and SOC) was used for the allocation (6). The allocation followed the order in which results were received and each participant was allocated to one of the 3 arms, depending on the next letter in the randomization sequence. If the participant was allocated to an intervention group (SMS or WBOTs), a reminder message was prepared accordingly and sent to the participant.

In this study, the assumption was that the average 82% treatment initiation rate reported in South African studies (7–9) would increase to 95% (country's NTCP target) (2) in each of the

arms with an intervention (SMS technology/WBOTs). The sample size was calculated for either intervention arm versus the control arm (standard of care). Based on a power of 80% and a level of significance of 0.05 to detect an increase in treatment initiation of 13% in either of the intervention arms, the required minimum sample size was estimated to be 104 positive TB patients in each group. The trial was powered to detect a difference between the SMS arm and the SOC arm and also to detect a difference between the WBOTs arm and the SOC arm but was not powered to detect a difference between the SMS arm and the WBOTs arm. There was no adjustment made for multiple comparisons in computation of p-values.

Interventions

The interventions are described below in detail for the different arms of the study.

Standard of care (No WBOTs paper slips and no SMS Technology)

Contact details including mobile phone numbers of patients with TB symptoms who were asked to submit sputum for TB testing were collected (as per the current standard of practice) and entered in the TB Case Identification Register and the study book. The patients were asked to return to the clinic for their test results after 2 days. The names and results of the patients enrolled in the study were checked for regularly in the TB Case Identification Register. The study patients who tested positive for TB were allocated to this arm if this arm was the next in the block randomization sequence. After 4 weeks, the TB patients who did not start treatment were noted. The clinics were aware that these patients would not be followed up.

SMS Technology

Contact details, including mobile phone numbers, of presumptive TB patients were entered in the TB Case Identification Register (as per standard of practice) and in the study book. The ones who submitted sputum were told to return after 2 days to collect their results. The names of the participants with positive test results were allocated to this arm if this was the next allocation in the block randomization sequence. These patients received SMS messages telling them that their results were ready at the facility. The messages were sent from the study mobile phone and the delivery receipt function was activated to get notification of messages successfully delivered. The design of the messaging was one way such that it was not possible for the recipient to reply. The messages were sent once but if no delivery notifications were received, they were resent two more times before labelling the participant as “not reachable”.

The TB treatment initiation registers at the clinic were checked regularly for names of these patients randomized to this arm for 4 weeks. The ones with positive TB test results but not initiated treatment were noted.

WBOTs paper slips

Contact details, including mobile phone numbers, of presumptive TB patients were entered in the TB Case Identification Register (as per standard of practice) and in the study book. The ones who submitted sputum were told to return after 2 days to collect their results. The patients were allocated to this arm if this arm was next in the block randomization sequence. The names and physical addresses of the patients who tested positive for TB and were allocated to this arm were given to the WBOTs (for delivery of the paper slips with the reminder message). The WBOTs were also given paper slips with the message advising patients to go to the clinic to collect TB results. The delivery of the paper slips by the WBOTs was added on to their daily routine schedule during the period of the study data collection. If the WBOTs did not find the patient at the named address, they left the paper slip (in a sealed envelope) with whoever was home. The WBOTs reported back to the Research Assistant on number of slips delivered and on the unsuccessful deliveries. In cases, where the patient had relocated or the address could not be found, up to 3 attempts were made before finally labelling the patient as "not found". Treatment initiation registers at the clinics were checked regularly for 4 weeks. The ones with a positive TB test result but not initiated treatment were noted.

Statistical Methods and Analysis: The primary outcome was the proportion of TB patients who initiated on treatment within 4 weeks of submitting sputum for diagnosis. A secondary outcome was the time for treatment initiation. STATA® version 14.2 software was used to analyze the data (6). To evaluate the primary outcome, descriptive frequency tables were used. The proportion initiated on treatment within 28 days was estimated for each study arm, and chi-square tests were used to compare proportions. Poisson regression with robust error variance was used to estimate relative risks of treatment initiation across the study arms (SMS/SOC/WBOTs). The SOC arm was used as the reference group in the regression models. Candidate variables for the models were arm, marital status, age, body mass index, employment status, alcohol consumption, gender, smoking, TB test disclosure, monthly income, prior clinic consultation, travel time to clinic, comorbidities, HIV status, history of TB contact and

[1]severity of TB symptoms. The selection of the variables in the adjusted analyses was based on both existing literature on variables known to be related to TB treatment initiation and on the use of the estimates and significance during univariate analyses followed by likelihood ratio forward selection of variables.

To test the null hypothesis of no difference in the time to treatment initiation for the study arms, Kaplan–Meier curves and the log-rank test were used. The duration of time in the study was calculated using the date of consent (sputum submission date) and the date treatment was started. Transferred out patients or those who died before starting treatment were censored from the analysis. For the transferred out patients, censoring was done at the date of transfer out. For those who died or were lost to follow-up, day 29 was taken as the censoring date. Cox regression analysis was used to determine associations and predictors of treatment initiation across the study groups at any given point in time during the study. The hazard ratio estimates from the Cox regression were adjusted for other variables. The variables selected were the same ones used in the Poisson regression. The proportional hazards assumption was checked using the Schoenfeld residuals.

2.5.4. Activity 4: To explore the experiences of WBOTs and TB patients during the implementation of the SMS and paper slip reminders to TB patients

Study Design: In-depth interviews with WBOT members and with some of the TB patients who received reminder messages were conducted at the 2 clinics where the trial had taken place. The data were collected retrospectively.

The list of contact details of the WBOT members who were involved in the trial was used to find them and arrange interviews. Interviews were conducted between 17 May 2021 and 16 July 2021. A semi-structured interview guide was used to allow for probing to get maximum information from participants. The participants were purposefully selected based on their availability and on the time frame for the data collection. They were provided with information on the study before they signed consent to participate. After seeking permission from the participants, the discussions were audio-recorded lasting about 40 minutes each. The topic areas included WBOT functions in the TB program, WBOT challenges, TB program knowledge, and individual experiences of distribution of the paper slip reminders.

[1] Symptoms of TB were categorized into “mild” and “not mild”. Moderate or severe symptoms were classified as “not mild” a participant was in this category if he/she had all or two of the following: bmi<18.5, coughtime>=2weeks and one or more previous consultations

Contact details of participants from the trial who had tested positive for TB and had received reminder messages were retrieved. These were used to reach out to them for participation.

Due to unforeseen challenges, the post-intervention interviews were delayed by over 1 year after the parent study had ended. Since this was after the trial had ended and also the patients had completed treatment, they were not being followed up at the clinic. Therefore, the contact with them was via telephone, and they were invited to participate in the interviews. The ones that could be located and were available, were interviewed. The interviews were conducted either physically or telephonically depending on participant preference. Of the 167 patients who had received reminder messages, 105 had received SMS messages while 62 had received paper slips.

Study setting: City of Johannesburg.

Study Population: Members of the WBOTs at the study sites and also TB patients who received reminder messages.
Inclusion criteria: WBOT members at the study sites who had been involved in the distribution of the paper slip reminders and TB patients who were part of the study and had received reminder messages (through either SMS message or paper slip).

Exclusion criteria: WBOT members who were not involved in the study and TB patients not enrolled in the study.

Sample Size and Data Collection: All available members of the WBOTs at the study sites who were part of the study were approached for participation. In the same way, all TB patients who were part of the trial and could be located were contacted and invited for interviews.
Structured interview guides were used for both TB patients and WBOTs. Purposive sampling for maximum variation was employed until saturation was reached. The audio-recorded data were transcribed and imported into Nvivo software (4) for coding and analysis. Content thematic analysis was used to analyze the data. The transcripts were first read through to get a sense of what each contained. Codes and sub-codes were then identified and put into categories. Themes emerged from these categories based on the topic areas of the interview guide.

The contents of this chapter can also be found in the methods sections of the respectively published manuscripts which are presented under the “Appendices” section. The information is also in the protocol manuscript published in the BMC Research Notes journal (10) which is also attached in the “Appendices” section.

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Microbiologically Confirmed Tuberculosis: Factors Associated with Pre-Treatment Loss to Follow-Up and Time to Treatment Initiation

3.1. Abstract

Background: The impact of new diagnostics on pre-treatment loss to follow up (Pre-treatment LTFU) has not been widely investigated. The reported rate of pre-treatment LTFU is however lower in studies where Xpert MTB/Rif (Xpert) has been used onsite as opposed to centrally. The use of the Xpert at point of care (POC) could have a role in reducing the pre-treatment LTFU rate among TB patients. We aimed to determine the pre-treatment LTFU rate and the time to treatment initiation as well as to describe associated factors in patients diagnosed with TB using POC Xpert or smear microscopy.

Method: Xpert machines were installed at 7 primary healthcare facilities in inner-city Johannesburg. POC Xpert TB testing was the primary diagnostic method for all patients although there were some patients who were tested using only laboratory-based smear microscopy (during power outages or machine operator off-sick). Data on patients' demographics, TB diagnostic test (Xpert or smear microscopy), test result, and time to treatment initiation were collected. Associations and predictors of pre-treatment LTFU and time to treatment initiation were explored.

Findings: A total of 1981 people with presumptive TB were tested (1743 using Xpert and 238 using smear). A bacteriological diagnosis of TB was made in 271 patients (90% Xpert; 10% smear). The median time to treatment initiation in the smear group was 9 days (IQR: 4-20) while those tested using Xpert had a median time of 0 days (IQR: 0-0). Pre-treatment LTFU was 22.5% with no difference between diagnostic groups ((22.9% versus 19%; p=0.8).

Conclusion: The Pre-treatment LTFU rate of 22.5% found in this study is much higher than the 5% target of the South African National TB Control Program. POC Xpert resulted in a significantly greater proportion of bacteriologically proven TB patients being started on treatment within 30 days of presentation. No risk factors associated with pre-treatment LTFU were identified.

Mwansa-Kambafwile J, Maitshotlo B, Black A. Microbiologically Confirmed Tuberculosis: Factors Associated with Pre-Treatment Loss to Follow-Up, and Time to Treatment Initiation. PLoS One. 2017 Jan 9;12(1):e0168659.

See Appendix 1

3.2. Introduction

Tuberculosis (TB) is a preventable and treatable communicable disease. Despite recent advances in TB diagnostics, TB remains a major contributor to global mortality. With a TB incidence of 834/100000, some of South Africa's TB patients were among the estimated 1.5 million deaths from the 9.6 million people who developed the disease worldwide in 2014 (1). Despite the importance of rapid treatment initiation in patients with TB for TB control, neither pre-treatment loss to follow up (LTFU) nor time to treatment initiation are included in routine TB programme outcome measures. TB patients already on treatment have been a focus of TB control programs in many countries. The emphasis has mostly been on ensuring that patients take their treatment. Not much attention has been paid to the patients who test positive for TB but never get initiated on treatment. TB patients who are lost before treatment is initiated continue to transmit infection and contribute to the burden of TB in communities.

Rapid diagnostic methods for TB such as Xpert MTB/RIF (Xpert) have been known to reduce the turn-around time between diagnosis and treatment. Except in a few instances, the testing has been used in centralized laboratory settings (2). Compared to smear, the use of the Xpert machine in centralized settings has not shown a reduction in mortality or an increase in the notification rate (3–5). Even when used on site as a "point of care" (POC) test, Xpert has failed to show a reduction in TB mortality and other important TB outcomes (6,7).

According to the South African National TB Guidelines, pre-treatment LTFU, are laboratory confirmed TB patients who are never commenced on TB treatment (8). A systematic review which assessed the magnitude of the pre-treatment LTFU rate in smear- or culture-positive TB patients in African and Asian studies found that this rate varies between 4% and 38% (9). A more recent study conducted in South Africa reported pre-treatment LTFU rates of 14.9 and 17.0% for Xpert and smear microscopy respectively; this was despite telephonic or home visit contact by study investigators at week 1 and month 1 into the trial (5). Pre-treatment LTFU in a study using Xpert as the initial diagnostic method as POC in a similar setting was 4% (6). Xpert as a POC may be a means to address high pre-treatment LTFU rates seen in National Tuberculosis Programmes (NTCP).

Appropriate TB treatment in a patient rapidly decreases infectivity, decreases transmission and is vital for TB control (10,11). Delaying TB treatment initiation or losing bacteriologically

confirmed TB patients before treatment is initiated contributes to on-going TB transmission in communities and to poor patient outcomes.

Using smear microscopy, Yimer and colleagues found a 27-day median time delay (between time of patient presentation and time of treatment initiation) that was as a result of health system delays (12). Although there is a 45% increase in bacteriologically confirmed TB case detection when using Xpert compared to smear microscopy (13) and the turnaround time for TB test results is said to decrease to five days when using laboratory-based Xpert (14), patients are still not initiated on treatment early. Causes of the delays vary from patient factors to health system factors. Factors that have previously been described to increase the risk for these delays are: increased turnaround time between sputum collection and result availability (15), male sex and older age (9). Cox and colleagues showed that the use of onsite Xpert reduced the time to TB treatment initiation from 8 days (IQR=2–27) using routine services to 4 days (IQR=2–8) using Xpert. The proportion initiated on treatment was also increased in the Xpert group compared to routine services (28% versus 23% respectively) although there was no impact on TB related morbidity or mortality (3).

Implementing POC testing for TB should reduce the impact of the health system factors and therefore reduce the diagnosis-treatment gap (16). A shortened time to treatment initiation would impact on on-going TB transmission. We aimed to determine the pre-treatment LTFU rate and the time to treatment initiation as well as to describe associated factors in patients diagnosed with TB.

3.3. Materials and Methods

This was a pragmatic observational study within a larger project (Region F TB Blitz) to assess the feasibility of implementing Xpert within primary healthcare facilities (PHCs). Between October 2011 and March 2012, 7 PHCs in inner-city Johannesburg implemented Xpert machines at point of care. These were operated by lay counsellors who had undergone thorough training on operation of the machine. The lay counsellors were funded by the study but were managed by the facility managers as part of the facility staff. In each facility, all persons with presumptive TB (as determined by the TB focal point nurse) were sent to the lay counsellor who collected sputum and tested it for TB using Xpert. Patients were told of the time it would take for a result and were invited to wait at the clinic or return for the result but that was not a

guarantee. However, some were unable to wait for the 2 hours and said they would return for results, but that was not a guarantee. The management of all patients was at the sole discretion of the TB focal point nurse.

Previous studies reporting on pre-treatment LTFU have used variable cut off times ranging from 30 to 90 days to define pre-treatment LTFU (9). We were unable to find a fixed cut off time for delayed treatment. However, it is known that there is a dose-response relationship between treatment delay and ongoing transmission of TB. It has been found that 30 days is the turning point as the risk of transmission is higher within the first 30 days of being symptomatic with TB (17).

Smear microscopy was the default diagnostic investigation if Xpert was not available at the time the patient presented to the clinic. There were some instances when smear microscopy was the only diagnostic test available at the time. Reasons for this were periods of Xpert machine downtime due to low temperature, electricity outages, software corrupted by viruses and cartridge shortages. The lay counsellors were also not replaced when they were ill or on leave.

As part of the main project and as part of routine data collection in facilities, data on the following were collected: patient demographics, time of TB test, test result, date and time of treatment initiation. The data were captured into an electronic TB register. For this study, pre-treatment LTFU was defined as patients diagnosed with TB and either documented as LTFU before treatment initiation in the TB register or diagnosed with TB but not evaluated (no outcome indicated in the TB identification register and never entered in the TB treatment register). STATA version 12 was used to run descriptive frequencies, proportions, regression analysis and survival analysis. We looked at two cut off times 30 days and 3 months

This research was a sub-study of a larger project called the “Region F TB Blitz” which looked at feasibility of point of care use of Xpert MTB/RIF machine for TB testing. Ethics approval was granted by the University of the Witwatersrand, Human Research Ethics Committee (M110233). Participants of the main study provided written consent for their data to be used for further research.

3.4. Results

A total of 2286 patients were tested for TB during the study period across the 7 PHC facilities. Of these, 13.3% (305) were already on TB treatment and these tests were routine follow up tests as per national TB guidelines for South Africa. The remaining 1981 patients were people who presented with presumptive TB (had one or more of the TB symptoms) (**Error! Reference source not found.**).

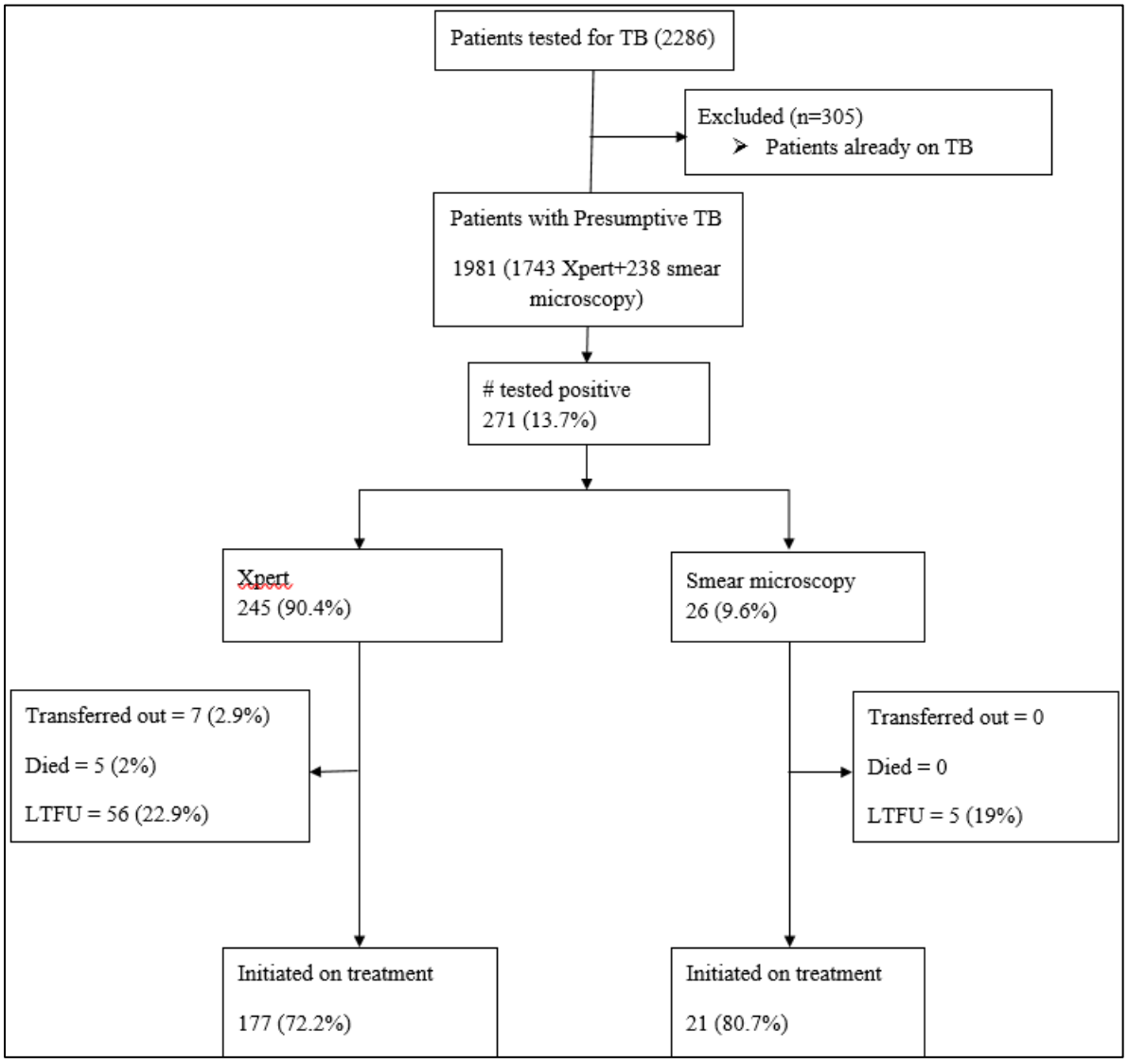


Figure 3.1: Patient flow and Eligibility Chart

Although not randomly allocated to diagnostic method (Xpert or smear microscopy) the events resulting in sputum smears being done were random and the participants were similar with regards to age, sex and HIV status (**Error! Reference source not found.**).

Table 3.1: Participant Characteristics

	Tested using Xpert (n=1743)	**Tested using smear (n=238)**	**p-value**
Age (years; IQR)	33 (28-39)	34 (29-40)	0.18
Male n (%)	880 (51)	135 (57)	0.08
HIV co-infected n (%)	1280 (74)	162 (68)	0.06

Two hundred and thirty-eight people (12%) had smear microscopy instead of Xpert as the initial diagnostic test.

Overall, the case detection rate was 13.7% (271/1981). The case detection rate for Xpert was 14.1% and for smear microscopy it was 10.9% (p=0.21).
The proportion of rifampicin resistance among the TB patients tested using Xpert was 6.5%. These patients were referred for MDR TB treatment as per national guidelines.

Of the overall 271 patients that tested positive for TB, 198 (73.1%) were started on treatment; 61 (22.5%) were LTFU prior to starting treatment; 5 (1.8%) died before starting treatment and 7 (2.6%) were transferred out of the facilities. The proportion of patients LTFU pre-treatment among the patients tested using Xpert was similar to the smear microscopy patients (23% versus 19% respectively; p=0.8).

Fifty-two percent (140/271) started treatment within a week of testing positive; and of these 78% (109/140) of them started treatment on the same day. Eighty-three percent (146/177) of the patients in the Xpert group were initiated on treatment on the same day of testing while five out of 21 patients (24%) from the smear microscopy group initiated on treatment were started on empiric TB treatment at their initial visit (p=0.001).
Whether or not treatment was initiated was not significantly associated with age, gender or with the type of test used for diagnosis (**Error! Reference source not found.**).

Table 3.2: Treatment Initiation

	Adjusted OR	**95% Confidence interval**
*Age (years)	0.95	0.90-1.03
Gender		
Female	Reference	
Male	0.87	0.50-1.51
Diagnostic test		
Smear	Reference	
Xpert	1.05	0.67–1.67

*Age was analyzed as a continuous variable

About 75% of the patients were initiated on treatment within 2 months of diagnosis and this is regardless of type of diagnostic test used (**Error! Reference source not found.**). Patients who tested using the Xpert were initiated on treatment earlier than those tested using smear microscopy (Log-rank p=0.01) (**Error! Reference source not found.**). The median time to treatment initiation (statistic used for the data not normally distributed) for patients that were tested using smear was nine days (IQR: 4-20) while those tested using Xpert had a median time of 0 days (IQR: 0-0). The proportion of patients diagnosed using Xpert and started on treatment before 30 days was different from the proportion from the smear microscopy group started on treatment before 30 days (85% versus 35% p<0.001).

In terms of duration before treatment initiation, females were initiated earlier than males (Log-rank p=0.03) (**Error! Reference source not found.**). The duration to treatment initiation did not differ among different HIV status categories that is HIV positive, HIV negative and HIV status unknown (Stratified Log rank p=1.0) (**Error! Reference source not found.**).

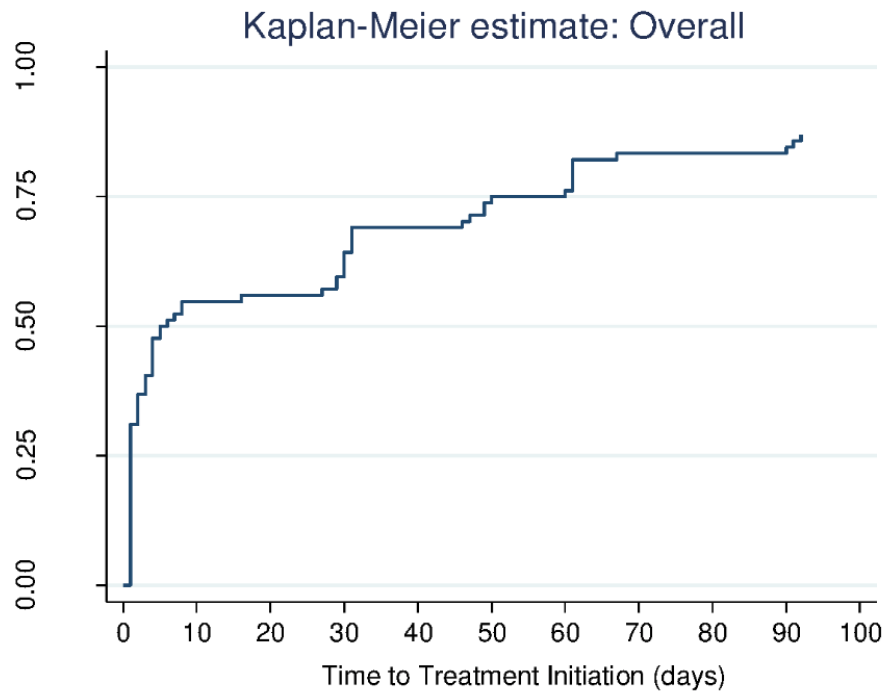


Figure 3.2: Overall Time to Treatment Initiation

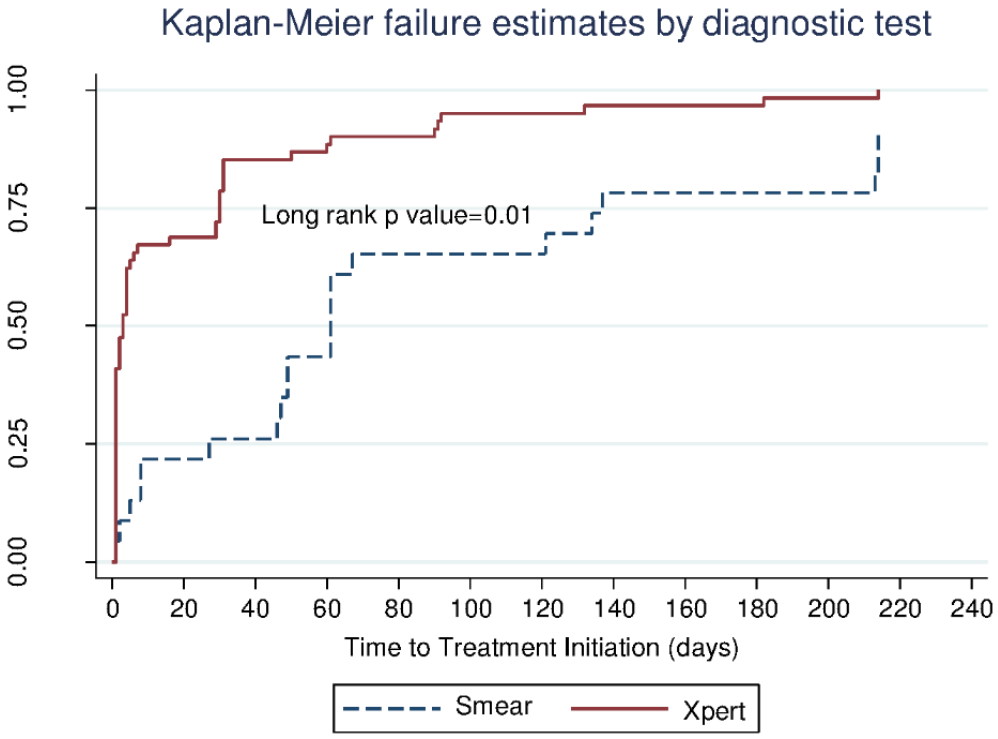


Figure 3.3: Time to Treatment Initiation By Testing Method

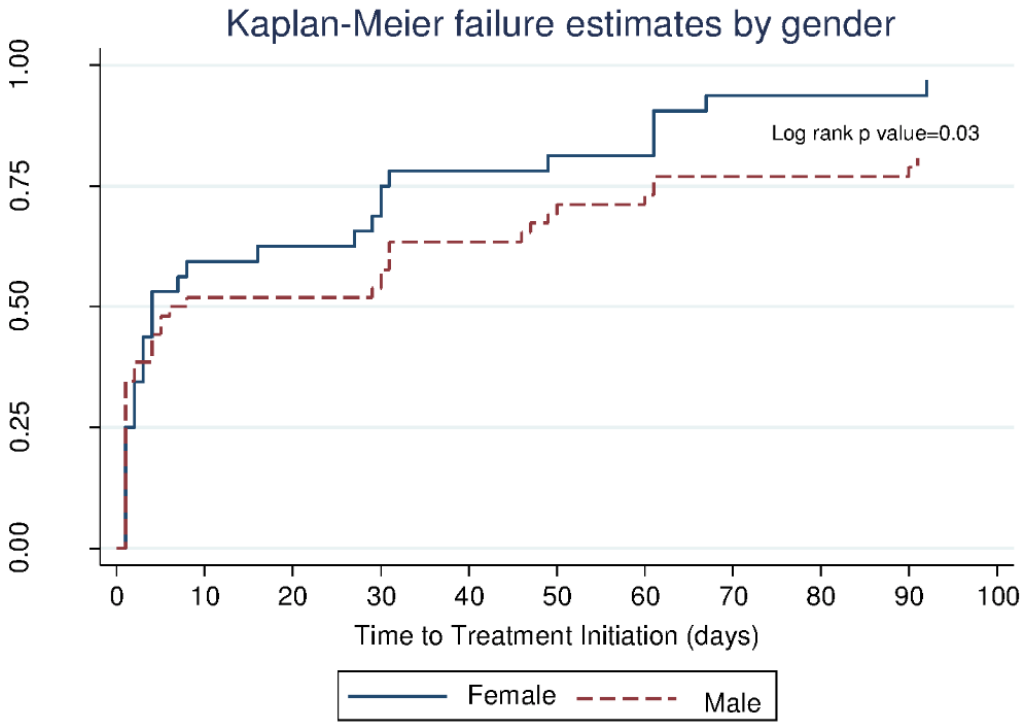


Figure 3.4: Time to Treatment Initiation By Gender

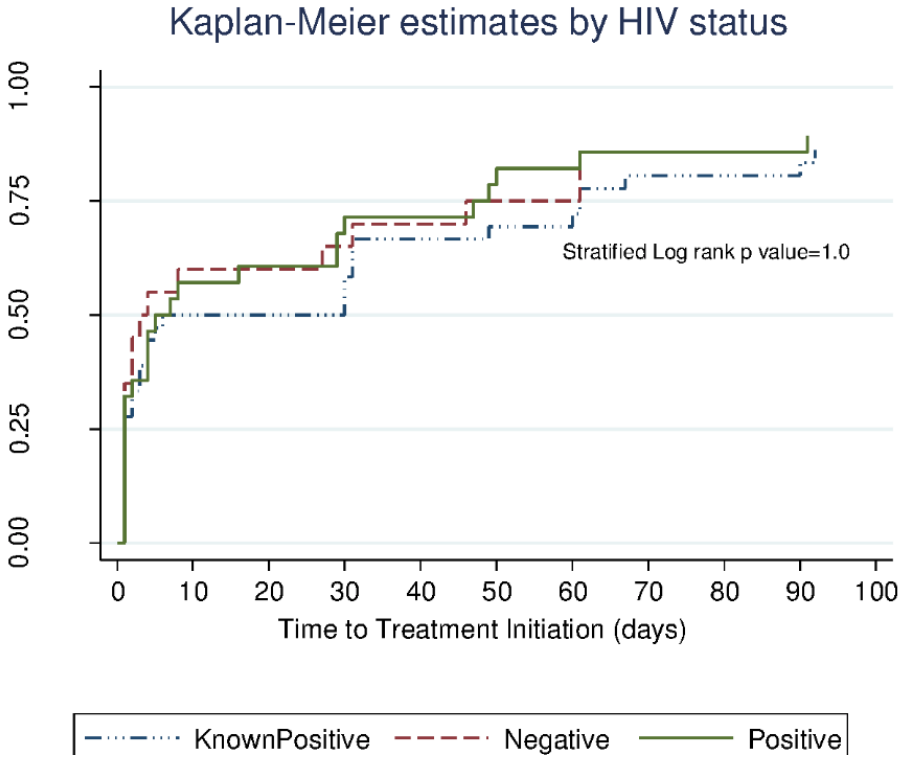


Figure 3.5: Time to Treatment Initiation By HIV Status

Twenty-seven percent (532/1981) of the patients tested negative for HIV. Thirty-six percent of the patients who tested HIV positive were newly diagnosed (516/1449). One of these was labelled as pre-treatment LTFU. Half of the remaining LTFU patients were known HIV positive while the others were HIV negative. However, the pre-treatment LTFU was similar in HIV negative and in HIV positive individuals (p=0.4).

3.5. Discussion

One of the principles of TB infection control is "prevent formation of infectious TB particles". Through administrative controls, this can be achieved. Initiating treatment in TB patients rapidly decreases infectiousness. The time to TB treatment initiation and pre-treatment LTFU play a role in the burden of TB in communities. The longer the time before TB treatment is initiated, the greater the risk of transmission of infection to other members of the communities. Prompt treatment is recognized as an essential part of TB control and has received a lot of focus, but how soon after diagnosis should treatment be started? From a Public Health view delay beyond 30 days is when risk of increased infection becomes significant (17).

In this setting of high HIV and TB prevalence, Xpert placed at PHC's showed a shorter time to treatment initiation when compared to cases diagnosed by laboratory based smear microscopy. These findings are consistent with other studies (3). Xpert at POC resulted in a significantly larger proportion of the patients who were initiated on treatment at their initial visit. Xpert at POC also resulted in a significantly larger proportion of patients initiated on treatment before 30 days and thus reducing the transmission risk of TB. The difference in time to initiation is unlikely to be as a result of different diagnostic tests and most likely reflects the shorter turnaround time and the readily accessible onsite results that the use of POC Xpert testing enables. The use of onsite technology allows for the gap seen between time of sputum being taken and the result linked to a patient to be overcome. Previous studies have shown that an increase in the turnaround time of diagnostic results increases pre-treatment LTFU (15,18).

We showed that a greater proportion of patients diagnosed by Xpert were started on treatment within 30 days when compared to laboratory based diagnosis by smear, despite empiric treatment being given to some patients diagnosed by smear microscopy prior to the results being available. The difference in decreased "early" pre-treatment LTFU is important as once treatment is delayed beyond 30 days from diagnosis risk of ongoing transmission increases

significantly (17). As in the TB-NEAT study (3), we found that the impact of earlier treatment initiation on the pre-treatment LTFU rate decreased over time and that proportions of patients initiated on treatment were similar at 54 days in TB-NEAT and 90 days in our study.
The other factor we identified as being associated with delayed treatment initiation was being male. However, this did not translate to a difference in pre-treatment LTFU rate between the 2 gender groups at 90 days.

Despite the availability of onsite results there was no difference in the proportion of patients with bacteriologically confirmed TB started on treatment at 90 days. The high percentage of confirmed TB patients not initiated on treatment in our study (22.5%) is of concern but not unique. An earlier study from Cape Town, South Africa reported 41% of TB suspects with one positive smear microscopy result did not start TB treatment at the PHC facility where they had been diagnosed (19). We were unable to identify gender, age, or HIV status as risk factors for pre-treatment LTFU.

In areas such as South Africa with high TB/HIV co-infection a high pre-treatment LTFU rate may perhaps be due to early deaths in this patient group as was described by Squire and colleagues (18). We excluded all known deaths from our analysis but did not check death registries to exclude early deaths in our group of patients with pre-treatment LTFU who could not be traced. We did however not find difference in pre-treatment LTFU between TB/HIV co-infected (either newly diagnosed HIV or known HIV positive) and HIV negative TB patients. Furthermore, the low rate of early deaths seen in the patients who had known outcomes suggests that early deaths are unlikely to explain the high pre-treatment LTFU rate in our study. We show that it is not only the TB/HIV co-infected patients who get lost to follow up. With the strong focus on HIV and TB integration, it is important for NTPs to not neglect HIV negative TB patients who may in fact be a larger transmission burden given that they are more likely to have cavitary disease. They also tend to live longer than untreated TB/HIV co-infected patients and so are more likely to transmit infection in the communities (20).

We have shown a high pre-treatment LTFU rate in our study. Unfortunately, this group of patients is excluded from the traditional NTP cohort outcomes analysis and are largely ignored. If TB is to be controlled, steps need to be taken to not only record and report on pre-treatment

LTFU but systems need to be put in place urgently to ensure that these patients are traced and appropriately treated.

There were several limitations with this study. It was not designed to compare Xpert TB/Rif with sputum smear. Also, the number of patients in the smear group was small and the diagnostic method used was not randomly allocated to the participants/tests. This study used secondary data to ascertain the prevalence of and factors associated with initial LTFU in the study area. There was no guarantee that all variables needed were in the dataset and limited the scope of the analysis. Lastly, this study was only carried out in urban clinics and the findings may not represent rural populations. Our results are, however, consistent with previous findings.

3.6. Conclusion

POC Xpert resulted in a significantly greater proportion of bacteriologically proven TB patients being started on treatment within 30 days of presentation when compared to laboratory based smear microscopy. Pre-treatment LTFU rate was found to be high but was not associated with sex, age or HIV sero-status. NTPs should ensure that they have working systems to manage a patient from time of TB suspicion to treatment completion and attention should be given to decreasing the diagnosis-treatment initiation gap (both time to treatment initiation and pre-treatment LTFU)

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Initial Loss To Follow up of Tuberculosis Patients in South Africa: Perspectives of Program Managers

4.1. Abstract

Introduction: Tuberculosis (TB) remains a serious public health problem in South Africa. Initial loss to follow up (LTFU) rates among TB patients are high, varying between 14.9% and 22.5%. From the perspective of patients, documented reasons for this include poor communication between patient and staff after testing, not being aware that results are ready and other competing priorities such as preference to go to work as opposed to seeking healthcare. Ward-based Outreach Teams (WBOTs) routinely conduct home visits to ensure adherence to medication for various conditions including TB. We aimed to explored reasons for TB initial loss to follow up from the perspectives of TB program managers and WBOT program managers, with a focus on the WBOT's (potential) role in reducing initial LTFU, in particular.

Methods: Key informant interviews with five WBOT program managers and four TB program managers were conducted. The interviews were audio-recorded, then transcribed and exported to NVivo 11 software for coding. A hybrid analytic approach consisting of both inductive and deductive coding was used to identify themes.

Results: The age of the nine managers ranged between 28 and 52 years old, of which two were male. They had been in their current position for between 2 to 12 years. Prior to treatment initiation, WBOTs screen household members for TB and refer them for TB testing if need be, but integration of the WBOT and TB programs is emphasized only after TB treatment has been initiated. Counseling of patients testing for TB is not guaranteed due to frequent staff rotations and staff shortages. Participants reported that possible dissatisfaction with services as well as stigma associated with the TB diagnosis could explain loss to follow up prior to treatment initiation.

Conclusion: Program managers view health system related factors such as staff rotations, poor communication with patients and lack of counseling as contributing to the problem of initial LTFU among TB patients. The integration of the WBOT and TB programs is limited to referring suspected cases for testing and patients already on treatment.

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See Appendix 2

4.2. Introduction

Although mortality due to tuberculosis (TB) in South Africa has been declining, the disease still tops the list of the "ten leading underlying natural causes of death, 2014–2016" (1). TB patients already on treatment have been a focus of TB control programs in many countries including South Africa. The emphasis has mostly been on ensuring that patients take their treatment. This has been evidenced from the implementation of directly observed therapy short-course (DOTS).

Initial LTFU rates in South Africa range between 14.9% and 18.0% (2,3). Although this upper limit rate corroborates the rate found in African studies in an earlier systematic review (4), a higher rate of 22.5% was found in a study conducted earlier to this one which was also part of the PhD work in inner-city Johannesburg, South Africa (5). This city is home to economic immigrants from other parts of the country as well as from other countries (6). A study conducted in the Western Cape province, a similar economic hub in South Africa, highlighted mobility and temporary migration as the most common reasons for missed appointments among patients on chronic medication because generally people travel to their homes of origin during the festive season or travel on other planned holidays (7).

There are various reasons for non-initiation of treatment for patients who test positive for TB. Breakdowns in communication between patients and providers are one reason why patients with varying conditions do not show up for appointments at healthcare facilities. A study conducted in different clinical departments at a regional hospital in South Africa found that at least 16% were unaware of their appointment date while 11% were unsure of when their actual appointment date was (8). The lack of proper communication between patient and healthcare provider with regards to next steps was also a cause for initial LTFU in India's TB program (9), showing that the problem is not unique to South Africa. Findings from two other studies conducted in India and Pakistan revealed that patients were not aware that their results were ready at the facilities (10,11) suggesting a breakdown in communication between the patients and the providers with regards to next steps at the time of testing. Poor counseling and general poor healthcare worker attitudes have been shown to contribute to patients being lost to follow up (12). Other reasons for not starting treatment are related to quality of the healthcare services rendered to patients either in form of structural barriers or lack of proper recording and reporting (13–15).

Patient related factors are also a cause for initial loss to follow up. “Being busy with other jobs” was found to be the main reason for non-initiation of treatment in a study conducted in India (16). Lack of motivation for a second visit and having other competing priorities are also reasons for TB patients not getting initiated on treatment (10,17). Other reasons reported are re-treatment, changing residence, feeling ashamed and alcohol consumption (12,18,19). Poverty, lack of education, not having someone to go with to the clinic, consulting traditional healers, social stigma and religious beliefs also contribute to initial LTFU (13,20,21).

In countries like Brazil (with a similar GDP as South Africa), the use of CHWs to take healthcare services to the community has been shown to be beneficial by improving access to services (22) and by reducing infant mortality rate (23). Within the structure of South Africa’s re-engineered primary healthcare (PHC) model are ward-based outreach teams (WBOTs). The WBOTs consist of a Team Leader (often a Professional Nurse but can be an Enrolled Nurse) and 6 CHWs including a Health Promoter (HP) and an Environmental Health Officer (EHP) (24). The WBOTS work within specific geographical areas of PHC facility total catchment areas. Their scope of work is centred on health promotion and prevention of disease. In the TB program, screening, tracing and treatment adherence support is more of WBOTs’ role than treatment initiation. This is part of their work and therefore no incentives are provided for doing this work (25)

The strategy of the South African TB control program is guided by strategies developed by the Department of Health for tackling HIV, STI and TB and is collectively known as HAST. HAST programs at the various levels of governance are managed by HAST managers. Historically, staff supervising TB programs were known as TB managers. Thus, HAST managers who were tasked to supervise the HIV and STI programs became collectively known as TB managers
With regards to TB services, the WBOTs’ work is to identify, support and follow-up TB patients and their contacts (24). We explored reasons for TB initial loss to follow up from the perspectives of TB program managers and WBOT program managers, with a focus on the WBOT’s (potential) role in reducing initial LTFU, in particular.

4.3. Methods

In depth interviews (IDIs) with TB/WBOT program managers were conducted in the City of Johannesburg district in South Africa between August 2018 and February 2019. This city is

inhabited predominantly by migrants (both national and regional) (6). This is a risk factor for loss to follow up of health services. Knowing more about loss to follow up in this region would assist the TB program nationally because South Africa as a whole serves as an economic hub, not only for the Southern African region, but for Africa at large. We defined WBOT Managers as regional coordinators or outreach team leaders for the WBOT program; and TB Managers were the HAST Managers for respective regional areas. The research and its objectives were shared with the respective directorates of the district who then provided names and contact details of 20 managers we could invite to participate in the research. A maximum of three telephonic attempts and one email over a period of five days were made to arrange an appointment before declaring a potential participant "unable to reach." The participants were conveniently selected depending on their availability. All interviews were conducted in English by the first author in the privacy of the participants' respective offices after written informed consent was obtained.

With the participants' verbal permission, the IDIs were audio-recorded, lasting on average about 35 minutes each. The interviewer also took notes. To ensure standardization of topics discussed, an interview guide was developed and used. As prompts to elicit discussions, the guide included the following topic areas: TB communication, WBOT functions and reasons for loss to follow up. Prior to data collection, this instrument was piloted with two managers working in programs other than the TB or WBOT programs and then refined before a final version was agreed upon. These data are not presented. The purpose of the pilot was to ensure that the questions were clear with no ambiguity in them. We wanted to know how best to phrase the questions to ensure clarity as well as the average time an interview would take before scheduling interview appointments.

The audio recordings were transcribed verbatim and the transcripts were systematically coded by the first author using NVivo 11 software (26). A codebook framework of the topic areas was created by the first author. The second author checked the reliability of the coding framework by recoding four of the transcripts using the framework. After this, a hybrid approach (27) was applied to code each transcript, first inductively and then according to deductive codes derived from factors identified in the literature. These were the grouped into themes aligned with the different concepts/topic areas.

4.4. Results

Of the twenty managers on the list provided, seven could not be reached and one manager who was reached by email said he had relocated out of the country. Nine of the twelve managers approached for participation accepted the invitation telephonically. The three who did not participate gave the following reasons for their unavailability: annual leave, illness and other commitments. Five WBOT managers and four TB managers (a.k.a. HAST managers) participated in the study. Participants were between 28 and 52 years of age and seven of the nine were female. Work experience in current position ranged from 2 to 12 years (**Error! Reference source not found.**)

Table 4.1: Characteristics of IDI Participants

Participant	Gender	Program Area	Duration in current position (years)
IDI 1	Female	HAST Program Manager	12
IDI 2	Male	HAST Program Manager	3
IDI 3	Female	WBOT Program Manager	10
IDI 4	Female	HAST Program Manager	7
IDI 5	Female	WBOT Program Manager	3
IDI 6	Female	WBOT Program Manager	2
IDI 7	Female	WBOT Program Manager	11
IDI 8	Male	WBOT Program Manager	8
IDI 9	Female	HAST Program Manager	6

Emerging themes were grouped under the following areas: TB program knowledge, WBOT functions and reasons for initial LTFU.

4.4.1. Knowledge of the TB Program

<u>WBOTs don't know how TB Program works</u>

The managers in the TB program knew how the program worked and how they work with the WBOTs. They were able to describe, step by step the procedure of treatment initiation. A HAST Program Manager (IDI 1) explained that *"We use GXP for testing. We ask patients to come back after 2 days for results".* In contrast, WBOT program managers were less clear. They did not know exactly how the TB program worked in terms of the procedure that is taken when a patient is found to be positive and needs to be put on treatment. *"I…I really don't know*

how they work in the TB program," explained a WBOT Program Manager who had been in her post for 10 years (IDI 3).

4.4.2. WBOT functions

Nature of Work

The WBOTs offer a wide range of services when they do the home visits. In terms of TB service delivery, the WBOTs screen household members for TB as they conduct routine home visits for chronic conditions likes diabetes and hypertension. Any household members with TB symptoms (cough, night sweats, fever, weight loss, etc.) is referred to the nearest facility for TB testing. At the facility, the TB nurse collects sputum from patient and sends to the laboratory for TB testing. A male WBOT Program Manager (IDI 8) had the following to say:

> *"What they do when they go to the household is uuuhhmm…they do screening for TB and they refer patients for TB testing. That's all they do".*

Participants also generally reported that the work of the WBOTs with regards to the TB program starts once a patient is initiated on TB treatment. A WBOT Program Manager with more than 10 years' experience in her program area (IDI 7) explained this:

> *"Those who have already started treatment but default along the way, those are the ones we focus on and we go out and trace them. But those ones who come to test and are told to come back for results...no those we do not focus on."*

Working Together

While TB program procedures were unclear to WBOT Program Managers, both groups of managers understood where their roles overlapped.

For patients not yet on TB treatment, everyone knew that WBOTs are involved in screening of household members for TB during their routine home visits, as reported earlier. There was then a gap between referral and TB patients being initiated on treatment, which is the period when initial LTFU occurs.

WBOTs also support the TB program in offering treatment adherence support during their home visits. During the home visits, they also trace treatment defaulters. The managers described how TB and WBOT programs work together when it comes to defaulter tracing of patients already initiated on treatment. A WBOT Program Manager (IDI7) described this process:

"TB people phone and if patient does not come, then they hand over the list of names of these people to the WBOT members who now go into the community to look for them."

A HAST Program Manager working in her position for seven years (IDI 4) echoed this description.

"For contacts it's not easy for them to come and it's also not easy for us to go to them. But we are working in close contact with the WBOTs."

There were no descriptions on how the TB program works with WBOTs to confirm referrals or to follow up on patients who had not yet initiated treatment.

4.4.3. Reasons for Initial Loss to Follow Up

Poor Communication with Patients

Participants reported that counseling of TB patients was lacking. A HAST Program Manager with six years' work experience in TB (IDI 9) expressed that counseling should be emphasized in a similar way as done in the HIV program.

"I think it's probably…patients are not counselled when they are tested…you know like in HIV. So the patients do not know the importance of starting treatment soon. So they just go home. And remember they test and are given a date when to come back and this is where the gap is. They normally don't come back on their own."

WBOT program managers also acknowledged that the WBOTs only focus on household visits as part of routine work and deal with patients who had visited the facilities only if they are part of the defaulter list that is given to them by the TB nurse for tracing of such patients. A WBOT Program Manager with three years' experience (IDI 5) reported that

"Mostly we are focusing on the household…so maybe if we also focus on the ones in clinic so that the same message goes everywhere, maybe it can work."

Apart from counseling of patients on TB, the general communication between nurses and patients with regards to next steps after testing for TB was also unclear. A HAST Program Manager with 12 years' experience (IDI 1) echoed this and explained that

"……they were not informed. Procedure was not explained to patient".

Health System Barriers

Both WBOT and TB program managers pointed out that the health system was a significant contributor to the problem of loss to follow up. Patient waiting times at facilities need to be

shortened so that this is not used as an excuse for "no-show" by patients. A WBOT district coordinator described how patients *"…give excuses that they are long queues"* as a cause for not starting treatment.

The need for patients to visit clinics to get tested for TB and initiate treatment, if found positive, relates to how nurses' roles are licensed. Despite WBOTs doing screening during the home visits, as indicated earlier, they are not allowed to conduct testing or initiate treatment. They rely on patients to act upon their referrals to facilities. The WBOTs cannot refer the patients to their team leader, if the latter is an enrolled nurse, for treatment initiation because enrolled nurses cannot prescribe medications in the South African healthcare system.

TB Managers expressed that it is important for all facility staff to get familiar with the TB program so that should the TB nurse not be available patient management is not interrupted. It is also important to keep the staff rotation period in a particular program area for longer than the current three months to ensure proper staff training in the respective program area. A HAST Program Manager working in TB for more than 10 years (IDI 1) had this to say

> *"…And then if someone comes to stand in for the TB sister, they will not attend to the patient thoroughly as they're supposed to, sometimes not even informing them about importance of ensuring they come back for the results."*

Participants reported that staff generally do not like to work in the TB room and are reluctant to acquaint themselves with systems and processes on TB patient management. As such, when the TB nurse is absent, either the TB room is locked for the day or the substitute staff member does not adequately manage the patients in terms diagnosis and treatment as well as counseling on next steps. Staff rotations which happen quite often also mean that the new person in the TB room has first to acquaint himself/herself before they can be deemed competent in TB patient management. However, it happens in most cases that as soon as they have settled in, it is time for another cycle of staff rotation. Participants suggested less staff rotation in the TB room and TB patient management education to all facility clinical staff so that continuity of optimal TB patient care is guaranteed.

Patient Responsibilities

Participants reported that patients' behavior is also a reason for their failure to initiate TB treatment. Patient relocation emerged strongly as a reason. A WBOT Program Manager (IDI 6) reported that *"……..patients are always relocating."* They move house and probably start seeking healthcare services at a facility close to their new home. When probed further regarding this, participants attributed the frequent relocating to economic migration of the people in the study area.

The managers also reported that provision of correct contact details is important as this makes it easier for the healthcare system to find a missing patient. According to the TB managers, patients give wrong phone numbers and wrong addresses. Unfortunately, this is only discovered at the point of defaulter tracing.

Patients "shopping around" for better health services was a reason also given by the managers. A male HAST Program Manager (IDI 2) had this to say:

> *"They like to confirm and they will come here and test and if they are positive here they will go to another facility to test. Maybe if still not satisfied, they will go to another."*

Sometimes patients get worse after testing, get admitted to hospital and therefore fail to return for the results. At this point, it is important that a relative or friend informs the facility so that the patient is not labelled as LTFU.

4.5. Discussion

The most critical findings from this study relate to how WBOTs may contribute to reductions in TB initial LTFU in the future. This study revealed that they screen household members for TB and offer treatment support to those already on treatment which are roles stipulated in their scope of work (24). TB nurses give lists of patients who have missed their appointments by over a week to WBOTs who go and trace these defaulters so that they can continue with their treatment. TB initiation is not among the functions of the WBOTs (24), but it could be added to the enrolled nurse function. Patients not initiated on treatment continue to spread TB in the community and thereby increase the TB burden (28,29). In line with task shifting, enrolled nurses in rural clinics of South Africa take on most of the roles of professional nurses (30) with the exception of medicine prescribing. They do not prescribe yet they are at times the Team Leaders for respective WBOTs. To ensure TB treatment initiation, it would be ideal to have a nurse who can prescribe medication. Revision of policy to train and allow enrolled nurses from

the WBOT program to prescribe TB drugs would assist in ensuring that patients start TB treatment promptly.

This study reinforced the two-fold reasons for initial LTFU: health system related and patient related. In terms of health system related factors for patients not initiating treatment, proper and adequate communication with patients is highly essential in ensuring optimal initiation and adherence to treatment. Divija and colleagues reported in their study that poor communication and education to the patient on next steps were reasons for initial LTFU (9). One of our study participants mentioned that it is important to put emphasis on proper counseling and education of patients with regards to TB as a disease. Therefore, it is expected that with optimal patient communication and counseling, patients would know that they need to inform the facility when they are leaving the facility catchment area. That way they can be referred and documented as such. Our findings suggest that training on counseling may benefit existing TB managers as well as WBOTs.

Good quality data in the TB program ensures optimal control of the disease. The design of TB data collection and reporting systems need to be such that they enable responses at the community level that are specific to gaps identified from the data (31). Properly documented records which are frequently updated can ensure that all patients have outcomes; and those missing appointments are timeously identified and appropriately followed up by the WBOTs.

Although Professional Nurses are the preferred team leaders, most WBOTs are led by Enrolled Nurses due to shortage of staff at the clinics. Enrolled Nurses are not licensed to prescribe TB treatment. This means traced patients cannot be given treatment unless they go to the clinic.

Although the patient-related factors were reported second-hand, they still are worth discussing. For instance, a factor such as relocation is not something the health system can control, but it can create systems to reduce LTFU such as ensuring that quality patient contact information is recorded at the time of TB testing (32). City of Johannesburg, where the study was conducted, is South Africa's economic hub and occupied predominantly by economic migrants from both within and outside the country (6). Although the city occupies an area of 1645km^2, it has a population of 4.4 million (33). This dense population could explain the high total headcount numbers and consequent high loss to follow up rates in the healthcare facilities within the city reported in an earlier study (5). A Malawian study looking at initial LTFU of antiretroviral therapy found that high burden facilities were more likely to have higher initial LTFU rates

than low burden facilities and attributed this to inadequate staffing leading to poor patient education and lack of counseling (34). In light of this and of the association between TB and HIV, it is important that the healthcare facilities be adequately staffed. Task-shifting strategies (30), whereby WBOTs could be involved in treatment initiation (such as explaining to patients on next steps after each consultation) to ensure minimal LTFU among TB patients, should be explored.

Another patient related factor that was reported by participants was that patients are tested at different facilities because they want to confirm the diagnosis. Patients go and test at other facilities to see if the result is the same. This finding is corroborated by a recent study that looked at health seeking pathways of patients with drug resistant tuberculosis (35). Courtwright and Turner found that some of the causes of TB stigma were: perceived transmission risk from infected people; poverty; and its association with HIV (36). Patients needing TB services sometimes do not go to healthcare facilities for fear of being labeled as HIV positive and this worsens the stigma around TB.

Among the limitations of this study was the fact that patient-related factors were reported by non-patients (healthcare staff), who are not actually faced with these challenges. Also, there is a chance that the Program Managers could have omitted some information on health system related factors as this would possibly make “bad incompetent managers”.

4.6. Conclusion

Program managers view health system related factors such as staff rotations, poor communication with patients and lack of counseling as contributing to the problem of initial LTFU among TB patients. The integration of the WBOT and TB programs is limited to referring suspected cases for testing and patients already on treatment. We have identified immediate opportunities to improve integration, e.g. engaging WBOTs to follow up with patients who have been tested, but not yet initiated as well as longer-term considerations, such as revisiting licensing rules around enrolled nurses being permitted to initiate TB treatment.

TB initial LTFU can be prevented by addressing health system related factors such as ensuring that patients are counselled, ensuring that competent TB treatment providers are present at all times to attend to patients and implementing policies that reduce stigma and protect TB patients as well as survivors of TB. In addition, there is need for regular meetings between the WBOT and TB programs at various levels of patient care to ensure optimal integration of the two programs.

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Treatment Initiation Among Tuberculosis Patients: The Role of Short Message Service (SMS) Technology and Ward-based Outreach Teams (WBOTs)

5.1. Abstract

Background: In South Africa, tuberculosis (TB) is a public health problem with treatment initiation failure rates varying between 14.9% and 25%. Lack of proper provider/patient communication on next steps after testing, not being aware that results are ready; and other competing priorities are some of the reasons for this failure. We aimed to assess the effectiveness of Short Message Service (SMS) technology and ward-based outreach teams (WBOTs) in improving TB treatment initiation. A 3-arm randomized controlled trial (Standard of care-SOC, SMS technology or WBOTs) was conducted between September 2018 and April 2020. Newly diagnosed TB patients randomly allocated to SMS and WBOTs groups were sent reminder messages (text message or paper slip respectively) that results were ready. Due to unforeseen challenges (financial and impact of the COVID 19 pandemic), implementation was only in two of the eight clinics planned.

Results: 314 TB patients were assigned to one of three groups (SOC=104, WBOTs=105, and SMS=105). Chi-square tests were used to compare proportions starting treatment (primary outcome). More patients in the SMS group (92/105; 88%) initiated treatment than in the SOC group (81/104; 78%), although this difference did not reach statistical significance (P=0.062). The time to treatment initiation was significantly shorter in the SMS group than in the SOC group (P<0.001). The proportions of patients initiated on treatment in the WBOTs group (45/62; 73%) and in the SOC group (44/61; 72%) were similar (P = 0.956). The times to treatment initiation for these two groups were also similar. The 3 group analysis yielded similar proportions initiated on treatment (P=0.048 for SMS/SOC comparison and P=0.956 for WBOTs/SOC comparison) but analysis of times to treatment initiation yielded some variations.

Conclusion: Reminder SMS messages sent to newly diagnosed TB patients improved the time to treatment initiation. Further research is required to show effect of the WBOTs intervention.

Mwansa-Kambafwile JRM, Chasela C, Levin J, Ismail N, Menezes C. Treatment initiation among tuberculosis patients: the role of short message service (SMS) technology and Ward-based outreach teams (WBOTs). BMC Public Health. 2022.

See Appendix 3

5.2. Introduction

Over the past decade, there has been an increase in the usage of mobile cellular phones globally with over 7 billion mobile cellular subscriptions by 2015 (1). Reminding patients through short message service (SMS) technology has been shown to improve adherence to various chronic medications for diseases such as diabetes and hypertension (2–6). This technology is also acceptable among patients who use it (7,8). It has been shown to improve return for appointments (9,10) as well as treatment initiation where messages with results were sent to healthcare workers (11,12).

The model of taking healthcare services to the communities has resulted in decreased infant mortality (13) and improved access to healthcare (14). Ward-Based Outreach Teams (WBOTs) are a cadre of staff (mostly CHWs) in South Africa's re-engineered primary healthcare (PHC) model, who offer services at household and community levels. For TB services, the teams identify, support and follow-up already diagnosed TB patients and their contacts with a minor or no role in treatment initiation (15).

We aimed to evaluate the effectiveness of the SMS technology and WBOTs in increasing the proportion who initiated treatment and in reducing the time to treatment initiation among TB patients.

5.3. Methods

Design

A randomized controlled trial (RCT) was conducted at two public sector primary level clinics in inner-city Johannesburg, South Africa. Participants were enrolled between 10 September 2018 to 25 March 2020 and the last date for follow up was 22 April 2020. The inner-city Johannesburg area has a population of 4.4 million and occupies a 1645km^2 area (16). Using data from the 2017 National TB Control Program (NTCP) report, the 8 clinics with the highest TB notification in the area were selected. Due to unforeseen financial challenges and the effects of the COVID 19 pandemic, the study was only implemented in two of these 8 clinics. These non-fee paying clinics service a generally low income population and offer holistic primary level healthcare services such as family planning, antenatal care and baby care among others.

Participants

The standard clinic practice as per National TB Control Program for South Africa (17) is that all patients accessing any healthcare services in any part of the clinic are screened for TB symptoms. Those found with TB symptoms (presumptive TB patients) are sent to the TB room for testing. During the study period, such patients who were eligible and consented to participation, were enrolled. Patients aged 18 years old and above, not yet diagnosed with TB, and who had submitted sputum to the TB nurse were eligible.

Sample size

It was assumed that the treatment initiation in this study would increase from the 82% average upper limit reported in South African studies (18–21) to 95% in each of the groups with an intervention (with either SMS technology or with WBOTs) as per target of the country's National TB Control Program (17). Based on a power of 80 % and a level of significance of 0.05 to detect an increase in treatment initiation of 13% in either of the intervention groups, we estimated a required minimum sample size of 104 positive TB patients in each group. The trial was powered to detect a difference between the SMS group and the SOC group and also to detect a difference between the WBOTs group and the SOC group, but was not powered to detect a difference between the SMS group and the WBOTs group.

Study Procedures

After obtaining written informed consent, patients meeting the inclusion criteria were interviewed using a pre-piloted structured questionnaire to obtain sociodemographic and clinical data. Their contact details, including mobile phone numbers they could be contacted on, were also recorded both in the TB case identification register and on the study data abstraction form.

To determine the level of knowledge of participants about TB, the following four questions were asked:

- "Before testing this time, had you heard about TB?"
- "Before testing this time, did you know how one can get TB?"
- "Before testing this time, did you know symptoms of TB?"
- "Before testing this time, did you know TB be can be cured?"

Knowledge level evaluation was made based on the number of "Yes" (correct) answers each patient scored. If a patient scored two or fewer correct answers, he or she was classified into

the "none or little knowledge" category; and then those that scored three or four correct answers were classified in the "adequate knowledge" category.
Symptoms of TB were categorized into “mild” and “not mild”. Moderate or severe symptoms were classified as “not mild” a participant was in this category if he/she had all or two of the following: bmi<18.5, coughtime>=2weeks and one or more previous consultations.

Patients were asked to return for results after two days as per national guidelines (17). Using a Stata generated pre-run block randomization sequence (block sizes ranging between 6 and 15) (22), participants who tested positive for TB were assigned to one of the three groups by a researcher not involved in participant enrolment (standard of care (SOC), WBOTs, or SMS). Patients allocated to either the SMS or the WBOTs group received reminder messages telling them that their results were ready at the facility while those in the SOC group did not receive any messages.

The reminder messages were sent through SMS messaging for those in the SMS group and through paper slip messages delivered by WBOTs for those allocated to the WBOTs group. The WBOTs were given the paper slips by the research assistants and they carried during their routine household visits. The paper slips had the physical addresses of the patients and this guided the WBOTs in locating the patients. Up to 3 attempts were made in trying to locate patients before finally labelling the patients as “not found”. Any undelivered paper slips were handed back to the study staff and were recorded. Delivery reports for the messages sent via SMS were noted.

To maintain confidentiality, the reminder message did not state details of why the person was needed at the clinic. In addition, the paper slips were delivered in sealed envelopes. The message was in English or isiZulu depending on language preference selected at study enrolment. The content was the same for both intervention groups and read as follows:
“*Good day, your results are ready at the clinic for your collection. You are advised to collect your results as soon as possible”.*
The TB case identification registers at the clinics were checked regularly for the results of the patients enrolled in the study. The names of those with a positive result were checked for in the hard copy TB treatment initiation registers where patients initiated on TB treatment are captured. This was also confirmed by checking patient details in the TB module of TIER.net

electronic register as well as using hard copy TB files which are opened once a patient is initiated on treatment. Participants with positive TB test results but not initiated on treatment within 4 weeks from the date of TB test were noted. The time to treatment initiation was measured and ascertained by calculating the number of days between date of sputum submission for TB testing and the date of TB treatment initiation.

Investigator and participant blinding

Research assistants checking for the outcomes of the patients were blinded to the different groups to which patients were allocated. They were not involved in randomization, intervention delivery and did not have access to participant data with respective intervention groups. This minimized observer ascertainment bias. Participants were told that they would receive one of the two interventions or neither (standard of care). However, depending on the type of reminder message they received or if they did not receive any message at all, they would be aware of their allocation group. Therefore, blinding was not possible and as such, participant ascertainment bias could not be avoided.

Study outcomes

We defined treatment initiation among TB patients as being started on TB treatment when one was diagnosed with TB. The primary outcome was the proportion initiated on treatment within 28 days from the date of submitting sputum. The secondary outcome was the time (in days) to treatment initiation.

Statistical Analysis

Data were analyzed using STATA® version 14.2 software (22). The study was not powered to compare the interventions against each other, but to compare each intervention against the standard of care (23).

To evaluate the primary outcome, we used descriptive frequency tables to determine the proportions of treatment initiation across the study groups. The proportion initiated on treatment within 28 days was estimated for each study group, and comparisons between proportions were carried out using a chi-square test. In order to estimate the 'risk' ratio for treatment initiation for an intervention group relative to the SOC group; and adjusting for other variables, Poisson regression models were fitted with robust estimation of standard errors, as recommended by Cummings (24). The use of robust standard errors is suggested since the

outcome (treatment initiation) is not rare, so the Poisson approximation to the binomial distribution will not be very accurate, and the usual Poisson standard errors will be too large (since essentially the Poisson distribution allows a participant to initiate TB treatment on more than one occasion). Candidate variables for the models to be used in addition to treatment group (with SOC as the reference level) were marital status, body mass index, alcohol consumption, smoking, monthly income, prior clinic consultation, comorbidities, age, gender, employment status, TB test disclosure, history of TB contact, travel time to the clinic, HIV status and severity of TB symptoms. These candidate variables were chosen from existing literature on variables known to be related to TB treatment initiation. The selection of variables in the final model was based on unadjusted analysis and forward selection of variables chosen by the unadjusted analysis.

We used Kaplan–Meier curves and the log-rank test to analyze the time to treatment initiation across the study groups. The time of submitting sputum for TB testing (date of signing informed consent) and the date of treatment initiation were used to calculate the duration of time in the study. Patients who were transferred out or died before treatment initiation were censored from the analysis. The transferred out patients were censored out at the date of transfer out, while for patients who died (and for whom the exact date of death was not known) or who were lost to follow-up, the censoring date was taken as day 29. The first reason for choosing day 29 for censoring was that research assistants checked for initiation of treatment in both the hard copy TB treatment initiation register and in the TB module of the TIER.net electronic register for 28 days following enrolment. The second reason was so that the Kaplan Meier plots will correctly show that the overall proportion of participants initiating treatment was less than 100%. We used Cox regression analysis to determine associations between treatment group and initiating treatment, adjusting for explanatory variables associated with time to initiation of treatment. The variables selected for inclusion in these models were the same variables that were used in the multivariable analysis for the primary outcome. The proportional hazards assumption was checked using the Schoenfeld residuals. A sensitivity analysis was carried out fitting a Cox regression model with censoring at day 3 rather than day 29 for those participants for whom the date of loss to follow-up was unknown. The “day 3” selection was based on the fact that the national guidelines advise that patients return for results within 2 days of TB testing (17).

5.4. Results

Of the 3147 patients who sought TB services during the study period, 2880 were eligible for enrolment into the study, and 2850 consented to participation (99% response rate).
Eighty-six percent (2448/2850) were negative while eleven percent (314/2850) were positive and 3% (88/2850) of the results were categorized as "other result". "Other result" category consisted of Xpert trace results as well as failed tests due to leakage or contamination.

Of the 88 patients with "other" test results, there were 41 patients with Xpert trace results. At the time of the data collection, the South African national guidelines (17) were not clear on the management of presumptive TB patients with Xpert trace results. As a result, the practice across facilities was not standardized with some facilities treating such patients as TB positive and initiating them on treatment while other facilities waited for TB culture result before confirming the diagnosis. Therefore, patients with such results were not randomized to any group. The 314 TB positive participants were randomly assigned to one of the 3 groups (SOC=104, WBOTs=105, and SMS=105).

Following operational challenges because of the COVID 19 pandemic, delivery of paper slips to the participants randomized to the WBOTs group was discontinued. However, randomization of the participants to the three groups using the predetermined block randomization sequence continued. **Error! Reference source not found.** illustrates the enrolment flow. The writing in *italic* is based on actual implementation numbers based on the WBOTs intervention.

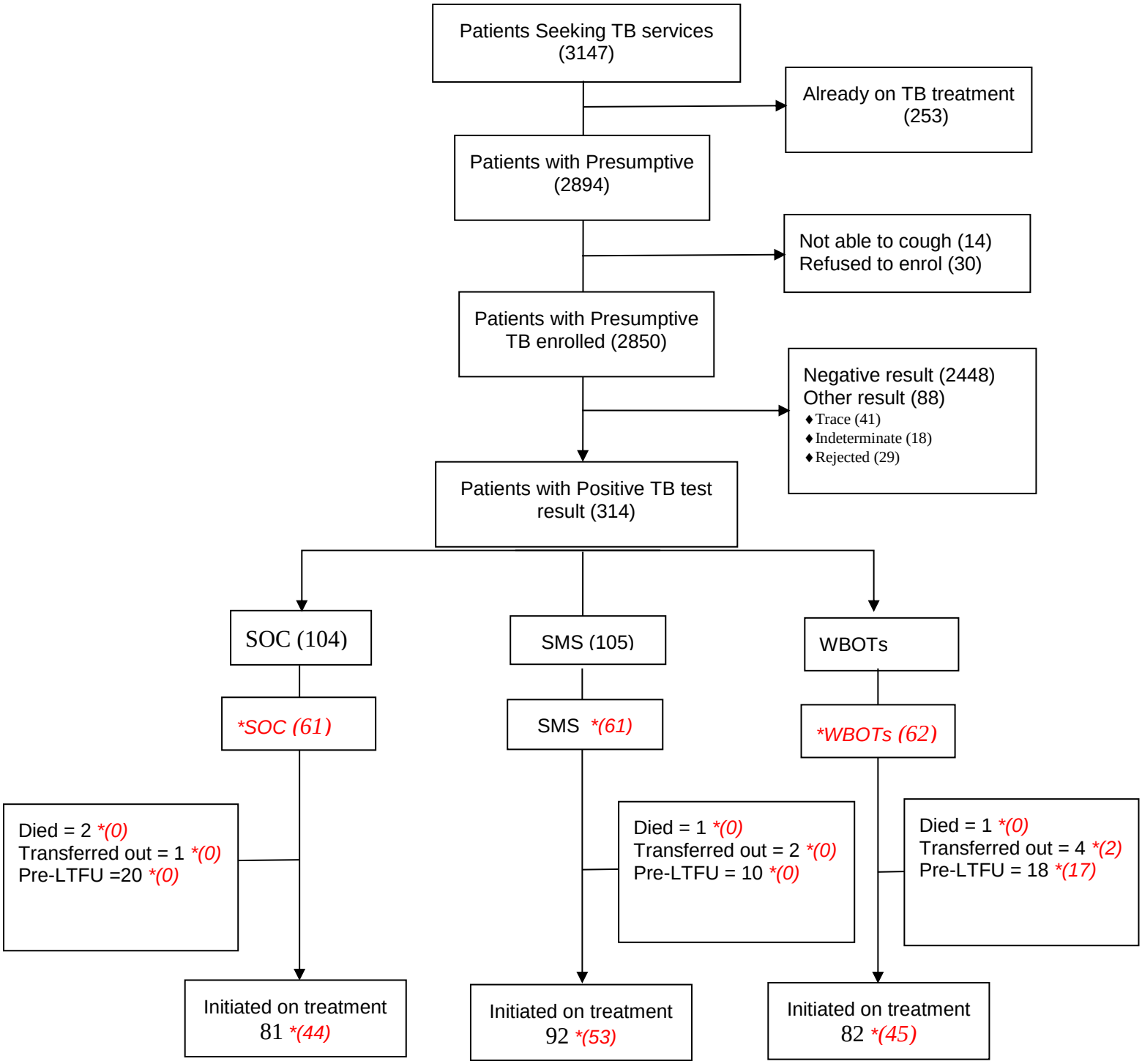


Figure 5.1: Participant Enrolment Flow Chart

**Numbers in line with implementation of WBOTs intervention*

Sociodemographic Characteristics

The three groups were similar in terms of sociodemographic data and therefore comparable (**Error! Reference source not found.**).

Table 5.1: Participant Characteristics

Sociodemographic Characteristics	**SOC (n=104)**	**SMS (n=105)**	**WBOTs (n=105)**
Age category			
<= 30 years n (%)	21 (20)	21 (20)	26 (25)
31 to 45 years n (%)	55 (53)	57 (54)	60 (57)
46 to 60 years n (%)	18 (17)	21 (20)	13 (12)
More than 60 years n (%)	10 (10)	6 (6)	6 (6)
Median age; years (IQR)	37 (31-49)	39 (32-46)	37 (31-42)
BMI range			
BMI<18.5 n (%)	21 (20)	19 (18)	21 (20)
BMI>=18.5 & BMI<25 n (%)	47 (45)	58 (55)	52 (49)
BMI>=25 & BMI<30 n (%)	28 (27)	19 (18)	27 (26)
BMI>=30 n (%)	8 (8)	9 (9)	5 (5)
Median BMI; kg/m^2 (IQR)	22.6 (19.1-26.2)	22.4 (19.4-25.1)	22.4 (19.1-26.0)
Gender			
Male n (%)	57 (55)	62 (59)	64 (61)
Female n (%)	47 (45)	43 (41)	41 (39)
Marital status			
Not married n (%)	86 (83)	87 (83)	86 (82)
Married n (%)	18 (17)	18 (17)	19 (18)
Highest level of education attained			
Primary or lower n (%)	29 (28)	23 (22)	25 (24)
Secondary or higher n (%)	75 (72)	82 (78)	80 (76)
Employment			
Not employed n (%)	45 (43)	50 (48)	47 (45)
Employed n (%)	59 (57)	55 (52)	58 (55)
Financial status			
Median monthly income; ZAR (IQR)	4000 (3000-6500)	4300 (3000-5500)	4400 (3500-5500)
Median # supporting financially (IQR)	1 (0-2)	1 (0-3)	1 (0-2)
Time to clinic			
<= 30 minutes	72 (69)	73 (70)	70 (67)
> 30 minutes	32 (31)	32 (30)	35 (33)
Alcohol consumption			
No	59 (57)	62 (59)	60 (57)
Yes	45 (43)	43 (41)	45 (43)
Smoking			
No	70 (67)	58 (55)	63 (60)
Yes	34 (33)	47 (45)	42 (40)
TB knowledge			
None or little (<=2 correct answers)	39 (38)	36 (34)	41 (39)

Adequate (>=3 correct answers)	65 (62)	69 (66)	64 (61)
Cough duration			
Less than 2 weeks	45 (43)	47 (45)	45 (43)
2 weeks or longer	59 (57)	58 (55)	60 (57)
Prior consultation			
No	85 (82)	79 (75)	84 (80)
Yes	19 (18)	26 (25)	21 (20)
Severity of TB symptoms			
Mild	82 (79)	84 (80)	85 (81)
Not mild	22 (21)	21 (20)	20 (19)
History of TB			
No	86 (83)	86 (82)	83 (79)
Yes	18 (17)	19 (18)	22 (21)
HIV status			
Positive	52 (50)	41 (39)	43 (41)
Negative	43 (41)	41 (39)	38 (36)
Unknown	9 (9)	23 (22)	24 (23)
On ART[#] (n=136)			
No	33 (63)	24 (59)	21 (49)
Yes	19 (37)	17 (41)	22 (51)
Comorbidities			
Diabetes	6 (6)	4 (4)	6 (6)
CVS problem*	12 (12)	5 (5)	2 (2)
Epilepsy	2 (2)	1 (1)	0 (0)
Asthma	1 (1)	4 (4)	0 (0)
Comorbidities including HIV			
No	44 (42)	60 (57)	57 (54)
Yes	60 (58)	45 (43)	48 (46)

*CVS - cardiovascular; [#]ART-Antiretroviral therapy

At least half of the participants in all the groups had been feeling unwell for more than two weeks at the time of presentation to the facility. Over three quarters of each group's participants had not sought medical attention for the current problem prior to study enrolment.

Overall, 43% (136/314) of the participants were HIV positive. Of these, 43% (58/136) were on ART (19 in the SOC group, 17 in the SMS group, and 22 in the WBOTs group). Thirty-one percent (18/58 - 5 in the SOC, 5 in the SMS, and 8 in the WBOT groups) of patients on ART had been on treatment for less than one month at the time they tested for TB. The proportion of patients who were not aware of their HIV status at the time of enrolment was 18% (56/314). Over half (30/58) of the patients on ART were not sure of the names of the drugs they were taking, and about half of these patients (53% - 16/30) had only been on treatment for less than a month.

5.4.1. Analysis of the SOC and SMS groups

This section highlights results of all the 209 patients randomized to SOC group (104) and SMS group (105) during the entire study period.

Proportions initiated on treatment

Three of the 209 patients were transferred out while another three died before treatment initiation. Of the 209 patients, 173 (83%) were initiated on treatment. There were 92/105 (88%) in the SMS group and 81/104 (78%) in the SOC group (P = 0.062). Patients in the SMS group were 12% more likely to initiate treatment than those in the SOC group (RR=1.12; 95% CI: 0.99 – 1.28). This effect size increased in the multivariable analysis (Table 2).

Time to treatment initiation

Patients in the SMS group were 2.8 times more likely to initiate treatment early than those in the SOC group (HR=2.77; 95% CI: 2.03 – 3.77). This effect size increased slightly when adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms (HR=3.29; 95% CI: 2.36 – 4.58) (**Error! Reference source not found.**). The estimates were increased when censoring was done at day 3.

Table 5.2: Treatment initiation in the SMS and SOC groups

	UNIVARIABLE FINDINGS N = 209)			***MULTIVARIABLE FINDINGS (N = 209)**		
	Unadjusted IRR	**Confidence Interval**	**p-value**	**Adjusted IRR**	**Confidence Interval**	**p-value**
Treatment Initiation						
Allocation group						
SOC	Ref					
SMS	1.12	0.99 – 1.28	0.066	1.15	1.02 – 1.31	0.026
	Unadjusted HR	**Confidence Interval**	**p-value**	**Adjusted HR**	**Confidence Interval**	**p-value**
Time to Treatment Initiation (Day 29 censoring)						
Allocation group						
SOC	Ref					
SMS	2.77	2.03 – 3.77	<0.001	3.29	2.36 – 4.58	<0.001
Time to Treatment Initiation (Day 3 censoring)						
Allocation group						
SOC	Ref					
SMS	4.67	3.30 – 6.60	<0.001	5.05	3.48 – 7.33	<0.001

*Adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms

The total analysis time at risk and under observation of the patients was 1357 days. Patients in the SMS group had a shorter time to treatment initiation than those receiving standard of care (SMS-4 days, IQR: 3-5 versus SOC- 8 days, IQR: 5-13). This difference was significant (P<0.001). At least half of the patients who initiated treatment in the SMS group had done so by the 4th day while it took 8 days for those in the SOC group. (**Error! Reference source not found.**).

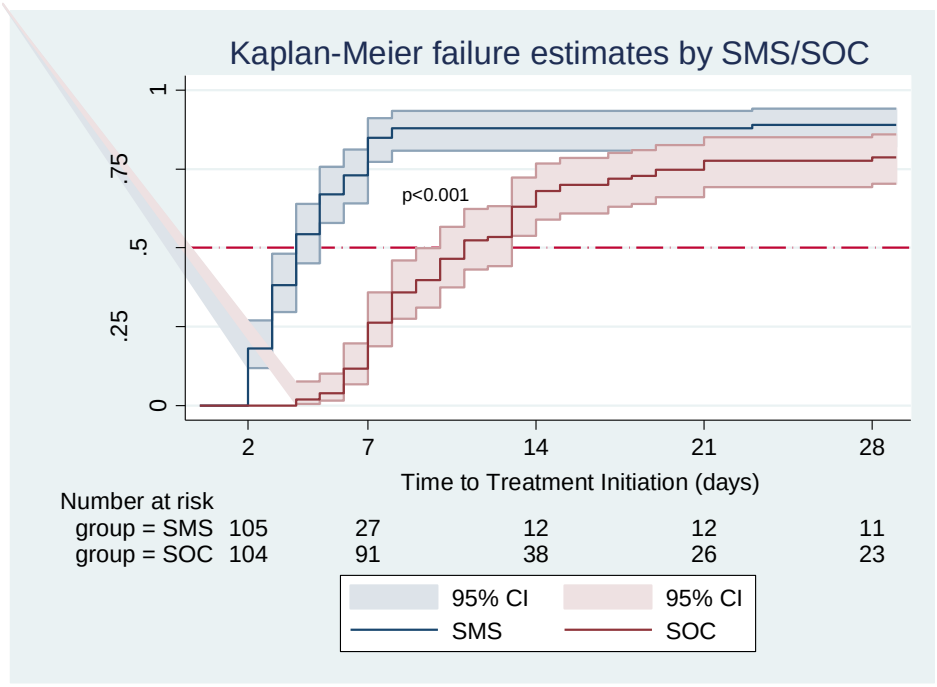


Figure 5.2: Time to treatment initiation for the SMS and SOC groups

5.4.2. Analysis of SOC and WBOTs groups

This section highlights results for SOC and WBOTs groups but restricted to the duration when paper slip reminders were implemented. The total number of patients analyzed was 123 (SOC=61 and WBOTs=62).

Proportions initiated on treatment

Three of the 123 patients were transferred out while two died before treatment initiation. Treatment was initiated in 72% (89/123) of them. The proportions in the SOC (44/61; 72%) and WBOTs (45/62; 73%) groups were similar (P = 0.956). The chances of initiating treatment

among patients in the 2 groups were also similar (IRR=1.01; 95% CI: 0.81 – 1.25). This effect reduced slightly in the multivariable analysis (Table 3).

Time to treatment initiation

At any particular time, patients in the WBOTs group were 18% more likely to initiate treatment than those in the SOC group (HR=1.18; 95% 0.78 – 1.79). When adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms, the effect size was similar (HR=1.11; 95% CI: 0.70 - 1.77) (**Error! Reference source not found.**). The estimates were increased when censoring was done at day 3.

Table 5.3: Treatment initiation in the WBOTs and SOC groups

	UNIVARIABLE FINDINGS (N = 123)			***MULTIVARIABLE FINDINGS (N = 123)**		
	Unadjusted IRR	**Confidence Interval**	**p-value**	**Adjusted IRR**	**Confidence Interval**	**p-value**
Treatment Initiation						
Allocation group						
SOC	Ref					
WBOTs	1.01	0.81 – 1.25	0.956	0.97	0.76 – 1.25	0.830
	Unadjusted HR	**Confidence Interval**	**p-value**	**Adjusted HR**	**Confidence Interval**	**p-value**
Time to Treatment Initiation (Day 29 censoring)						
Allocation group						
SOC	Ref					
WBOTs	1.18	0.78 – 1.79	0.434	1.11	0.70 - 1.77	0.654
Time to Treatment Initiation (Day 3 censoring)						
Allocation group						
SOC	Ref					
WBOTs	1.59	1.04 – 2.43	0.033	1.64	0.98 - 2.73	0.059

*Adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms

The total analysis time at risk and under observation of the patients was 1809 days. Patients in the WBOTs group had a shorter time to treatment initiation (8 days, IQR: 6-29) than those in the SOC group (13 days, IQR: 7-29). This difference was significant (log-rank P<0.001). At least half of the patients who initiated treatment in the WBOTs group had done so by the 8th day while it took 13 days for those in the SOC group (**Error! Reference source not found.**).

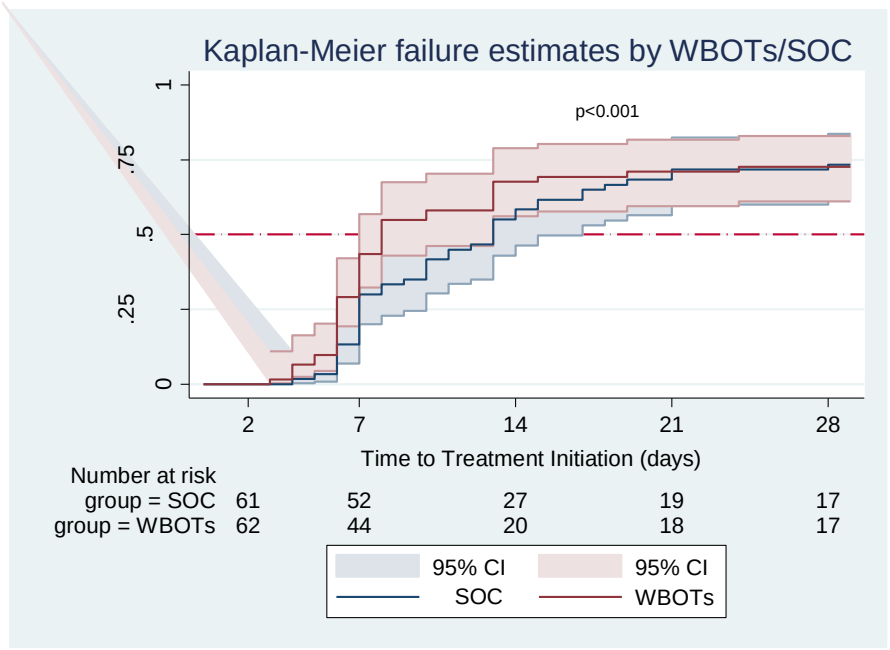


Figure 5.3: Time to treatment initiation for the SOC and WBOTs groups

5.4.3. Analysis of SOC, SMS and WBOTs groups

This section highlights results from all 3 randomization groups (SOC, SMS and WBOTs) but restricted to the duration when paper slip reminders were implemented. The total number of patients analyzed was 184 (SOC=61, SMS=61 and WBOTs=62).

Proportions initiated on treatment

Five of the 184 patients were transferred out while three died before treatment initiation. Treatment was initiated in 77% (142/184) of them. There were 53/61 (87%) in the SMS group and 44/61 (72%) in the SOC group and 45/62 (73%) in the WBOTs group (P = 0.087).

Patients in the SMS group were 20% more likely to initiate treatment than those in the SOC group (IRR=1.20; 95% CI: 1.00 – 1.45) while those in the WBOTs group were 1% more likely to initiate treatment than those in the SOC group (IRR=1.01; 95% CI: 0.81 – 1.58). However, these findings were not significant and the effect sizes for both SMS and WBOTs interventions did not differ much in the adjusted analyses (Table 4).

Time to treatment initiation

At any particular time, patients in the SMS group were 3.3 times more likely to initiate treatment earlier than those in the SOC group (HR=3.27; 95% CI: 2.17 – 4.93). Patients in the WBOTs group were 14% more likely to initiate treatment than those in the SOC group.

However, this finding was not significant (HR=1.14; 95% CI: 0.75 – 1.73). When adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms, the effect size for the SMS group increased slightly (HR=3.53; 95% CI: 2.27 – 5.48) whilst that for WBOTs decreased (HR=1.11; 95% CI: 0.71 - 1.72). The estimates were increased when censoring was done at day 3. **Error! Reference source not found.** show the findings in the 3 group comparison.

Table 5.4: Treatment initiation in the 3 groups

	UNIVARIABLE FINDINGS (N = 184)			***MULTIVARIABLE FINDINGS (N = 184)**		
	Unadjusted IRR	**Confidence Interval**	**p-value**	**Adjusted IRR**	**Confidence Interval**	**p-value**
Treatment Initiation						
Allocation group						
SOC	Ref					
SMS	1.20	1.00 – 1.45	0.048	1.21	1.00 – 1.47	0.049
WBOTs	1.01	0.81 – 1.25	0.956	0.98	0.78 – 1.24	0.883
	Unadjusted HR	**Confidence Interval**	**p-value**	**Adjusted HR**	**Confidence Interval**	**p-value**
Time to Treatment Initiation (Day 29 censoring)						
Allocation group						
SOC	Ref					
SMS	3.27	2.17 – 4.93	<0.001	3.53	2.27 – 5.48	<0.001
WBOTs	1.14	0.75 – 1.73	0.531	1.11	0.71 - 1.72	0.657
Time to Treatment Initiation (Day 3 censoring)						
Allocation group						
SOC	Ref					
SMS	4.61	2.99 – 7.10	<0.001	4.71	2.98 – 7.45	<0.001
WBOTs	1.47	0.96 – 2.23	0.076	1.40	0.88 – 2.23	0.151

*Adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms

The total analysis time at risk and under observation of the patients was 2242 days. Patients in the SMS group had a shorter time to treatment initiation than those receiving standard of care (SMS-4 days, IQR: 3-6 versus SOC - 13 days, IQR: 7-29). Patients in the WBOTs group also had a shorter time to treatment initiation compared to those in the SOC group (WBOTs – 8 days, IQR: 6-29 versus SOC - 13 days, IQR: 7-29). At least half of the patients who initiated treatment in the SMS group had done so by the 4th day while it took 8 and 13 days for those in the WBOTs and SOC groups respectively (**Error! Reference source not found.**).

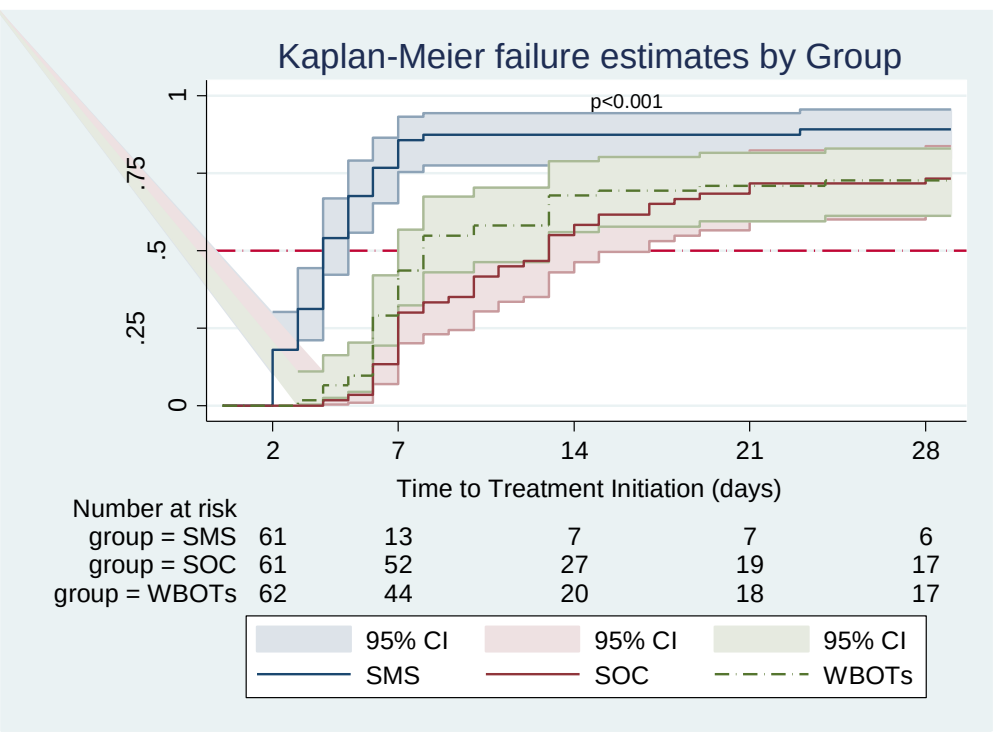


Figure 5.4: Time to treatment initiation for the SMS, SOC and WBOTs groups

5.5. Discussion

We have some evidence that sending reminder messages to presumptive TB patients does ensure that patients diagnosed with TB are initiated on treatment. In the analysis of SMS group versus the SOC group, we found that the proportions of TB patients initiated on treatment in the 2 groups were similar. However, we found that the duration between sputum submission and treatment initiation across the three groups was shortest in the SMS group. Among the ones who initiated treatment in the groups, at least half of those in the SMS group had done so by the fourth day while it took 8 days and 13 days for half of the participants in the WBOTs and SOC groups respectively to initiate treatment.

We found TB/HIV co-infection and ART coverage rates lower than what was reported for South Africa in the 2020 WHO Global TB Report (43% versus 58% TB/HIV co-infection rate and 43% versus 85% ART coverage rate) (25). The low co-infection rate could be explained by the fact that a substantial proportion of patients (18% - 55/314) were not aware of their HIV status. If we suppose that at least half of these patients were actually positive, the total proportion of HIV positive patients would be similar to the national rate reported. The low ART coverage was possibly because some patients had recently been diagnosed with HIV

(29% had been on ART for less than a month) and were being screened for TB before ART could be initiated.

5.5.1. SMS Technology

Although there has been a tremendous increase in mobile cell phone usage over the past decade (1), we were cognisant of the fact that not everyone possessed a smartphone with messaging applications other than SMS such as WhatsApp, Hangout, etc. Therefore, we used the simple SMS messaging platform to cater for people who did not have smartphones. In addition, we opted to keep the process plain and simple by sending a notification message and patients would receive the results at the facilities. Sending actual results to patients and to keep results confidential, would have added some complexity (such as using pin numbers) to the study design process. This could potentially result in patients failing to access their results as was the case in the study by Maraba and colleagues where the majority of the 20% of patients who failed to receive their results reported a lack of understanding of the process (12).

Our findings on the effectiveness of SMS technology corroborate other studies (10–12). The patients in the SMS group were more likely to initiate treatment than those in the SOC group. This was similar to what Wagstaff and colleagues found in their study where recipients of SMS messages were more likely to return to the clinic within the requested 2 days for results than the control group (10). Although we found a reasonable proportion of patients in the SMS group initiated on treatment, the 12% loss to follow up before treatment initiation was still higher than the 5% national target (17). Therefore, there is need for more effort (both on a patient level and on a healthcare facility level) to ensure that all patients diagnosed with TB are initiated on treatment appropriately.

5.5.2. WBOTs paper slips

Our results show similar proportions of patients initiated on treatment (73% versus 72%) and similar durations between testing and treatment initiation (8 days versus 13 days) in the WBOTs and SOC groups respectively. It is important to consider what the work of the WBOTs entails. The scope of TB program related work of the WBOTs puts emphasis on TB screening during household visits for possible sputum testing referral to respective facilities; and on treatment adherence for those already initiated on treatment (15,26). There is no explicit

documentation in their scope of work that speaks to their role in ensuring treatment initiation among all patients diagnosed with TB. Their role is limited to referring symptomatic patients they find during home visits for testing and to ensuring treatment adherence among those already on treatment (15,26). A study conducted among WBOTs and TB program managers revealed that integration of the two programs through regular meetings could improve treatment initiation among TB patients (26).

WBOTs have the potential to play a key role in ensuring treatment initiation among TB patients in communities. In some settings, this cadre of healthcare staff has been pivotal in taking healthcare services to the community level and has contributed tremendously to reduction in infant mortality as well as to general good health status of the population through improved access to healthcare services (13,14).

Although we relied on and utilized the schedule of the WBOTs to send out the paper slip reminders, we tried to emphasize the importance of the study. We also conducted a revision session on the basics of TB since gaps in TB knowledge among CHWs have been found (27,28) and scores in TB clinical knowledge and skills do worsen with an increase in the time since last training (29). A South African study showed that CHWs are willing to conduct TB related work but they do require ongoing tailor-made training and access to TB information materials (30). With adequate capacity building, empowerment and support, the WBOTs can hugely contribute to the success of the TB program.

The SMS and WBOTs interventions are applicable to settings similar to ours. They are also relevant and may be applicable to other settings. They focus on addressing some of the patient-related and healthcare system-related reasons for failure to initiate TB treatment such as lack of communication and forgetfulness.

5.6. Conclusion

Reminder messages to patients do play an important role in TB treatment initiation. SMS messaging is an affordable, feasible option that national TB programs can use. There is need for further research to show effect of WBOTs since implementation of this intervention was suboptimal (fewer patients than planned were exposed to the intervention in this trial). With

proper integration of TB and WBOTs programs, WBOTs have the potential to contribute to improved treatment initiation.

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Experiences of Tuberculosis Patients and Ward-Based Outreach Teams (WBOTs) in Implementation of Interventions to Improve Tuberculosis Treatment Initiation#

6.1. Abstract

Background

In South Africa, the target for Tuberculosis (TB) initial loss to follow up (LTFU) is yet to be achieved (14.9%/22.5% versus 5% national target). Poor provider/patient communication resulting in lack of clarity on next steps, patients not prioritizing their healthcare and patients not knowing that their results are ready at the clinic where test was done are some reasons for initial LTFU. An interventional trial testing the use of reminder messages was conducted. We aimed to explore the experiences of the study participants as well as of the implementers in the trial.

Methods

In-depth interviews were conducted with 10 WBOT members and 15 trial participants. The interviews were audio-recorded, transcribed, and exported to Nvivo 11 for coding and analysis.

Results

The WBOTs were involved in TB screening and in ensuring TB patients on treatment adhered to treatment. Their knowledge of TB improved after the training they received during preparation for the trial implementation. Their involvement in treatment initiation (delivering the reminder paper slips) was something new and possible to incorporate into their daily schedule. The challenges they faced during the trial were similar to what they encountered during their routine work. The TB patients reported fear and worry during the trial when they received reminder messages to go back for their results. TB stigma was one of the reasons for this.

Conclusion

WBOTs have the potential to contribute more to the TB program through their holistic involvement in both preventative and curative medicine including treatment initiation. Policies to reduce TB stigma need to be in place for the reminder message system to work effectively as an intervention to reduce TB initial LTFU

Keywords**:** TB, treatment initiation, WBOTs, paper slips, reminders

 # Submitted to the BMC Public Health

6.2. Introduction

National TB Control Programs (NTCP) in many countries have focused on tuberculosis (TB) patients already on treatment i.e. ensuring that they take their treatment. The implementation of Directly Observed Therapy Short-Course (DOTS) is evidence for this (1).

Poor provider/patient communication resulting in lack of clarity on next steps, patients not prioritizing their healthcare and patients not knowing that their results are ready at the clinic where test was done are some reasons for initial LTFU (2–6). Sending reminder messages to patients who have tested for TB to go back to the health facility for their results is beneficial in both increasing the return rate of patients and in reducing initial LTFU (7,8). SMS reminders have the advantage of delivery in real-time. Another way to remind patients to honour their appointments is by sending paper slip reminders delivered by Ward based Outreach Teams (WBOTs) (8).

The benefits of having the WBOTs as part of the healthcare delivery service in South Africa have been well documented. Since the inception of the re-engineered PHC model, the PHC facilities have been functioning better. A process evaluation conducted in Mpumalanga Province found an improvement in priority indicators like immunisation coverage, treatment adherence, and TB cure rates. Another finding from the survey was a reduction in the utilitsation of the PHC services at facilities since healthcare services are being delivered to the communities (9). Another survey conducted among recipients of the WBOT services in a different province showed a high level of satisfaction with the services (10) even though less than 100% of the community was aware of the existence of WBOTs and their services (11).

The delivery of reminder paper slips by WBOTs has the potential to reduce TB initial LTFU. A trial conducted in inner-city Johannesburg South Africa which tested interventions to reduce TB initial LTFU found an improvement in treatment initiation when SMS reminders were used but the effect of paper slip reminders delivered by WBOTs could not be ascertained due to suboptimal implementation of the intervention (8). WBOTs are a cadre of staff that can be utilized to ensure that patients testing for TB return to the facility for their results. Understanding the WBOTs' exact role in treatment initiation and having insight on what they know about the TB program is a starting point with regards to using this cadre of staff in TB treatment initiation services.

Having knowledgeable and competent CHWs ensures optimal care of patients. In a previous study conducted in Papua New Guinea, CHWs who were assessed on clinical competency obtained low scores which worsened the further away the assessment was from last training. For optimal healthcare service delivery, closer on-site supervision and semi-annual training were recommended (12). Findings from a Malawian study showed that CHWs could not function as adherence supporters due to a lack of knowledge of TB (13). Three other studies also found a lack of TB knowledge as a limitation to CHW work performance (14–16). In Honduras, CHWs were able to manage 80% of local health problems after they were capacitated with knowledge and skills (17,18). CHWs would need some training on TB for them to be treatment supervisors (19).

The views and experiences of research participants in a study testing interventions are unique and their knowledge of the interventions is known to be different from those of professionals and policymakers (20). Assessments of participant satisfaction highlight their perspectives of an intervention (20,21). It is important to consider the experiences of potential recipients of a proposed intervention being tested as there is a possibility of it becoming policy and being implemented. Similarly, the views of trial participants in a study that tested the effectiveness of reminder messages (SMS messages and paper slips delivered by WBOTs) to reduce TB initial LTFU (8) are important to document and need to be considered.

Exploring the WBOTs' and patients' experiences in a trial can potentially contribute to how policy around this problem can be structured and implemented. We aimed to explore the knowledge and nature of the work of the WBOTs concerning TB treatment initiation services and to understand their experience as well as the experiences of the study participants in an interventional trial.

6.3. Methods

This was a sub-study of a 3 arm trial (Initial Loss to Follow Up Among Tuberculosis Patients: The Role of Ward-Based Outreach Teams and Short Message Service Technology) which was conducted in the City of Johannesburg in South Africa between September 2018 and April 2020 (8). In this study, reminder messages were sent to patients who tested positive through SMS and through paper slips delivered by WBOT members: The reminder message read as follows:

"Good day, your results are ready at the clinic for your collection. You are advised to collect your results as soon as possible".

The WBOTs delivered the paper slips during their routine daily home visits. These paper slips were prepared and given to them by the research assistant. The research assistant also sent out the SMS messages from the study mobile phone.

In this sub-study, we conducted in-depth interviews at the 2 clinics where the trial had taken place with WBOT members and with the TB patients who had received reminder messages. Due to unforeseen challenges, the post-intervention interviews were delayed by over 1 year after the parent study had ended. Interviews with WBOT members were conducted between 17 May 2021 and 16 July 2021 while the patient interviews were held between 19 July 2021 and 17 September 2021.

6.3.1. WBOT Interviews

The list of contact details of the WBOT members who were involved in the trial was used to find them and schedule interviews. The topic areas included WBOT functions in the TB program, WBOT challenges, TB program knowledge, and individual experiences of distribution of the paper slip reminders. The first author conducted all the interviews which were held at the participants' respective facilities. The language of communication was English since all participants had at least secondary level education.

6.3.2. Patient Interviews

Contact details of participants from the trial who had tested positive for TB and had received reminder messages were retrieved. These were used to reach out to them for participation. Since this was after the trial had ended and also the patients had completed treatment, they were not being followed up at the clinic. Therefore, the contact with them was via telephone, and they were invited to participate in the interviews. The ones that could be located and were available, were interviewed. The interviews were conducted by the first author either physically or telephonically depending on participant preference. The interviews were conducted in English or Zulu depending on the patients' language preference. The topic areas included emotions, confidentiality, challenges, other individual experiences on receiving the reminders, and suggested recommendations for the TB program.

For both TB patients and WBOTs, semi-structured interview guides were used to allow for probing to get maximum information from participants. The patient interview guide had 2 versions (English and Zulu). The English interview guide was translated to Zulu and then back translated to ensure uniformity of the 2 versions. The participants were purposefully selected based on their availability and on the time frame for the data collection. They were provided with information on the study before they signed consent to participate. After obtaining permission from the participants, the discussions were audio-recorded lasting about 40 minutes each. The audio-recorded data were transcribed and imported into Nvivo software (22) for coding and analysis. The transcripts from the patient interviews which were in Zulu were first translated to English before being analyzed. The transcripts were first read through to get a sense of what each contained. Content thematic analysis was used to analyze the data. Codes and sub-codes were then identified and put into categories. Themes emerged from these categories based on the topic areas of the interview guides. The first and second authors shared the transcripts to agree on the framework and therefore ensure the reliability of the coding framework.

Ethical approval

The University of the Witwatersrand's Human Research Ethics Committee granted ethics approval to conduct the study in October 2017 (M170651). Additional approval by the Johannesburg District Research Committee (DRC 2017-08-0001) was granted and the study was registered on the South African National Health Research Database (GP2017 GP_201708_24).

6.4. Results

6.4.1. Patient Interviews

A total of 167 patients who had received reminder messages (105 SMS messages and 62 paper slip messages). Since this was about 1 year after the parent study had ended, getting a hold of the trial patients was a challenge as some had changed contact numbers while some of the ones that could be reached had either relocated or were not available due to other competing priorities.

Contact was successfully made with 43 of the 167 patients. Twenty-five of them committed to having an interview and 11 of them came to the venue for the interview while 4 were interviewed telephonically. Their age ranged from 23 years to 65 years with the majority being

male (**Error! Reference source not found.**). The effects of the reminder messages were reported using the following themes which emerged (emotions/feelings, encouragement/confidence, and stigma). Participants reported experiencing various emotions upon receiving the reminder messages. Some were happy while others were worried. Participants also reported that receiving the reminder message did influence their decision to go back to collect the results.

Table 6.1: Characteristics of the TB Patients

Participant #	**Age (years)**	**Gender**	**Message type**
P01	27	Male	SMS
P02	61	Female	SMS
P03	45	Male	SMS
P04	35	Female	SMS
P05	35	Female	SMS
P06	45	Male	SMS
P07	35	Male	SMS
P08	32	Male	paper slip
P09	35	Male	paper slip
P10	65	Male	paper slip
P11	24	Female	paper slip
P12	31	Male	paper slip
P13	32	Female	paper slip
P14	23	Male	paper slip
P15	41	Female	paper slip

All the participants had taken treatment for 6 months and the median time to treatment initiation was 7 days (IQR: 4 – 8). Eight participants had received reminder messages through paper slips while 7 had received them through SMS messages.

Emotions/Feelings

Participants reported having experienced various emotions upon receiving the reminder messages. Some were happy that their results were ready and that they would get to know

whether they had TB or not. They said it gave them hope knowing that TB is curable. A 24-year-old female participant who had received a paper slip reminder (P11) had this to say:

> *"It gave me relief that I would finally know what was wrong with me, not knowing was more concerning for me than being told I had TB and starting treatment. I had heard that TB".*

Other participants had negative feelings when they received the reminder messages. They felt unsure, worried or concerned. A 35-year-old female who had received the message as an SMS on her phone (P05) reported that she was worried because she only saw the message some hours after the time displayed on the phone as the time message was received. She was concerned by this as she was not sure if her housemate had seen and read it. She said that her other concern was not being able to go to work if her result was positive. She explained the following:

> *"Yhoo! My housemate is nosy and the fact that my phone was just lying around that day worried me. Although I knew the positive result was not on the message but you never know these things. Also, you know some of us work on commission, so now the thought of what if result is positive meant no work and no money".*

Encouragement/Confidence

The majority of the participants said that the message made a difference to their decision to return to the clinic. Some said that although the thought of going back to collect their results had crossed their minds, the message made them put that on top of their "To do list". A 32-year-old female who had received a paper slip reminder (P13) had this to say:

> *"Working on commission, I just want to work, work and work, no time for other things. So the message made me realize that I need to take time off for my health".*

For some participants, the reminder message they received took away the fear of going back to the clinic for their results. A 23-year-old male who had received a paper slip reminder (P14) had this to say:

> *"I know I am young and I could not stand the news of being told I have TB. So I had no guts to go back there. I just wanted to forget I even took the test. But then the message helped me build that confidence and I thought to myself……oh wow!! These people actually care about me that they are reminding me."*

Except for 3 participants who had received paper slip reminder messages and reported a preference for SMS reminders, everyone was happy with the respective methods in which they

had received the reminder messages. Some of the ones who had received SMS reminders said that they need to be careful not to leave their phone to ensure no one else sees the message but them. Likewise, some of the ones who received paper slip reminders said it is best if they are home to receive the paper slip themselves.

A 41-year-old female who had received an SMS reminder (P04) reported that stigma was the main problem with receiving the message. She said"

> *"You know if people know you have TB it is a problem. So you don't want to be seen going to a TB clinic otherwise the whole community will be talking behind your back and they will not want to have anything to do with you."*

6.4.2. WBOT Interviews

Of the 20 who had been involved in the trial, a total of 10 WBOT members participated in the interviews (adequate for qualitative research). Participants were aged between 25 and 50 years old and the majority were female (7 out of 10). In terms of duration of work experience as a WBOT member, 2 years was the shortest whilst 18 years was the longest duration (**Error! Reference source not found.**).

Table 6.2: Characteristics of WBOT members

Participant	Gender	Age (years)	Duration as a WBOT member
IDI 1	Female	30	5
IDI 2	Male	29	3
IDI 3	Female	41	10
IDI 4	Female	50	15
IDI 5	Male	28	3
IDI 6	Female	25	2
IDI 7	Female	32	7
IDI 8	Male	49	18
IDI 9	Female	27	4
IDI 10	Female	37	6

Nature of work, achievements, and challenges

Participants reported that their usual work involves going from house to house to ensure everyone who is on treatment for any chronic condition takes their medication. They said that

a typical day starts with them working within the facilities for about 2 hours before they go out in the field. Every week, the WBOT leader allocates the team members to different unit areas in the facility such as family planning, chronic diseases, and paediatrics. They assist the nurses working there with whatever they are asked to do for example giving sputum bottles to patients with presumptive TB.

For their fieldwork, the nurses give the WBOTs lists of patients to visit on particular days. They move in groups of 5 or 6 people. During the household visits, they do different tasks depending on what they find. They also check that patients are adherent to their treatment.

A 30-year-old female participant with 5 years' experience (IDI 1) said that*:*

> *"If we find that there is someone who is having diabetes, we do education about diabetes……. And we also distribute condoms"*.

With regards to TB-related work, this participant said that they conduct symptomatic TB screening and advise those with TB symptoms to go to the facility for further tests. She explained as follows:

> *"Our forms have a TB screening there. There are questions..... "Is there someone who has a cough for more than two weeks?" or "Sweating, Loss of Appetite?." Yeah. We have to ask those questions. If yes, then we will start educating them. We refer them to the clinic if there is someone who is coughing more than two weeks, coughing up blood, we refer them."*

The WBOTs reported that they feel their good deeds yield blessings. A 37-year-old female participant who had been a WBOT member for 6 years (IDI 10) had this to say

> *"Now he is okay. He is working. He is getting a R7000 salary here. He is very happy. Anytime he sees us he buys us cool drink."*
>
> Patients relocating without communicating with the facility, walking long distances, and having low income were some of the challenges the WBOT members highlighted. Low income is a potential source of job dissatisfaction. A 29-year-old male participant (IDI 2) reported that *"The only thing is the salary. We are on a stipend. So it's making us not to like our jobs sometimes. You understand? That's the problem".*

It was also acknowledged by the participants that the challenges they encountered prior to their involvement in the study such as transport and language barrier were still present during the study period. Sometimes the homes they needed to visit were far apart and they had to walk.

With regards to the language barrier, some of the households had foreigners who were not able to hold a full conversation in any of the South African languages. This made communication quite difficult. An additional challenge to this was that the majority of the foreigners seem to prefer to seek healthcare services from local private doctors. A 32-year old female participant working as a WBOT member for 7 years (IDI 7) said that it is important for foreigners to have valid residence permits when they went to the facility and she expressed the following:

> *"Valid papers. Valid papers when I say Valid papers: passport, asylum, ID but it should be valid. So if you don't have a valid paper here they don't care if you have TB or what they'll send you out".*

She further recommended the deportation of TB patients that were foreign nationals as a solution. She added:

> *"The only thing that we need to do, is to have another new strategy. If you identify someone with TB neh, you call metro police, you snatch the person, you put them together, and send them to their country, you understand?".*

Other challenges encountered in their daily duties were the high crime rate in the area and that they move in fear. Because they are not officially employed, they do not have health insurance and this further imposes a further risk to their wellbeing. A 50-year-old participant with 15 years work experience (IDI 4) narrated the following:

> *"We are always reminded that we are not covered. If a dog bites you, if you see a house with a dog it's your own risk if you enter that house because when the dog bites you, we don't have medical aid. And then when they rob you or rape you or when you break your leg, or the car hits you, it's your own risk".*

TB knowledge

Participants admitted to having insufficient TB knowledge before the trial was conducted. They neither had sufficient knowledge of the disease nor did they know exactly how the TB program operated. They knew that TB is a disease and that one needs to take medication once diagnosed with it. However, some of them did not know details of how TB is diagnosed and the types of TB. Through the basic TB training offered before the fieldwork of the trial, they were able to consolidate their TB knowledge as well as understand how their role as WBOTs fits into the TB program. A 25-year-old (IDI 6) participant shared the following:

"Before the study, what I understood was that to know if it is TB we test only the sputum. And results come back after 2 weeks….uuuhhm..actually I was confusing what the 2 weeks was for. But now I learned that the 2 weeks is for waiting to start ARVs if on TB treatment and that it is 2 days for the result to come"

Experience of the paper slip distribution

The participants reported that the process of distributing the paper slips for TB treatment initiation was new. They said it was quick although sometimes they needed to go back in case they did not find anyone home.

The WBOTs reported that distributing the reminder paper slips was not very different from their daily work. They still needed to go to the houses in the area with or without the paper slips. A 41-year-old female participant (IDI 3) explained her experience saying:

"In my 10 years of this work, I have not done something like this but it is good because it is not extra. Plus, I didn't have to talk much explaining things. I just had to ask for the person and give the paper".

6.5. Discussion

The findings show that the WBOTs have an important role in the healthcare system. Their contribution is in both preventative medicine (through contact tracing) and curative medicine (through their treatment adherence monitoring). With regards to TB-related work, our findings were similar to what program managers reported in an earlier study (23). The WBOTs screened household members for TB and referred those with TB symptoms to the facility for further testing and confirmation of the diagnosis. They also traced and conducted adherence counseling for TB patients not honoring their respective follow-up appointments at the facility. This study, like an earlier South African study where CHW training on comprehensive TB/HIV/PMTCT integrated care, showed increased uptake of TB services and linkage to care (24), and explored the integration of services. It has shown that the WBOTs' role in linkage to TB care, in particular treatment initiation, is possible and beneficial but is an area needing exploration. WBOTs can be utilized to deliver reminder paper slips informing patients to collect their TB test results from the facilities. This would further strengthen and fulfill the motto of "taking healthcare to the community".

We found that knowledge of TB as a disease and generally how the TB program works was not a strength of the WBOTs before their training and involvement in the trial. This was not

surprising since TB training is not always done (13) and it has been documented that scores on knowledge of TB are low among CHWs and these can worsen with increased time since last training (12). It is important to acknowledge that TB knowledge capacity building of the WBOTs is the first step if we have to achieve the objective of improved linkage to care in the TB program.

Some of the challenges that WBOTs encounter in their daily duties which we found were patient relocation and lack of communication. Some patients already being followed up would not inform the WBOTs of their intention to relocate. This was also a problem during the distribution of the reminder paper slips as information that the patient had relocated would only be known once WBOTs were at the respective houses and neighbors or new occupants would tell them that the person they were looking for had moved out. On the other hand, the lack of communication was a result of the language barrier due to some patients being foreign nationals and not being able to speak local languages or communicate effectively in English. This finding of the failure to communicate in this study is bordered on the patients' failure to communicate which is a contrary finding in previous studies that found that the healthcare providers' failure to communicate effectively was the reason for patients' failure to initiate treatment (2,23,25). Other challenges the WBOTs faced in their work were safety and low income. They received monthly stipends which they said were not given regularly and were not enough. The stipend payments are said to range between R1 800–R3 500 per month (26). This finding of inadequate and irregular payment of stipends is similar to a previous study conducted in another province in South Africa (27). The WBOTs also said that their job was risky. They reported that their fears range from dog bites to theft and for the females, even the threat of rape. They said they did not have health insurance cover as this was not covered in their work contract and that they could not afford medical aid premiums.

The WBOTs mentioned that transport was also a challenge as they had to walk long distances to cover the allocated number of households and with little income, this burden was no lighter. The use of mobile technology would probably help WBOTs communicate with the patients they did not find at their respective homes in case the patients were not far away but within the neighborhood. That way, the trip would not be a wasted one. This would improve their performance as was shown by Braun and colleagues in their systematic review study (28).

A qualitative study on perceptions of the role of WBOTs with key informants conducted in Kwa Zulu Natal, South Africa revealed that although WBOTs deliver chronic medication, their work schedule was unclear (29). Therefore, there is a need to understand the actual role of the WBOTs and in particular, with regards to TB services. In addition, following up people who have had a TB test and ensuring that they are started on treatment should be a task for all WBOT members. Implementation of WBOT work is limited by difficulties with formalization and training of CHWs and appropriate task shifting to nurses (30). It is therefore not surprising that their TB knowledge is low. Research conducted in both urban and rural parts of the Free State Province of South Africa showed that about a third of the CHWs had not received TB training assessing over half of them had no formal training on HIV counselling and testing (13). The contribution of this cadre of staff to the TB programme could be enhanced with training and supervision (31,32).

An important finding from this research which will require further engagement by immigration and health authorities so as to inform policy direction is the issue of access to TB services for foreign nationals. This includes both legal and illegal immigrants. Because TB is prevalent in South Africa and can be transmitted in public places especially in places of overcrowding, anyone can get the disease. It is important that TB patients are put on treatment to reduce transmission. Therefore, if foreigners are denied access to healthcare, they will not be put on treatment and will spread the disease to other people around them, including indigenous South Africans. There is need for policy guidance regarding this issue so that everyone is protected against TB.

The TB patients who were interviewed reported that they had experienced various emotions upon receiving the reminder messages. Some were happy while others were worried. Being happy was probably associated with the peace of mind that comes with knowing that they will understand their health status better. Those that were worried were probably pessimistic and thought of the worst of their illness.

Another contributing factor to being worried could have been associated with the stigma around TB. Studies have shown that TB stigma does exist and have explained its cause to the link between this disease and HIV/AIDS (33,34). The patients in our study reported that there was no way of knowing if anyone, other than themselves, had seen the reminder message and this

worried them. We also found that despite the worry of receiving the reminder messages, participants did not mind how they had received the reminder messages (paper slip or SMS). Participants also reported that receiving the reminder message did influence their decision to go back to collect the results. The study area is populated with migrants, who in some instances, do not possess valid residency permits and this does impact their health seeking behavior (35). Therefore, they work mostly as casual laborers with little or no sick leave benefits. Because they need the income, some choose to go to work instead of seeking further healthcare services for fear of a positive TB test result and the subsequent loss of income.

During the initial phase of the COVID 19 pandemic, most services (including TB services) offered at health facilities were disrupted due to the national lockdown restrictions. The impact of the pandemic on the TB care cascade was as follows: the TB testing numbers were reduced due to fewer people seeking healthcare services and also due to healthcare facilities prioritizing COVID 19 testing to TB testing. Patients presenting with cough were investigated for COVID 19 only and not for TB (36).

The delay in conducting the post-trial patient interviews as a result of the COVID 19 pandemic impacted negatively on the data collected. Firstly, the number of patients interviewed was small relative to the total number of participants in the trial who had tested positive for TB. However, this sample was adequate to answer the objective using qualitative methods. Another limitation in this study was the inability to hear voices of the ones who were lost to follow up. This can create gaps in understanding the issues around the topic. Also, there is a possibility that recall bias could have affected the quality of the responses from the participants since there was at least 12 months between trial participation and these post-trial interviews.

6.6. Conclusion

The experiences of both the TB patients and of the WBOT members who participated in the trial on interventions to reduce TB initial LTFU point to the benefits of the interventions as well as to the need to review the scope of work and the conditions of service for the WBOTs. Participants experienced different emotions when they received the reminder messages. TB stigma needs to be eradicated for the benefits of the interventions to be appreciated.

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Discussion

TB is still a public health problem in South Africa. This is despite the tremendous efforts by the national TB control program to reduce the burden of TB in the country. Prevention of TB (through contact tracing and prevention therapy especially in HIV co-infected patients) and adherence to TB treatment have for a long time been the focus of the national TB control program. Despite having a national target of less than 5% TB initial defaulter rate (1), there has not been adequate attention paid to patients who test TB positive but not started on treatment.

The results of this PhD work have shown that measures to ensure all TB patients initiate treatment can be put in place to control this deadly, yet preventable and curable disease. The risk of transmission of infection from the patient to other members in the communities increases with increase in duration before TB treatment is initiated (2). Patients with pulmonary TB produce infectious particles as they cough. Prevention of the formation of infectious TB particles is one of the principles of TB infection control which can be used in the control of this disease. Initiating treatment in TB patients is an administrative control measure that rapidly decreases infectiousness. TB patients initiated on treatment stop producing the infectious particles and consequently stop being infectious about 2 weeks after initiation (3,4). A reduction in infectiousness means less transmissibility and therefore a reduction in the burden of the disease in communities.

This PhD work looked at reminder messages to newly diagnosed TB patients as an intervention to promote treatment initiation. This chapter discusses the results obtained from each of the objectives of the PhD work.

7.1. Initial LTFU rate and the time to treatment initiation among patients tested for TB at PHC facilities in inner-city Johannesburg

The results from the first objective quantified the problem of initial loss to follow up among TB patients in the study area. An overall 22.5% initial LTFU rate was found (5). The migratory nature of the population is a possible contributor to the high initial LTFU rate. Being the economic hub of South Africa, Johannesburg is occupied by people from different parts of the country as well as from other countries who are there for work but occasionally return to their homes to visit their families (6).

The data used for this objective were collected before the Xpert TB diagnostic test was rolled out at centralized laboratories nationwide and therefore smear microscopy was the routine test used in the TB program. The finding of no difference in proportions initiated on treatment at day 90 post submission of sputum for TB test was contrary to the expectation that a point of care TB diagnostic test translates to improved treatment initiation amongst those diagnosed with the disease. The superiority of Xpert at the point of care is evidenced at the initial visit as well as the period before 30 days from the sputum submission date where there is a significantly larger proportion of the patients initiated on treatment in this group compared to the smear microscopy group. The fact that results were available onsite soon after sputum submission could explain this.

The time to treatment initiation analysis also shows that Xpert at the point of care is superior to smear microscopy. There was an improvement in two indicators (proportion of patients who initiated treatment before 30 days and the relatively short time to treatment initiation). These could contribute to reduced transmission of TB (2–4).

Another major finding was the HIV status of the participants. Due to the dual epidemic and the syndemic relationship between TB and HIV, there is a nationwide emphasis and campaign on the integration of TB and HIV services. Analysis of initial LTFU rates and early mortality rates in this study showed no difference in the comparison of the HIV positive versus the HIV negative TB patients. This finding is similar to the findings of the prevalence survey which was conducted in South Africa between 2017 and 2019 (after this study was conducted) (7). The latter is an important group that does not receive as much attention and care as the TB/HIV co-infected patients. If not initiated on treatment, they contribute more to the burden of disease due to cavitary disease presentation (8). This means that national TB control programs need to ensure optimal and timely treatment initiation among newly diagnosed TB patients who are HIV negative in the same way that they do for the HIV co-infected TB patients.

7.2. Reasons for initial LTFU from the perspective of TB Program Managers and WBOT Managers

This qualitative study revealed what managers of the TB program and those of the WBOTs program thought about the problem of initial LTFU among TB patients. The reasons for initial LTFU are either patient-related or health system-related. The former was not possible to

ascertain firsthand from this study. However, the study did provide information on health system-related factors which, if addressed, could also address some of the patient-related factors. The recording/capturing and storage of patient information is a health system-related factor (9) which if done properly, could be a solution to the problem of "no-show" for appointments by patients for example due to relocation. The patients can be contacted telephonically or physically if they do not return for appointments provided their contact details and appointment date are properly captured and their files are timeously checked. TB data collection and reporting systems need to be designed in such a way that gaps identified from the data are resolved using responses specific to the gaps (10).

Proper counselling and education to patients by clinicians was reported by one of the managers as a solution for the initial LTFU. This is supported by the fact that Divija and colleagues found poor communication and lack of education among patients seeking TB services in India as a cause for initial LTFU (11). Therefore, if there is effective communication between clinicians and the patients, the latter can make the effort to inform the facility when they decide to relocate. That way, such patients can be transferred out accordingly and not labelled as initial LTFU patients. This is another way that solving a health system-related factor also serves as a solution for a patient-related factor for initial LTFU.

There is limited integration between the TB and the WBOT programs. The role of the WBOTs in the delivery of TB services is limited to TB symptomatic screening and adherence to treatment, with no role in treatment initiation (12). Although WBOTs are led by professional nurses, it is not uncommon to have enrolled nurses lead the teams (12). It is also worth noting that, except for drug prescriptions, enrolled nurses working in rural areas of South Africa take on roles of professional nurses due to a shortage of the latter (13). Therefore, there is a need to consider having enrolled nurses who are part of the WBOT program be allowed to prescribe TB drugs. Furthermore, the other members of the WBOTs could complement the work of the enrolled nurses in their respective teams by counselling and explaining to patients on next steps after a consultation. This would broaden the WBOTs' scope of work to include TB treatment initiation and therefore reduce initial LTFU.

Another indication of limited integration between the WBOT and the TB program in this study was when one of the participants who was a WBOT manager reported that she was not familiar

with how the TB program operated. TB knowledge in the WBOT program as a whole seems to be inadequate as was found in a South African study that looked at TB knowledge and competence among CHWs who are an integral part of these teams (14). Regular training of WBOTs on TB as a disease as well as how the TB program operates would ensure this cadre of staff is adequately capacitated to support the TB program optimally.

Participants also reported "shopping around" as a patient-related factor to initial LTFU among TB patients. This is where patients keep getting tested at different facilities (including the ones outside their catchment area) after receiving an initial TB positive result with the hope of getting a negative TB test result. This finding in this study is similar to the findings reported by Bhattacharya and colleagues who looked at health seeking pathways of patients with drug resistant tuberculosis (15). An explanation for this "shopping around" could be stigma. The association of TB with HIV was one of the causes of stigma which was found in a systematic review of the literature on TB stigma (16). For some patients, stigma leads them to hiding their symptoms and not seeking healthcare services in time (17). This delay in seeking healthcare services can result in symptoms worsening and this becomes a barrier to seeking healthcare (18).

The impact of TB stigma goes beyond the period of illness and the patients' households. TB control programs can advocate protecting patients from stigma by aligning national policies to the WHO End TB Strategy of "zero suffering" (19). Sensitizing employers to support employees with TB and also to promote employment opportunities for TB survivors is one of the ways to raise global consciousness around the TB stigma (20). This is very important especially for areas with economic migrants.

7.3. The effectiveness of WBOTs/SMS technology in reducing initial LTFU among TB patients.

The findings from this 3-arm (SOC, WBOTs or SMS) individual randomized controlled trial show some benefits of sending reminder messages to presumptive TB patients. Among other challenges, the stop in implementation of the interventions during COVID reduced the sample size making it difficult to see the effects of the interventions. The proportion of patients initiated on treatment in the SMS arm was similar to the one in the SOC arm (P = 0.062). A comparison of the time to treatment initiation from the time of sputum submission across the three groups

showed that the SMS arm had the shortest time. Treatment was initiated by the fourth day in at least half of the patients in the SMS arm. This time was longer for patients in the WBOTs arm (8 days) and for those in the SOC arm (13 days).

SMS messages

The use of mobile cell phones has increased over the past decade (21). However, not everyone owns a smartphone with advanced messaging platforms such as WhatsApp and Hangout. This PhD work used the simple SMS messaging platform to cater for people with simple basic phones. The message sent was to inform the patient that the result was ready and the patient was advised to return to the facility to collect the results. The message did not contain any results. Sending results in the SMS message would have entailed putting complex measures (such as using pin numbers) in place to maintain confidentiality. Such complexity could result in failure to access results. This was a finding in the study by Maraba and colleagues where participants reported that their lack of understanding of the process was the cause of failure to access results (22).

As was found in prior studies (22–24), a comparison of participants in the SMS and SOC arm showed that the ones in the former arm were more likely to initiate treatment than the ones in the latter arm. Wagstaff and colleagues also had a similar finding in their study where they had more participants in the SMS arm return for results within 2 days of testing (23). A 12% loss to follow up before treatment initiation was found in the SMS arm of this trial. Although this was better than that found in the SOC arm (22%), it is still higher than the 5% national target (1). This shows that there is still work to be done in order to achieve the national target and this work should entail efforts, not only at the patient and facility levels but also at policy-making level to ensure optimal TB advocacy.

WBOTs paper slips

The trial results show similar proportions of TB patients initiated on treatment in the WBOTs and SOC groups (73% versus 72% respectively). Durations in the two arms between testing and treatment initiation were similar (8 days in the WBOTs arm and 13 days in the SOC arm). There are two plausible explanations for these results. Firstly, the COVID 19 pandemic started during the data collection period. The WBOTs were unable to continue with delivery of the paper slips due to the national lockdown restrictions that were put in place as part of South

Africa's disaster management. Therefore, the implementation of the WBOTs was suboptimal and this reduced the sample size to see a difference. Secondly, a consideration of the WBOTs scope of work is worth noting. Their TB program related work entails TB screening during routine household visits. During these visits, household members are asked if they have any TB symptoms, and the ones found with some are referred to respective facilities. The WBOTs also ensure that the TB patients already initiated on treatment adhere to their treatment (12,25). Their role in the initiation of TB treatment is limited, if not non-existent. The interviews with managers from the WBOTs and TB programs, conducted prior to the trial, revealed that regular meetings between the two programs could improve their the integration and consequently improve treatment initiation among TB patients (25). For optimal functioning of the TB program, there is need for integration of the WBOT and TB programs.

CHWs, who are the majority in a WBOT, are an important cadre of healthcare staff who take healthcare services to the community level. Through them, there has been improved access to healthcare services and this has ultimately led to reduced infant mortality and general good health status of the population in some settings (26,27). Because they are willing to conduct TB related work, WBOTs could play an important role in TB treatment initiation in communities. However, they need to be supported through training and provision of information materials if they have to function optimally (28). However, adequate capacity building, empowerment, and support would have to be employed for this to be achievable. This is because TB knowledge among CHWs is low (14,29) and their scores in TB clinical knowledge and skills deteriorate with time since the last training increases (30). In light of the above and although the trial was pragmatic, the WBOTs were trained on the basics of TB at the start of the trial. This was to ensure they had basic TB knowledge, were familiar with the TB stationery, and understood the TB care cascade for patients.
Addressing patient-related reasons and healthcare system-related reasons for failure to initiate TB treatment can help prevent TB initial LTFU.

7.4. Experiences of TB patients and of WBOTs during the implementation of the SMS and paper slip reminders to TB patients.

Due to the COVID 19 pandemic, the randomized trial ended prematurely and the data for this piece of the PhD work were collected about 16 months into the pandemic. The interviews were conducted with WBOT members who had participated in the distribution of paper slips with

the reminder message. Interviews were also conducted with TB patients who had been enrolled in the trial. At the time of the TB patient interviews, the patients had completed their respective treatment courses and therefore were no longer TB patients per se, but were previous TB patients who had participated in the trial during the time they were on TB treatment. The delay in conducting the interviews on the patients and health care workers could have resulted in recall bias.

7.4.1. WBOT Interviews

The findings from the WBOT interviews show that in terms of their general role, the WBOTs play an important role in the healthcare system. Their contribution is in both preventative medicine (through contact tracing) and curative medicine (through their treatment adherence monitoring). With regards to TB-related work, the findings were similar to what program managers reported in an earlier study (25). In the trial, the WBOTs did their routine work.

The additional trial-specific task that they were involved in was the delivery of the paper slips which had the reminder messages. These were given to patients who had submitted sputum for TB testing and the message was a reminder to go back to the facility to collect the results. The WBOTs reported that delivering the reminder paper slips during the trial was something new and they felt was possible to incorporate into their daily schedule.

This study has shown that the WBOTs' role in linkage to TB care (through delivery of paper slips), particularly treatment initiation, is possible and beneficial but is an area needing exploration. This finding was also seen in a South African study where CHW training on comprehensive TB/HIV/PMTCT integrated care showed increased uptake of TB services and linkage to care (31). This would further strengthen and fulfil the motto of "taking healthcare to the community".

Before the WBOTs' training and involvement in the trial, the pre-training assessment scores revealed that knowledge of TB as a disease and generally how the TB program works was not their strength. This was not surprising since TB training among CHWs is not always done (14) and it has been documented that scores on knowledge of TB are low among CHWs and these can worsen with increased time since the last training (30). It is important to acknowledge that

TB knowledge capacity building among WBOTs is the first step if the objective of improved linkage to care in the TB program is to be achieved.

Some of the challenges that WBOTs encounter in their daily duties which were found during the interviews were patient relocation and lack of communication. Some patients already being followed up would not inform the WBOTs of their intention to relocate. This was also a problem during the distribution of the paper slips as information that the patient had relocated would only be known once WBOTs were at the respective houses and neighbors or new occupants would tell them that the person they were looking for had moved out. On the other hand, the lack of communication was a result of the language barrier due to some patients being foreign nationals and not being able to speak local languages or failure to communicate effectively in English. This finding of failure to communicate in this study is bordered on the patients' failure to communicate which is a contrary finding to previous studies that found that the healthcare providers' failure to communicate effectively was the reason for patients' failure to initiate treatment (11,25,32).

Other challenges the WBOTs faced in their work were safety and low income. They received monthly stipends which they said were not given regularly and was not enough. The stipend payments are said to range between R1 800–R3 500 per month (33). This finding is similar to a previous study conducted in another province in South Africa (34). The WBOTs also said that their job was risky. They reported that their fears range from dog bites to theft and for the females, even the threat of rape. They said they did not have health insurance cover as this was not covered in their work contract and that they could not afford medical aid premiums.

The WBOTs mentioned that transport was also a challenge as they had to walk long distances to cover the allocated number of households and with little or no income, this burden was no lighter. The use of mobile technology would probably help WBOTs communicate with the patients they did not find at their respective homes in case the patients were not far away but within the neighbourhood at the time they are being looked for. That way, the trip would not be a wasted one. This would improve their performance as was shown by Braun and colleagues in their systematic review study (35).

7.4.2. Patient Interviews

Interviewing the participants of the trial gave an understanding of their experiences during the trial. Participants reported that they had experienced various emotions upon receiving the reminder messages. Some were happy while others were worried. Being happy was probably associated with the peace of mind that comes with knowing that they will understand their health status better. Those that were worried were probably pessimistic and thought of the worst of their illness.

Participants also reported that receiving the reminder message did influence their decision to go back to collect the results. As mentioned in the sections above, the study area is populated with migrants, who in some instances, do not possess valid residency permits. Therefore, they work mostly as casual laborers with little or no sick leave benefits. Because they need the income, some choose to go to work instead of seeking further healthcare services for fear of a positive TB test result and the subsequent loss of income.

Stigma also played a role in terms of the worry experienced by recipients of the reminder messages. There was no way of knowing if anyone, other than themselves, had seen the reminder message and this worried the patients. As explained in the previous sections above, TB stigma is one of the reasons patients do not return for clinic appointments. Despite the worry of receiving the reminder messages, participants did not mind how they had received the reminder messages (paper slip or SMS).

During the initial phase of the COVID 19 pandemic, most services (including TB services) offered at health facilities were disrupted due to the national lockdown restrictions. The impact of the pandemic on the TB care cascade was as follows: the TB testing numbers were reduced due to fewer people seeking healthcare services and also due to healthcare facilities prioritizing COVID 19 testing to TB testing. Patients presenting with cough were investigated for COVID 19 only and not for TB.

The delay in conducting the post-trial patient interviews due to the COVID 19 pandemic impacted negatively on the data collected. Of the 314 participants in the trial, 167 had received reminder messages. However, only 43 of them were successfully contacted and 15 were interviewed. In addition, it is a possibility that recall bias could have affected the quality of the

responses from the participants since there were at least 12 months between trial participation and these post-trial interviews.

7.5. Strengths and Limitations

The major strength of this PhD work lies in the evidence that reminder messages to patients who have tested for TB do improve TB treatment initiation among them. An additional strength was the rigorous methodological approach utilizing mixed methods with the inclusion of an RCT and knowing that RCTs are high ranking in terms of strength of the evidence. However, there were some limitations.

The WBOTs did their usual daily routine and the paper slip distribution was an additional task for them. This meant that the latter was not their primary focus and so the assistance was not consistent. The WBOTs also experienced challenges during their routine work such as lack of transport and fierce dogs in the yards of patients. Other limitations were: possible under-estimation of treatment initiation due to missing some TB patients whilst checking the registers manually, and patients not seeing their reminder SMS messages due to phone sharing. Health system challenges included poor recording and reporting of contact details by facility staff which could have hindered the delivery of the paper slips. The inability to know the impact of the interventions on treatment completion was a limitation since patients were not followed up beyond the point of treatment initiation. Financial resources were a challenge which led to implementation of the study at two of the planned eight sites and this resulted in reduced sample size. Lastly, the inability to complete the field work optimally due to the COVID 19 pandemic was the setback for this doctoral work. Paper slip delivery by the WBOTs was disrupted and the post-trial interviews were also delayed and this could have affected recall of events by participants significantly.

7.6. Conclusion

TB initial LTFU can be prevented by having consistent optimal provision of TB services through availability of knowledgeable and competent TB treatment providers. In addition, policies that target reduction of TB stigma and protection of TB patients/survivors need to be implemented. To ensure optimal integration of the WBOT and TB programs, there is a need for regular meetings and interaction between the two programs to address the challenges TB patients encounter in their respective treatment journeys. Also, it is important to remind patients to go back to collect their results so that they can be initiated on appropriate TB treatment if

necessary. In addition to sending SMS messages to patients, there is need to enhance community follow up of patients with suspected TB who have had a TB test at a facility. Being a community-based cadre of workers, WBOTs have a role to play and building their capacity through education and training is key. Reminder messages to patients testing for TB should be made into policy and implemented effectively to ensure a reduction in TB initial LTFU. This could subsequently reduce the burden of TB in South Africa.

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PLOS ONE

RESEARCH ARTICLE

Microbiologically Confirmed Tuberculosis: Factors Associated with Pre-Treatment Loss to Follow-Up, and Time to Treatment Initiation

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Abstract

Background

The impact of new diagnostics on pre-treatment loss to follow up (Pre-treatment LTFU) has not been widely investigated. The reported rate of pre-treatment LTFU is however lower in studies where Xpert MTB/Rif (Xpert) has been used onsite as opposed to centrally. The use of the Xpert at point of care (POC) could have a role in reducing the pre-treatment LTFU rate among TB patients. We aimed to determine the pre-treatment LTFU rate and the time to treatment initiation as well as to describe associated factors in patients diagnosed with TB using POC Xpert or smear microscopy.

Method

Xpert machines were installed at 7 primary healthcare facilities in inner-city Johannesburg. POC Xpert TB testing was the primary diagnostic method for all patients although there were some patients who were tested using only laboratory-based smear microscopy (during power outages or machine operator off-sick). Data on patients' demographics, TB diagnostic test (Xpert or smear microscopy), test result, and time to treatment initiation were collected. Associations and predictors of pre-treatment LTFU and time to treatment initiation were explored.

Findings

A total of 1981 people with presumptive TB were tested (1743 using Xpert and 238 using smear). A bacteriological diagnosis of TB was made in 271 patients (90% Xpert; 10% smear). The median time to treatment initiation in the smear group was 9 days (IQR: 4–20) while those tested using Xpert had a median time of 0 days (IQR: 0–0). Pre-treatment LTFU was 22.5% with no difference between diagnostic groups (p = 0.8).

Conclusion

The Pre-treatment LTFU rate of 22.5% found in this study is much higher than the 5% target of the South African National TB Control Program. POC Xpert resulted in a significantly

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greater proportion of bacteriologically proven TB patients being started on treatment within 30 days of presentation. No risk factors associated with pre-treatment LTFU were identified.

Introduction

Tuberculosis (TB) is a preventable and treatable communicable disease. Despite recent advances in TB diagnostics, TB remains a major contributor to global mortality. With a TB incidence of 834/100000, some of South Africa's TB patients were among the estimated 1.5 million deaths from the 9.6 million people who developed the disease worldwide in 2014 [1]. Despite the importance of rapid treatment initiation in patients with TB for TB control, neither pre-treatment loss to follow up (LTFU) nor time to treatment initiation are included in routine TB programme outcome measures. TB patients already on treatment have been a focus of TB control programs in many countries. The emphasis has mostly been on ensuring that patients take their treatment. Not much attention has been paid to the patients who test positive for TB but never get initiated on treatment. TB patients who are lost before treatment is initiated continue to transmit infection in communities. This is an important group of people as they contribute to the burden of TB in communities.

Rapid diagnostic methods for TB such as Xpert MTB/RIF (Xpert) have been known to reduce the turn-around time between diagnosis and treatment. Except in a few instances, the testing has been used in centralized laboratory settings [2]. Compared to smear, the use of the Xpert machine in centralized settings has not shown a reduction in mortality or an increase in the notification rate [3–5]. Even when used on site as a "point of care" (POC) test, Xpert has failed to show a reduction in TB mortality and other important TB outcomes [6, 7].

According to the South African National TB Guidelines, pre-treatment LTFU, are laboratory confirmed TB patients who are never commenced on TB treatment [8]. A systematic review which assessed the magnitude of the pre-treatment LTFU rate in smear- or culture-positive TB patients in African and Asian studies found that this rate varies between 4% and 38% [9]. A more recent study conducted in South Africa reported pre-treatment LTFU rates of 14.9 and 17.0% for Xpert and smear microscopy respectively; this was despite telephonic or home visit contact by study investigators at week 1 and month 1 into the trial [5]. Pre-treatment LTFU in a study using Xpert as the initial diagnostic method in a similar setting was 4% [6]. Xpert as a POC may be a means to address high pre-treatment LTFU rates seen in National Tuberculosis Programmes (NTP).

Appropriate TB treatment in a patient rapidly decreases infectivity, decreases transmission and is vital for TB control [10, 11]. Delaying TB treatment initiation or losing bacteriologically confirmed TB patients before treatment is initiated contributes to on-going TB transmission in communities and to poor patient outcomes.

Using smear microscopy, Yimer and colleagues found a 27 day median time delay (between time of patient presentation and time of treatment initiation) that was as a result of health system delays [12]. Although there is a 45% increase in bacteriologically confirmed TB case detection when using Xpert compared to smear microscopy [13] and the turnaround time for TB test results is said to decrease to five days when using laboratory-based Xpert [14], patients are still not initiated on treatment early. Causes of the delays vary from patient factors to health system factors. Factors that have previously been described to increase the risk for these delays are: increased turnaround time between sputum collection and result availability [15], male sex and older age [9]. Cox and colleagues showed that the use of onsite Xpert reduced the time

to TB treatment initiation and it decreased pre-treatment LTFU although there was no impact on TB related morbidity or mortality [3].

Implementing POC testing for TB should reduce the impact of the health system factors and therefore reduce the diagnosis-treatment gap [16]. A shortened time to treatment initiation would impact on on-going TB transmission. We aimed to determine the pre-treatment LTFU rate and the time to treatment initiation as well as to describe associated factors in patients diagnosed with TB.

Materials and Methods

This was a pragmatic observational study within a larger project (Region F TB Blitz) to assess the feasibility of implementing Xpert within primary healthcare facilities (PHCs). Between October 2011 and March 2012, 7 PHCs in inner-city Johannesburg implemented Xpert machines at point of care. These were operated by lay counsellors who had undergone thorough training on operation of the machine. The lay counsellors were funded by the study but were managed by the facility managers as part of the facility staff. In each facility, all persons with presumptive TB (as determined by the TB focal point nurse) were sent to the lay counsellor who collected sputum and tested it for TB using Xpert. Patients were told of the time it would take for a result and were invited to wait at the clinic or return for the result. The management of all patients was at the sole discretion of the TB focal point nurse.

Previous studies reporting on pre-treatment LTFU have used variable cut off times ranging from 30 to 90 days to define pre-treatment LTFU [9]. We were unable to find a fixed cut off time for delayed treatment. However, it is known that there is a dose-response relationship between treatment delay and ongoing transmission of TB. It appears that 30 days is the turning point where a significant increase in the risk for TB transmission occurs [17].

Smear microscopy was the default diagnostic investigation if Xpert was not available at the time the patient presented to the clinic. There were some instances when smear microscopy was the only diagnostic test available at the time. Reasons for this were periods of Xpert machine downtime due to low temperature, electricity outages, software corrupted by viruses and cartridge shortages. The lay counsellors were also not replaced when they were ill or on leave.

As part of the main project and as part of routine data collection in facilities, data on the following were collected: patient demographics, time of TB test, test result, date and time of treatment initiation. The data were captured into an electronic TB register. For this study, pre-treatment LTFU was defined as patients diagnosed with TB and either documented as LTFU before treatment initiation in the TB register or diagnosed with TB but not evaluated (no outcome indicated in the TB identification register and never entered in the TB treatment register). STATA version 12 was used to run descriptive frequencies, proportions, regression analysis and survival analysis. We looked at two cut off times 30 days and 3 months

This research was a sub-study of a larger project called the "Region F TB Blitz" which looked at feasibility of point of care use of Xpert MTB/RIF machine for TB testing. Ethics approval was granted by the University of the Witwatersrand, Human Research Ethics Committee (M110233). Participants of the main study provided written consent for their data to be used for research.

Results

A total of 2286 patients were tested for TB during the study period across the 7 PHC facilities. Of these, 13.3% (305) were already on TB treatment and these tests were routine follow up tests as per national TB guidelines for South Africa. The remaining 1981 patients were people who presented with presumptive TB (had one or more of the TB symptoms) (Fig 1).

Although not randomly allocated to diagnostic method (Xpert or smear microscopy) the events resulting in sputum smears being done were random and the participants were similar with regards to age, sex and HIV status Table 1.

Two hundred and thirty eight people (12%) had smear microscopy instead of Xpert as the initial diagnostic test.

Overall, the case detection rate was 13.7% (271/1981). The case detection rate for Xpert was 14.1% and for smear microscopy it was 10.9% (p = 0.21).

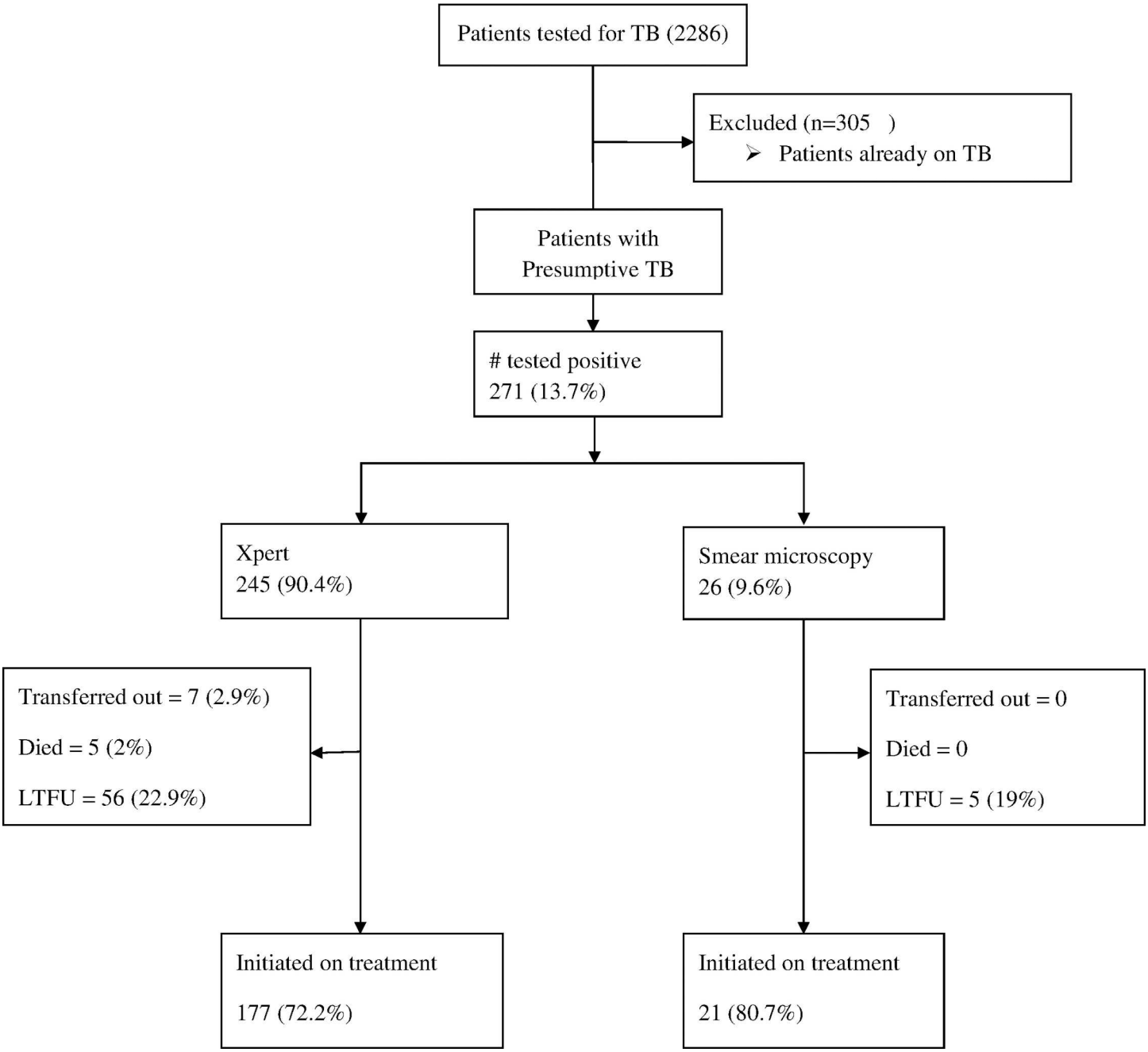


Fig 1. Patient flow and eligibility chart. Patients with presumptive TB tested for TB between October 2011 and March 2012 using either smear microscopy or Xpert were eligible.

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Table 1. Characteristics of persons suspected of TB by diagnostic test.

	Tested using Xpert (n = 1743)	Tested using smear (n = 238)	p-value
Age (years; IQR)	33 (28–39)	34 (29–40)	0.18
Male n (%)	880 (51)	135 (57)	0.08
HIV co-infected n (%)	1280 (74)	162 (68)	0.06

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The proportion of rifampicin resistance among the TB patients tested using Xpert was 6.5%. These patients were referred for MDR TB treatment as per national guidelines.

Of the overall 271 patients that tested positive for TB, 198 (73.1%) were started on treatment; 61 (22.5%) were LTFU prior to starting treatment; 5 (1.8%) died before starting treatment and 7 (2.6%) were transferred out of the facilities. The proportion of patients LTFU pre-treatment among the patients tested using Xpert was similar to the smear microscopy patients (23% versus 19% respectively; p = 0.8).

Fifty two percent (140/271) started treatment within a week of testing positive; and of these 78% (109/140) of them started treatment on the same day. Eighty three percent (146/177) of the patients in the Xpert group were initiated on treatment on the same day of testing while five out of 21 patients (24%) from the smear microscopy group initiated on treatment were started on empiric TB treatment at their initial visit (p = 0.001).

Whether or not treatment was initiated was not significantly associated with age, gender or with the type of test used for diagnosis (Table 2).

About 75% of the patients were initiated on treatment within 2 months of diagnosis and this is regardless of type of diagnostic test used (Fig 2). Patients who tested using the Xpert were initiated on treatment earlier than those tested using smear microscopy (Log-rank p = 0.01) (Fig 3). The median time to treatment initiation for patients that were tested using smear was nine days (IQR: 4–20) while those tested using Xpert had a median time of 0 days (IQR: 0–0). The proportion of patients diagnosed using Xpert and started on treatment before 30 days was different from the proportion from the smear microscopy group started on treatment before 30 days (85% versus 35% p<0.001).

In terms of duration before treatment initiation, females were initiated earlier than males (Log-rank p = 0.03) (Fig 4). The duration to treatment initiation did not differ among different HIV status categories that is HIV positive, HIV negative and HIV status unknown (Stratified Log rank p = 1.0) (Fig 5).

Twenty seven percent (532/1981) of the patients tested negative for HIV. Thirty six percent of the patients who tested HIV positive were newly diagnosed (516/1449). One of these was labelled as pre-treatment LTFU. Half of the remaining LTFU patients were known HIV positive while the others were HIV negative. However, the pre-treatment LTFU was similar in HIV negative and in HIV positive individuals (p = 0.4).

Table 2. Treatment initiation (within 3 months) in patients with bacteriologically confirmed TB by age, gender and diagnostic method.

		Adjusted OR	95% Confidence interval
***Age**		0.95	0.90–1.03
Gender	*Female*	Reference	
	Male	0.87	0.50–1.51
Diagnostic test	*Smear*	Reference	
	Xpert	1.05	0.67–1.67

*Age was analysed as a continuous variable.

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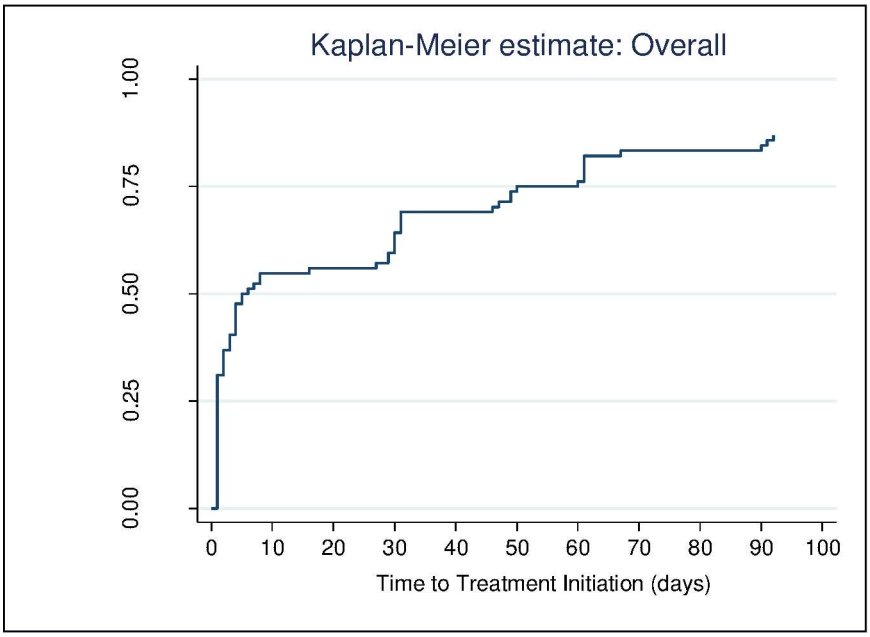


Fig 2. Kaplan-Meier curve showing the time to treatment initiation (in days) for all patients regardless of test method used. It shows the proportion of TB patients initiated on treatment at different time points.

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Discussion

One of the principles of TB infection control is "prevent formation of infectious TB particles". Through administrative controls, this can be achieved. Initiating treatment in TB patients

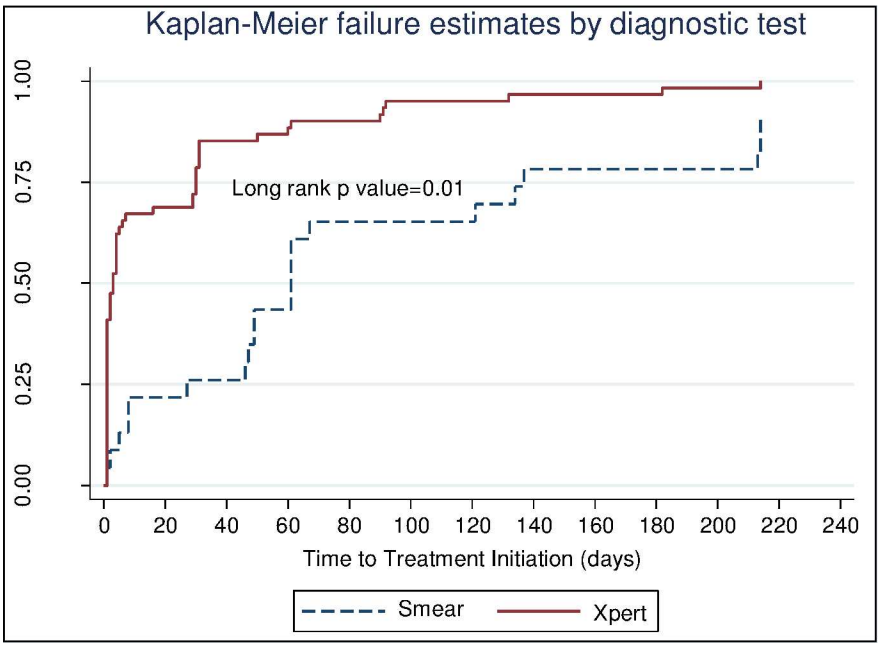


Fig 3. Kaplan-Meier curve showing the time to treatment initiation (in days). The broken line is showing proportion of TB patients diagnosed using smear while the continuous line is for patients diagnosed using Xpert.

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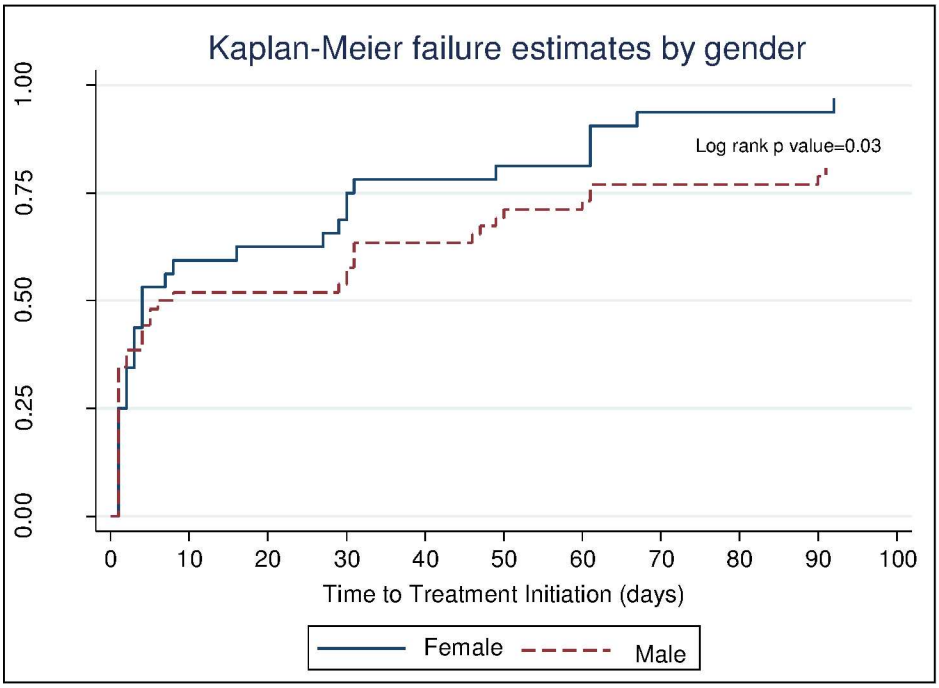


Fig 4. Kaplan-Meier curve showing the time to treatment initiation (in days). It shows proportion of patients initiated on treatment at different time points for males (broken line) and for females (continuous line).

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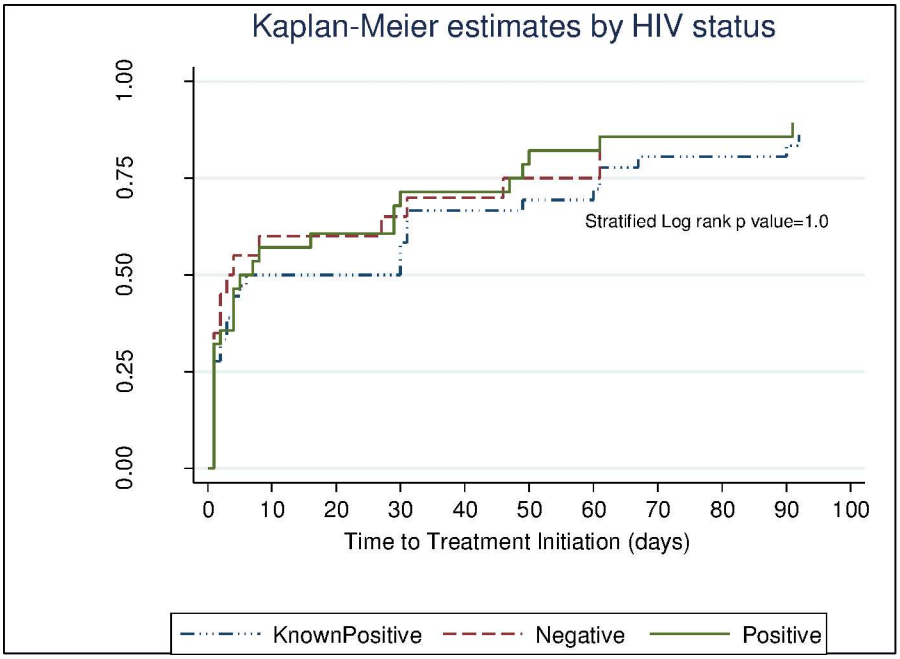


Fig 5. Kaplan-Meier curve showing the time to treatment initiation by HIV status (in days). The 3 groups are HIV positive (continuous line), HIV negative (broken line) and patients with unknown HIV status (broken line with dots).

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rapidly decreases infectiousness. The time to TB treatment initiation and pre-treatment LTFU play a role in the burden of TB in communities. The longer the time before TB treatment is initiated, the greater the risk of transmission of infection to other members of the communities.

Prompt treatment is recognised as an essential part of TB control and has received a lot of focus, but how soon after diagnosis should treatment be started? From a Public Health view delay beyond 30 days is when risk of increased infection becomes significant [17].

In this setting of high HIV and TB prevalence Xpert placed at PHC's showed a shorter time to treatment initiation when compared to cases diagnosed by laboratory based smear microscopy. These findings are consistent with other studies [3]. Xpert at POC resulted in a significantly larger proportion of the patients who were initiated on treatment at their initial visit. Xpert at POC also resulted in a significantly larger proportion of patients initiated on treatment before 30 days and thus reducing the transmission risk of TB. The difference in time to initiation is unlikely to be as a result of different diagnostic tests and most likely reflects the shorter turnaround time and the readily accessible onsite results that the use of POC Xpert testing enables. The use of onsite technology allows for the gap seen between time of sputum being taken and the result linked to a patient to be overcome. Previous studies have shown that an increase in the turnaround time of diagnostic results increases pre-treatment LTFU [15, 18]. We showed that a greater proportion of patients diagnosed by Xpert were started on treatment within 30 days when compared to laboratory based diagnosis by smear, despite empiric treatment being given to some patients diagnosed by smear microscopy prior to the results being available. The difference in decreased "early" pre-treatment LTFU is important as once treatment is delayed beyond 30 days from diagnosis risk of ongoing transmission increases significantly [17]. As in the TB-NEAT study [3], we found that the impact of earlier treatment initiation on the pre-treatment LTFU rate decreased over time and that proportions of patients initiated on treatment were similar at 54 days in TB-NEAT and 90 days in our study.

The other factor we identified as being associated with delayed treatment initiation was being male. However, this did not translate to a difference in pre-treatment LTFU rate between the 2 gender groups at 90 days.

Despite the availability of onsite results there was no difference in the proportion of patients with bacteriologically confirmed TB started on treatment at 90 days. The high percentage of confirmed TB patients not initiated on treatment in our study (22.5%) is of concern but not unique. An earlier study from Cape Town, South Africa reported 41% of TB suspects with one positive smear microscopy result did not start TB treatment at the PHC facility where they had been diagnosed [19]. We were unable to identify gender, age, or HIV status as risk factors for pre-treatment LTFU.

In areas such as South Africa with high TB/HIV co-infection a high pre-treatment LTFU rate may perhaps be due to early deaths in this patient group as was described by Squire and colleagues [18]. We excluded all known deaths from our analysis but did not check death registries to exclude early deaths in our group of patients with pre-treatment LTFU who could not be traced. We did however not find difference in pre-treatment LTFU between TB/HIV co-infected (either newly diagnosed HIV or known HIV positive) and HIV negative TB patients. Furthermore, the low rate of early deaths seen in the patients who had known outcomes suggests that early deaths are unlikely to explain the high pre-treatment LTFU rate in our study.

We show that it is not only the TB patients who are co-infected with HIV who get lost to follow up. With the strong focus on HIV and TB integration it is important for NTPs to not neglect HIV negative TB patients who may in fact be a larger transmission burden given that they are more likely to have cavitary disease [20]. They also tend to live longer than untreated TB/HIV co-infected patients and so are more likely to transmit infection in the communities.

We have shown a high pre-treatment LTFU rate in our study. Unfortunately this group of patients is excluded from the traditional NTP cohort outcomes analysis and are largely ignored. If TB is to be controlled, steps need to be taken to not only record and report on pre-treatment LTFU but systems need to be put in place urgently to ensure that these patients are traced and appropriately treated.

There are several limitations with this study. It was not designed to compare Xpert TB/Rif with sputum smear. Also, the number of patients in the smear group was small and the diagnostic method used was not randomly allocated to the participants/tests. Lastly, this study was only carried out in Urban clinics and the findings may not represent rural populations. Our results are however consistent with previous findings.

Conclusion

POC Xpert resulted in a significantly greater proportion of bacteriologically proven TB patients being started on treatment within 30 days of presentation when compared to laboratory based smear microscopy. Pre-treatment LTFU rate was found to be high but was not associated with sex, age or HIV sero-status. NTPs should ensure that they have working systems to manage a patient from time of TB suspicion to treatment completion and attention should be given to decreasing the diagnosis-treatment initiation gap (both time to treatment initiation and pre-treatment LTFU).

Supporting Information

S1 File. Dataset. It shows details of test results of patients.
(XLSX)

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Author Contributions

Conceptualization: JMK AB.

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Initial loss to follow up of tuberculosis patients in South Africa: perspectives of program managers

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Abstract

Background: Tuberculosis (TB) remains a serious public health problem in South Africa. Initial loss to follow up (LTFU) rates among TB patients are high, varying between 14.9 and 22.5%. From the perspective of patients, documented reasons for this include poor communication between patient and staff after testing, not being aware that results are ready and other competing priorities such as preference to go to work as opposed to seeking healthcare. Ward-based Outreach Teams (WBOTs) routinely conduct home visits to ensure adherence to medication for various conditions including TB. We explored reasons for TB initial loss to follow up from the perspectives of TB program managers and WBOT program managers, with a focus on the WBOT's (potential) role in reducing initial LTFU, in particular.

Methods: Key informant interviews with five WBOT program managers and four TB program managers were conducted. The interviews were audio-recorded, then transcribed and exported to NVivo 11 software for coding. A hybrid analytic approach consisting of both inductive and deductive coding was used to identify themes.

Results: The age of the nine managers ranged between 28 and 52 years old, of which two were male. They had been in their current position for between 2 to 12 years. Prior to treatment initiation, WBOTs screen household members for TB and refer them for TB testing if need be, but integration of the two programs is emphasized only after TB treatment has been initiated. Counseling of patients testing for TB is not guaranteed due to frequent staff rotations and staff shortages. Participants reported that possible dissatisfaction with services as well as stigma associated with the TB diagnosis could explain loss to follow up prior to treatment initiation.

Conclusion: Program managers view health system related factors such as staff rotations, poor communication with patients and lack of counseling as contributing to the problem of initial LTFU among TB patients. The integration of the WBOT and TB programs is limited to referring suspected cases for testing and patients already on treatment.

Keywords: TB treatment, Initial loss to follow up, Program managers, South Africa

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Background

Although mortality due to tuberculosis (TB) in South Africa has been declining, the disease still tops the list of the "ten leading underlying natural causes of death, 2014–2016" [1]. The incidence of this deadly yet preventable disease in South Africa is currently 567/100000 population in the general population and 340/100000 among individuals living with HIV [2]. TB patients already on treatment have been a focus of TB control programs in many countries including South Africa. The emphasis has mostly been on ensuring that patients take their treatment. This has been evidenced from the implementation of directly observed therapy short-course (DOTS).

In South Africa, a patient with presumptive TB in whom a productive cough is among the presenting symptoms is asked to provide a sputum sample for laboratory testing using Xpert MTB/Rif (Xpert), culture or smear-microscopy testing based on the screening algorithm. Although laboratory turnaround time for Xpert is 2 h, the patient is asked to come back after 2 days to cater for transportation time and delivery of result to the facility. When the patient returns and if Xpert TB test result is positive, treatment is supposed to be initiated on the same day or within 5 days [3]. The patient is also asked to submit another sputum sample for smear microscopy as a baseline for monitoring treatment progress. Patients who test positive for TB but never get initiated on treatment are known as initial loss to follow up (LTFU) patients [3].

Initial LTFU rates in South Africa range between 14.9 and 18.0% [4, 5]. Although this upper limit rate corroborates the rate found in African studies in an earlier systematic review [6], a higher rate of 22.5% was found in another study conducted in inner city Johannesburg, South Africa [7]. This city is home to economic immigrants from other parts of the country as well as from other countries [8]. A study conducted in the Western Cape province, a similar economic hub in South Africa, highlighted mobility and temporary migration as the most common reasons for missed appointments among patients on chronic medication because generally people travel to their homes of origin during the festive season or travel on other planned holidays [9].

There are various reasons for non-initiation of treatment for patients who test positive for TB. Breakdowns in communication between patients and providers are one reason why patients with varying conditions do not show up for appointments at healthcare facilities. A study conducted in different clinical departments at a regional hospital in South Africa found that at least 16% were unaware of their appointment date while 11% were unsure of when their actual appointment date was [10]. The lack of proper communication between patient and healthcare provider with regards to next steps was also a cause for initial LTFU in India's TB program [11], showing that the problem is not unique to South Africa. Findings from two other studies conducted in India and Pakistan revealed that patients were not aware that their results were ready at the facilities [12, 13] suggesting a breakdown in communication between the patients and the providers with regards to next steps at the time of testing. Poor counseling and general poor healthcare worker attitudes have been shown to contribute to patients being lost to follow up [14]. Other reasons for not starting treatment are related to quality of the healthcare services rendered to patients either in form of structural barriers or lack of proper recording and reporting [15–17].

Patient related factors are also a cause for initial loss to follow up. "Being busy with other jobs" was found to be the main reason for non-initiation of treatment in a study conducted in India [18]. Lack of motivation for a second visit and having other competing priorities are also reasons for TB patients not getting initiated on treatment [12, 19]. Other reasons reported are re-treatment, changing residence, feeling ashamed and alcohol consumption [14, 20, 21]. Poverty, lack of education, not having someone to go with to the clinic, consulting traditional healers, social stigma and religious beliefs also contribute to initial LTFU [15, 22, 23].

In countries like Brazil (with a similar GDP as South Africa), the use of community healthcare workers to take healthcare services to the community has been shown to be beneficial by improving access to services [24] and by reducing infant mortality rate [25]. Within the structure of South Africa's re-engineered primary healthcare (PHC) model are ward-based outreach teams (WBOTs). The WBOTs consist of a Team Leader (often a Professional Nurse but can be an Enrolled Nurse) and 6 Community Healthcare Workers (CHWs) including a Health Promoter (HP) and an Environmental Health Officer (EHP) [26]. The WBOTS work within specific geographical areas of PHC facility total catchment areas. Their scope of work is centred on health promotion and prevention of disease. In the TB program, screening, tracing and treatment adherence support is more of WBOTs' role than treatment initiation. This is part of their work and therefore no incentives are provided for doing this work [27].

The strategy of the South African TB control program is guided by strategies developed by the Department of Health for tackling HIV, STI and TB and is collectively known as HAST. HAST programs at the various levels of governance are managed by HAST managers. Historically, staff supervising TB programs were known as TB managers. Thus, HAST managers who were tasked to supervise the HIV and STI programs became collectively known as TB managers.

With regards to TB services, the WBOTs' work is to identify, support and follow-up TB patients and their contacts [26]. We explored reasons for TB initial loss to follow up from the perspectives of TB program managers and WBOT program managers, with a focus on the WBOT's (potential) role in reducing initial LTFU, in particular.

Methods

This exploratory qualitative study was part of a bigger study looking at interventions to reduce initial loss to follow up among TB patients. The study is entitled "Initial Loss to Follow Up Among Tuberculosis Patients: The Role of Ward-Based Outreach Teams and Short Message Service (SMS) Technology" [27]. In depth interviews (IDIs) with TB/WBOT program managers were conducted in the City of Johannesburg district in South Africa between August 2018 and February 2019. This city is inhabited predominantly by migrants (both national and regional) [8]. This is a risk factor for loss to follow up of health services. Knowing more about loss to follow up in this region would assist the TB program nationally because South Africa as a whole serves as an economic hub, not only for the Southern African region, but for Africa at large. We defined WBOT Managers as regional coordinators or outreach team leaders for the WBOT program; and TB Managers were the HAST Managers for respective regional areas. The research and its objectives were shared with the respective directorates of the district who then provided names and contact details of 20 managers we could invite to participate in the research. A maximum of three telephonic attempts and one email over a period of 5 days were made to arrange an appointment before declaring a potential participant "unable to reach." The participants were conveniently selected depending on their availability. Of the twenty managers on the list provided, seven could not be reached and one manager who was reached by email said he had relocated out of the country. Nine of the twelve managers approached for participation accepted the invitation telephonically. The three who did not participate gave the following reasons for their unavailability: annual leave, illness and other commitments. All interviews were conducted in English by the first author in the privacy of the participants' respective offices after written informed consent was obtained.

With the participants' verbal permission, the IDIs were audio-recorded, lasting on average about 35 min each. The interviewer also took notes. To ensure standardization of topics discussed, an interview guide was developed and used. As prompts to elicit discussions, the guide included the following topic areas: TB communication, WBOT functions and reasons for loss to follow up. Prior to data collection, this instrument was piloted with two managers working in programs other than the TB or WBOT programs and then refined before a final version was agreed upon. These data are not presented. The purpose of the pilot was to ensure that the questions were clear with no ambiguity in them. We wanted to know how best to phrase the questions to ensure clarity as well as the average time an interview would take before scheduling interview appointments.

The audio recordings were transcribed verbatim and the transcripts were systematically coded by the first author using NVivo 11 software [28]. A codebook framework of the topic areas was created by the first author. The second author checked the reliability of the coding framework by recoding four of the transcripts using the framework. After this, a hybrid approach [29] was applied to code each transcript, first inductively and then according to deductive codes derived from factors identified in the literature. These were the grouped into themes aligned with the different concepts/topic areas.

Results

Five WBOT managers and four TB managers (a.k.a. HAST managers) participated in the study. Participants were between 28 and 52 years of age and seven of the nine were female. Work experience in current position ranged from 2 to 12 years (Table 1).

Table 1 Characteristics of IDI participants

Participant	Gender	Program Area	Duration in current position (years)
IDI 1	Female	HAST Program Manager	12
IDI 2	Male	HAST Program Manager	3
IDI 3	Female	WBOT Program Manager	10
IDI 4	Female	HAST Program Manager	7
IDI 5	Female	WBOT Program Manager	3
IDI 6	Female	WBOT Program Manager	2
IDI 7	Female	WBOT Program Manager	11
IDI 8	Male	WBOT Program Manager	8
IDI 9	Female	HAST Program Manager	6

Emerging themes were grouped under the following areas: TB program knowledge, WBOT functions and reasons for initial LTFU.

Knowledge of the TB program

WBOTs don't know how TB program works

The managers in the TB program knew how the program worked and how they work with the WBOTs. They were able to describe, step by step the procedure of treatment initiation. A HAST Program Manager (IDI 1) explained that *"We use GXP for testing. We ask patients to come back after 2 days for results".* In contrast, WBOT program managers were less clear. They did not know exactly how the TB program worked in terms of the procedure that is taken when a patient is found to be positive and needs to be put on treatment. *"I…I really don't know how they work in the TB program,"* explained a WBOT Program Manager who had been in her post for 10 years (IDI 3).

WBOT functions

Nature of work

The WBOTs offer a wide range of services when they do the home visits. In terms of TB service delivery, the WBOTs screen household members for TB as they conduct routine home visits for chronic conditions likes diabetes and hypertension. Any household members with TB symptoms (cough, night sweats, fever, weight loss, etc.) is referred to the nearest facility for TB testing. At the facility, the TB nurse collects sputum from patient and sends to the laboratory for TB testing. A male WBOT Program Manager (IDI 8) had the following to say:

> "What they do when they go to the household is uuuhhmm…they do screening for TB and they refer patients for TB testing. That's all they do".

Participants also generally reported that the work of the WBOTs with regards to the TB program starts once a patient is initiated on TB treatment. A WBOT Program Manager with more than 10 years' experience in her program area (IDI 7) explained this:

> "Those who have already started treatment but default along the way, those are the ones we focus on and we go out and trace them. But those ones who come to test and are told to come back for results...no those we do not focus on."

Working together

While TB program procedures were unclear to WBOT Program Managers, both groups of managers understood where their roles overlapped.

For patients not yet on TB treatment, everyone knew that WBOTs are involved in screening of household members for TB during their routine home visits, as reported earlier. There was then a gap between referral and TB patients being initiated on treatment, which is the period when initial LTFU occurs.

WBOTs also support the TB program in offering treatment adherence support during their home visits. During the home visits, they also trace treatment defaulters. The managers described how TB and WBOT programs work together when it comes to defaulter tracing of patients already initiated on treatment. A WBOT Program Manager (IDI7) described this process:

> "TB people phone and if patient does not come, then they hand over the list of names of these people to the WBOT members who now go into the community to look for them."

A HAST Program Manager working in her position for 7 years (IDI 4) echoed this description.

> "For contacts it's not easy for them to come and it's also not easy for us to go to them. But we are working in close contact with the WBOTs."

There were no descriptions on how the TB program works with WBOTs to confirm referrals or to follow up on patients who had not yet initiated treatment.

Reasons for initial loss to follow up

Poor communication with patients

Participants reported that counseling of TB patients was lacking. A HAST Program Manager with 6 years' work experience in TB (IDI 9) expressed that counseling should be emphasized in a similar way as done in the HIV program.

> "I think it's probably…patients are not counselled when they are tested…you know like in HIV. So the patients do not know the importance of starting treatment soon. So they just go home. And remember they test and are given a date when to come back and this is where the gap is. They normally don't come back on their own."

WBOT program managers also acknowledged that the WBOTs only focus on household visits as part of routine work and deal with patients who had visited the facilities only if they are part of the defaulter list that is given to them by the TB nurse for tracing of such patients. A WBOT Program Manager with 3 years' experience (IDI 5) reported that

> "Mostly we are focusing on the household…so maybe if we also focus on the ones in clinic so that

the same message goes everywhere, maybe it can work."

Apart from counseling of patients on TB, the general communication between nurses and patients with regards to next steps after testing for TB was also unclear. A HAST Program Manager with 12 years' experience (IDI 1) echoed this and explained that

"……they were not informed. Procedure was not explained to patient".

Health system barriers

Both WBOT and TB program managers pointed out that the health system was a significant contributor to the problem of loss to follow up. Patient waiting times at facilities need to be shortened so that this is not used as an excuse for "no-show" by patients. A WBOT district coordinator described how patients *"…give excuses that they are long queues"* as a cause for not starting treatment.

The need for patients to visit clinics to get tested for TB and initiate treatment, if found positive, relates to how nurses' roles are licensed. Despite WBOTs doing screening during the home visits, as indicated earlier, they are not allowed to conduct testing or initiate treatment. They rely on patients to act upon their referrals to facilities. The WBOTs cannot refer the patients to their team leader, if the latter is an enrolled nurse, for treatment initiation because enrolled nurses cannot prescribe medications in the South African healthcare system.

TB Managers expressed that it is important for all facility staff to get familiar with the TB program so that should the TB nurse not be available patient management is not interrupted. It is also important to keep the staff rotation period in a particular program area for longer than the current 3 months to ensure proper staff training in the respective program area. A HAST Program Manager working in TB for more than 10 years (IDI 1) had this to say

"…And then if someone comes to stand in for the TB sister, they will not attend to the patient thoroughly as they're supposed to, sometimes not even informing them about importance of ensuring they come back for the results."

Participants reported that staff generally do not like to work in the TB room and are reluctant to acquaint themselves with systems and processes on TB patient management. As such, when the TB nurse is absent, either the TB room is locked for the day or the substitute staff member does not adequately manage the patients in terms diagnosis and treatment as well as counseling on next steps. Staff rotations which happen quite often also mean that the new person in the TB room has first to acquaint himself/herself before they can be deemed competent in TB patient management. However, it happens in most cases that as soon as they have settled in, it is time for another cycle of staff rotation. Participants suggested less staff rotation in the TB room and TB patient management education to all facility clinical staff so that continuity of optimal TB patient care is guaranteed.

Patient responsibilities

Participants reported that patients' behavior is also a reason for their failure to initiate TB treatment. Patient relocation emerged strongly as a reason. A WBOT Program Manager (IDI 6) reported that *"……..patients are always relocating."* They move house and probably start seeking healthcare services at a facility close to their new home.

The managers also reported that provision of correct contact details is important as this makes it easier for the healthcare system to find a missing patient. According to the TB managers, patients give wrong phone numbers and wrong addresses. Unfortunately, this is only discovered at the point of defaulter tracing.

Patients "shopping around" for better health services was a reason also given by the managers. A male HAST Program Manager (IDI 2) had this to say:

"They like to confirm and they will come here and test and if they are positive here they will go to another facility to test. Maybe if still not satisfied, they will go to another."

Sometimes patients get worse after testing, get admitted to hospital and therefore fail to return for the results. At this point, it is important that a relative or friend informs the facility so that the patient is not labelled as LTFU.

Discussion

The most critical findings from this study relate to how WBOTs may contribute to reductions in initial LTFU in the future. Currently, the role of the WBOTs in the TB program is limited to symptomatic screening and to tracing of patients who default their TB treatment [26]. TB nurses give lists of patients who have missed their appointments by over a week to WBOTs who go and trace these defaulters so that they can continue with their treatment. TB initiation is not among the functions of the WBOTs [26], but it could be added to the enrolled nurse function. Patients not initiated on treatment continue to spread TB in the community and thereby increase the TB burden [30, 31]. In line with task shifting,

enrolled nurses in rural clinics of South Africa take on most of the roles of professional nurses [32] with the exception of medicine prescribing. Revision of policy to train and allow enrolled nurses from the WBOT program to prescribe TB drugs would assist in ensuring that patients start TB treatment promptly.

This study reinforced the two-fold reasons for initial LTFU: patient related and health system related. Although the patient-related factors were reported second-hand, they still are worth discussing. For instance, a factor such as relocation is not something the health system can control, but it can create systems to reduce LTFU such as ensuring that quality patient contact information is recorded at the time of TB testing [33]. City of Johannesburg, where the study was conducted, is South Africa's economic hub and occupied predominantly by economic migrants from both within and outside the country [8]. Although the city occupies an area of 1645km^2, it has a population of 4.4 million [34]. This dense population could explain the high total headcount numbers and consequent high loss to follow up rates in the healthcare facilities within the city reported in an earlier study [7]. A Malawian study looking at initial LTFU of antiretroviral therapy found that high burden facilities were more likely to have higher initial LTFU rates than low burden facilities and attributed this to inadequate staffing leading to poor patient education and lack of counseling [35]. In light of this and of the association between TB and HIV, it is important that the healthcare facilities be adequately staffed. Task-shifting strategies [32], whereby WBOTs could be involved in treatment initiation (such as explaining to patients on next steps after each consultation) to ensure minimal LTFU among TB patients, should be explored.

Another patient related factor that was reported by participants was that patients are tested at different facilities because they want to confirm the diagnosis. Patients go and test at other facilities to see if the result is the same. This finding is corroborated by a recent study that looked at health seeking pathways of patients with drug resistant tuberculosis [36]. Courtwright and Turner found that some of the causes of TB stigma were: perceived transmission risk from infected people; poverty; and its association with HIV [37].

In terms of health system related factors for patients not initiating treatment, proper and adequate communication with patients is highly essential in ensuring optimal initiation and adherence to treatment. Divija and colleagues reported in their study that poor communication and education to the patient on next steps were reasons for initial LTFU [11]. One of our study participants mentioned that it is important to put emphasis on proper counseling and education of patients with regards to TB as a disease. Therefore, it is expected that with optimal patient communication and counseling, patients would know that they need to inform the facility when they are leaving the facility catchment area. That way they can be referred and documented as such. Our findings suggest that training on counseling may benefit existing TB managers as well as WBOTs.

Good quality data in the TB program ensures optimal control of the disease. The design of TB data collection and reporting systems need to be such that they enable responses at the community level that are specific to gaps identified from the data [38]. Properly documented records which are frequently updated can ensure that all patients have outcomes; and those missing appointments are timeously identified and appropriately followed up by the WBOTs.

Although Professional Nurses are the preferred team leaders, most WBOTs are led by Enrolled Nurses due to shortage of staff at the clinics. Enrolled Nurses are not licensed to prescribe TB treatment. This means traced patients cannot be given treatment unless they go to the clinic.

Conclusion

Program managers view health system related factors such as staff rotations, poor communication with patients and lack of counseling as contributing to the problem of initial LTFU among TB patients. The integration of the WBOT and TB programs is limited to referring suspected cases for testing and patients already on treatment. We have identified immediate opportunities to improve integration, e.g. engaging WBOTs to follow up with patients who have been tested, but not yet initiated as well as longer-term considerations, such as revisiting licensing rules around enrolled nurses being permitted to initiate TB treatment.

TB initial LTFU can be prevented by addressing health system related factors such as ensuring that patients are counselled, ensuring that competent TB treatment providers are present at all times to attend to patients and implementing policies that reduce stigma and protect TB patients as well as survivors of TB. In addition, there is need for regular meetings between the WBOT and TB programs at various levels of patient care to ensure optimal integration of the two programs.

Abbreviations

TB: Tuberculosis; LTFU: Loss to follow up; WBOT: Ward-based outreach team; WHO: World health organization; DOTS: Directly observed therapy short-course; Xpert: Xpert MTB/Rif; PHC: Primary healthcare; CHWs: Community healthcare workers; HP: Health promoter; EHP: Environmental health officer

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JMK, CC and CM conceptualized the study. JMK collected the data. JMK and SJ analysed the data. JMK drafted the manuscript. SJ, CM, CC and NI reviewed the manuscript. Final manuscript was read and approved by all authors.

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Availability of data and materials
The transcripts are not publicly available due to confidentiality agreements with the participants.

Ethics approval and consent to participate
Ethics approval for the study was granted in October 2017 by the University of the Witwatersrand's Human Research Ethics Committee (M170651). The study was also approved by the Johannesburg District Research Committee (DRC 2017-08-0001) and registered with the South African National Health Research Database (GP2017 GP_201708_24). Informed written consent was sought by first explaining the study and its procedures/implications to a potential participant. All participants who consented were interviewed privately to protect their confidentiality. Participants were assured that reports emanating from the research would not contain their personal identifying information.

Consent for publication
Not applicable.

Competing interests
None declared.

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Treatment initiation among tuberculosis patients: the role of short message service (SMS) technology and Ward-based outreach teams (WBOTs)

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Abstract

Background: In South Africa, tuberculosis (TB) is a public health problem with treatment initiation failure rates varying between 14.9 and 25%. Lack of proper provider/patient communication on next steps after testing, not being aware that results are ready; and other competing priorities are some of the reasons for this failure. We aimed to assess the effectiveness of Short Message Service (SMS) technology and ward-based outreach teams (WBOTs) in improving TB treatment initiation. A 3-arm randomized controlled trial (Standard of care-SOC, SMS technology or WBOTs) was conducted between September 2018 and April 2020. Newly diagnosed TB patients randomly allocated to SMS and WBOTs groups were sent reminder messages (text message or paper slip respectively) that results were ready. Due to unforeseen challenges (financial and impact of the COVID 19 pandemic), implementation was only in two of the eight clinics planned.

Results: 314 TB patients were assigned to one of three groups (SOC = 104, WBOTs = 105, and SMS = 105). Chi-square tests were used to compare proportions starting treatment (primary outcome). More patients in the SMS group (92/105; 88%) initiated treatment than in the SOC group (81/104; 78%), although this difference did not reach statistical significance ($P = 0.062$). The time to treatment initiation was significantly shorter in the SMS group than in the SOC group ($P < 0.001$). The proportions of patients initiated on treatment in the WBOTs group (45/62; 73%) and in the SOC group (44/61; 72%) were similar ($P = 0.956$). The times to treatment initiation for these two groups were also similar. The 3 group analysis yielded similar proportions initiated on treatment ($P = 0.048$ for SMS/SOC comparison and $P = 0.956$ for WBOTs/SOC comparison) but analysis of times to treatment initiation yielded some variations.

Conclusion: Reminder SMS messages sent to newly diagnosed TB patients improved the time to treatment initiation. Further research is required to show effect of the WBOTs intervention.

Trial registration: Retrospectively registered with the Pan African Clinical Trial Registry (PACTR202101914895981).

The trial was registered with the Pan African Clinical Trial Registry on 25 January, 2021 (ref: PACTR202101914895981; https://pactr.samrc.ac.za). The registration was retrospective due to an oversight. Nevertheless, the protocol details outlined in our ethics application were strictly adhered to.

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Introduction

Tuberculosis (TB) is a public health problem in South Africa. The incidence of this preventable infection is currently 615/100000 population and the HIV co-infection

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rate is 58% [1] . Despite a decline in mortality, TB topped the country's list of the ten leading underlying natural causes of death in 2015–2017 [2]. Patients whose TB test results are positive but never get initiated on treatment are known as initial loss to follow up (LTFU) patients. In South Africa, initial LTFU rates range between 12 and 17.9% [3–6] but can be as high as 22% in densely populated cities with migrant populations such as the inner-city Johannesburg [7] and is even higher in rural settings [8].

South Africa's TB targets for treatment success rate and for initial LTFU rate are greater than 90% and less than 5% respectively [9]. The former is the proportion of new positive TB patients cured, plus the number completed treatment but not meeting the criteria for "cure" or "failure". The denominator for this is the total number of new positive pulmonary TB patients registered [9]. However, the number of patients who initiate treatment is not all those who are eligible but only a proportion of them [8, 10]. Therefore, it is possible that the success rate is an overestimate due to the assumption that the initial LTFU rate is negligible and not factored in.

Over the past decade, there has been an increase in the usage of mobile cellular phones globally with over 7 billion mobile cellular subscriptions by 2015 [11]. Reminding patients through short message service (SMS) technology has been shown to improve adherence to various chronic medications [12–16]. This technology is also acceptable among patients who use it [17, 18]. It has been shown to improve return for appointments [19, 20] as well as treatment initiation where messages with results were sent to healthcare workers [21, 22].

The model of taking healthcare services to the communities has resulted in decreased infant mortality [23] and improved access to healthcare [24]. Ward-Based Outreach Teams (WBOTs) are a cadre of staff (mostly community healthcare workers) in South Africa's re-engineered primary healthcare (PHC) model, who offer services at household and community levels. For TB services, the teams identify, support and follow-up already diagnosed TB patients and their contacts with a minor or no role in treatment initiation [25].

We aimed to evaluate the effectiveness of the SMS technology and WBOTs in increasing the proportion who initiated treatment and in reducing the time to treatment initiation among TB patients.

Methods

According to the South African National Tuberculosis Control Programme guidelines, presumptive TB patients who have a productive cough should produce sputum on the spot, and this specimen is sent to the laboratory for testing using the Xpert MTB/Rif (Xpert) machine if available. Alternatively, smear microscopy is used as the diagnostic test. Although the laboratory turnaround time for Xpert is theoretically 2 h, the patient is asked to come back for results after 2 days. This is to cater for the transportation time and delivery of results to the PHC facility. If the TB test result is positive and the patient comes after the 2 days, treatment is initiated the same day or within 5 days. A second sputum sample is collected in cases where the diagnosis was made using Xpert. This sample, which is sent for smear microscopy, is a baseline for monitoring before changing from intensive phase to continuation phase of treatment and at the time of discharge from treatment [9].

Design

A randomized controlled trial (RCT) was conducted at two public sector primary level clinics in inner-city Johannesburg, South Africa. Participants were enrolled between 10 September 2018 to 25 March 2020 and the last date for follow up was 22 April 2020. The inner-city Johannesburg area has a population of 4.4 million and occupies a 1645km^2 area [26]. Using data from the 2017 National TB Control Program (NTCP) report, the 8 clinics with the highest TB notification in the area were selected. Due to unforeseen financial challenges and the effects of the COVID 19 pandemic, the study was only implemented in two of these 8 clinics. These non-fee paying clinics service a generally low income population and offer holistic primary level healthcare services such as family planning, antenatal care and baby care among others.

Participants

The standard clinic practice as per National TB Control Program for South Africa [9] is that all patients accessing any healthcare services in any part of the clinic are screened for TB symptoms. Those found with TB symptoms (presumptive TB patients) are sent to the TB room for testing. During the study period, such patients who were eligible and consented to participation, were enrolled. Patients aged 18 years old and above, not yet diagnosed with TB, and who had submitted sputum to the TB nurse were eligible.

Sample size

It was assumed that the treatment initiation in this study would increase from the 82% average upper limit reported in South African studies [3–5, 7] to 95% in each of the groups with an intervention (with either SMS technology or with WBOTs) as per target of the country's National TB Control Program [9]. Based on a power of 80% and a level of significance of 0.05 to detect an increase in treatment initiation of 13% in either of the

intervention groups, we estimated a required minimum sample size of 104 positive TB patients in each group. The trial was powered to detect a difference between the SMS group and the SOC group and also to detect a difference between the WBOTs group and the SOC group, but was not powered to detect a difference between the SMS group and the WBOTs group.

Study procedures

After obtaining written informed consent, patients meeting the inclusion criteria were interviewed using a pre-piloted structured questionnaire to obtain sociodemographic and clinical data. Their contact details, including mobile phone numbers they could be contacted on, were also recorded both in the TB case identification register and on the study data abstraction form.

To determine the level of knowledge of participants about TB, the following four questions were asked:

- "Before testing this time, had you heard about TB?"
- "Before testing this time, did you know how one can get TB?"
- "Before testing this time, did you know symptoms of TB?"
- "Before testing this time, did you know TB be can be cured?"

Knowledge level evaluation was made based on the number of "Yes" (correct) answers each patient scored. If a patient scored two or fewer correct answers, he or she was classified into the "none or little knowledge" category; and then those that scored three or four correct answers were classified in the "adequate knowledge" category.

Patients were asked to return for results after 2 days as per national guidelines [9]. Using a Stata generated prerun block randomization sequence (block sizes ranging between 6 and 15) [27], participants who tested positive for TB were assigned to one of the three groups by a researcher not involved in participant enrolment (standard of care (SOC), WBOTs, or SMS). Patients allocated to either the SMS or the WBOTs group received reminder messages telling them that their results were ready at the facility while those in the SOC group did not receive any messages.

The reminder messages were sent through SMS messaging for those in the SMS group and through paper slip messages delivered by WBOTs for those allocated to the WBOTs group. The WBOTs were given the paper slips by the research assistants and they carried during their routine household visits. The paper slips had the physical addresses of the patients and this guided the WBOTs in locating the patients. Up to 3 attempts were made in trying to locate patients before finally labelling the patients as "not found". Any undelivered paper slips were handed back to the study staff and were recorded. Delivery reports for the messages sent via SMS were noted.

To maintain confidentiality, the reminder message did not state details of why the person was needed at the clinic. In addition, the paper slips were delivered in sealed envelopes. The message was in English or isiZulu depending on language preference selected at study enrolment. The content was the same for both intervention groups and read as follows:

> *"Good day, your results are ready at the clinic for your collection. You are advised to collect your results as soon as possible".*

The TB case identification registers at the clinics were checked regularly for the results of the patients enrolled in the study. The names of those with a positive result were checked for in the hard copy TB treatment initiation registers where patients initiated on TB treatment are captured. This was also confirmed by checking patient details in the TB module of TIER.net electronic register as well as using hard copy TB files which are opened once a patient is initiated on treatment. Participants with positive TB test results but not initiated on treatment within 4 weeks from the date of TB test were noted. The time to treatment initiation was measured and ascertained by calculating the number of days between date of sputum submission for TB testing and the date of TB treatment initiation.

Investigator and participant blinding

Research assistants checking for the outcomes of the patients were blinded to the different groups to which patients were allocated. They were not involved in randomisation, intervention delivery and did not have access to participant data with respective intervention groups. This minimized observer ascertainment bias. Participants were told that they would receive one of the two interventions or neither (standard of care). However, depending on the type of reminder message they received or if they did not receive any message at all, they would be aware of their allocation group. Therefore, blinding was not possible and as such, participant ascertainment bias could not be avoided.

Study outcomes

We defined treatment initiation among TB patients as being started on TB treatment when one was diagnosed with TB. The primary outcome was the proportion initiated on treatment within 28 days from the date of submitting sputum. The secondary outcome was the time (in days) to treatment initiation.

Statistical analysis

Data were analysed using STATA® version 14.2 software [27]. The study was not powered to compare the interventions against each other, but to compare each intervention against the standard of care [28].

To evaluate the primary outcome, we used descriptive frequency tables to determine the proportions of treatment initiation across the study groups. The proportion initiated on treatment within 28 days was estimated for each study group, and comparisons between proportions were carried out using a chi-square test. In order to estimate the 'risk' ratio for treatment initiation for an intervention group relative to the SOC group; and adjusting for other variables, Poisson regression models were fitted with robust estimation of standard errors, as recommended by Cummings [29]. The use of robust standard errors is suggested since the outcome (treatment initiation) is not rare, so the Poisson approximation to the binomial distribution will not be very accurate, and the usual Poisson standard errors will be too large (since essentially the Poisson distribution allows a participant to initiate TB treatment on more than one occasion). Candidate variables for the models to be used in addition to treatment group (with SOC as the reference level) were marital status, body mass index, alcohol consumption, smoking, monthly income, prior clinic consultation, comorbidities, age, gender, employment status, TB test disclosure, history of TB contact, travel time to the clinic, HIV status and severity of TB symptoms. These candidate variables were chosen from existing literature on variables known to be related to TB treatment initiation. The selection of variables in the final model was based on unadjusted analysis and forward selection of variables chosen by the unadjusted analysis.

We used Kaplan–Meier curves and the log-rank test to analyse the time to treatment initiation across the study groups. The time of submitting sputum for TB testing (date of signing informed consent) and the date of treatment initiation were used to calculate the duration of time in the study. Patients who were transferred out or died before treatment initiation were censored from the analysis. The transferred out patients were censored out at the date of transfer out, while for patients who died (and for whom the exact date of death was not known) or who were lost to follow-up, the censoring date was taken as day 29. The first reason for choosing day 29 for censoring was that research assistants checked for initiation of treatment in both the hard copy TB treatment initiation register and in the TB module of the TIER.net electronic register for 28 days following enrolment. The second reason was so that the Kaplan Meier plots will correctly show that the overall proportion of participants initiating treatment was less than 100%. We used Cox regression analysis to determine associations between treatment group and initiating treatment, adjusting for explanatory variables associated with time to initiation of treatment. The variables selected for inclusion in these models were the same variables that were used in the multivariable analysis for the primary outcome. The proportional hazards assumption was checked using the Schoenfeld residuals. A sensitivity analysis was carried out fitting a Cox regression model with censoring at day 3 rather than day 29 for those participants for whom the date of loss to follow-up was unknown. The "day 3" selection was based on the fact that the national guidelines advise that patients return for results within 2 days of TB testing [9].

Results

Of the 3147 patients who sought TB services during the study period, 2880 were eligible for enrolment into the study, and 2850 consented to participation (99% response rate).

Eighty six percent (2448/2850) were negative while 3% (88/2850) of the results were categorized as "other result". "Other result" category consisted of Xpert trace results as well as failed tests due to leakage or contamination.

Of the 88 patients with "other" test results, there were 41 patients with Xpert trace results. At the time of the data collection, the South African national guidelines [9] were not clear on the management of presumptive TB patients with Xpert trace results. As a result, the practice across facilities was not standardized with some facilities treating such patients as TB positive and initiating them on treatment while other facilities waited for TB culture result before confirming the diagnosis. Therefore, patients with such results were not randomized to any group.

Eleven percent (314/2850) of the participants tested positive for TB. These were randomly assigned to one of the 3 groups (SOC = 104, WBOTs = 105, and SMS = 105).

Following operational challenges because of the COVID 19 pandemic, delivery of paper slips to the participants randomized to the WBOTs group was discontinued. However, randomization of the participants to the three groups using the predetermined block randomization sequence continued. Figure 1 below illustrates the enrolment flow. The writing in *italic* is based on actual implementation numbers based on the WBOTs intervention.

Sociodemographic characteristics

The three groups were similar in terms of sociodemographic data and therefore comparable (Table 1).

At least half of the participants in all the groups had been feeling unwell for more than two weeks at the time of presentation to the facility. Over three quarters of

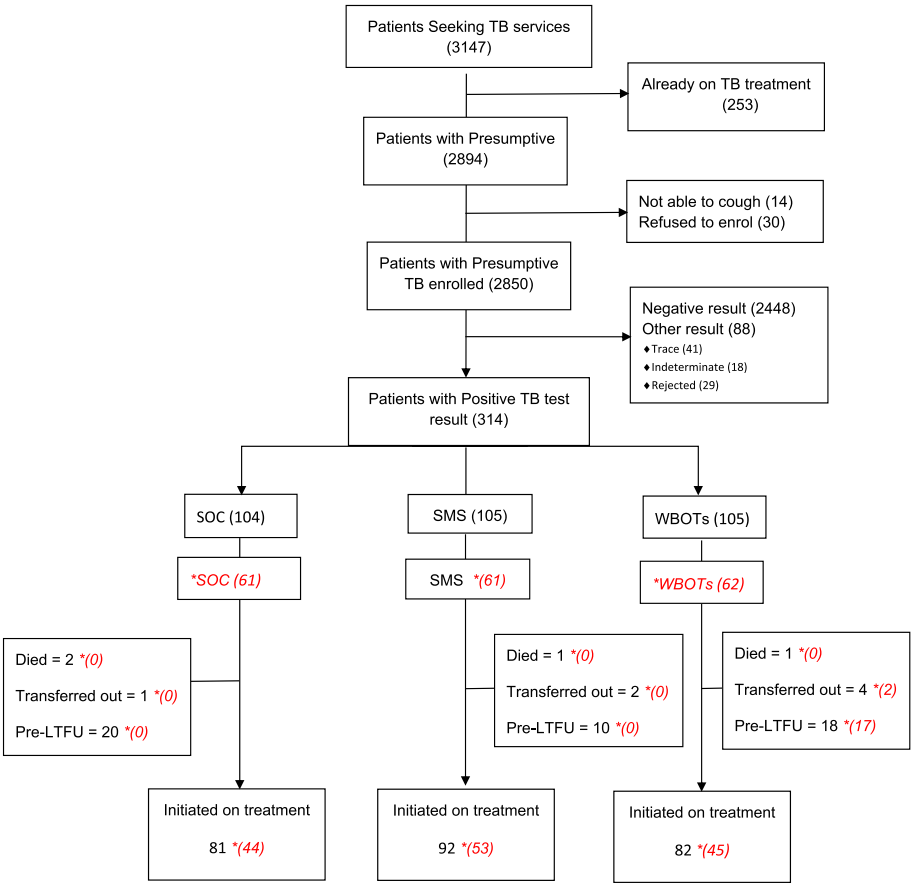


Fig. 1 Participant Enrolment Flow Chart. *Numbers in line with implementation of WBOTs intervention

each group's participants had not sought medical attention for the current problem prior to study enrolment.

Overall, 43% (136/314) of the participants were HIV positive. Of these, 43% (58/136) were on ART (19 in the SOC group, 17 in the SMS group, and 22 in the WBOTs group). Thirty-one percent (18/58–5 in the SOC, 5 in the SMS, and eight in the WBOT groups) of patients on ART had been on treatment for less than one month at the time they tested for TB. The proportion of patients who were not aware of their HIV status at the time of enrolment was 18% (56/314).

Over half (30/58) of the patients on ART were not sure of the names of the drugs they were taking, and about half of these patients (53% - 16/30) had only been on treatment for less than a month.

Analysis of the SOC and SMS groups

This section highlights results of all the 209 patients randomized to SOC group (104) and SMS group (105) during the entire study period.

Proportions initiated on treatment

Three of the 209 patients were transferred out while another three died before treatment initiation. Of the 209 patients, 173 (83%) were initiated on treatment. There were 92/105 (88%) in the SMS group and 81/104 (78%) in the SOC group ($P=0.062$). Patients in the SMS group were 12% more likely to initiate treatment than those in the SOC group (RR = 1.12; 95% CI: 0.99–1.28). This effect size increased in the multivariable analysis (Table 2 and Table S1).

Time to treatment initiation

At any particular time, patients in the SMS group were 2.8 times more likely to initiate treatment early than those in the SOC group (HR = 2.77; 95% CI: 2.03–3.77). This effect size increased slightly when adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms (HR = 3.29; 95% CI: 2.36–4.58) (Table 2 and Table S2). The estimates were increased when censoring was done at day 3.

Table 1 Participant characteristics

Sociodemographic Characteristics	SOC ($n=104$)	SMS ($n=105$)	WBOTs ($n=105$)
Age category			
<= 30 years n (%)	21 (20)	21 (20)	26 (25)
31 to 45 years n (%)	55 (53)	57 (54)	60 (57)
46 to 60 years n (%)	18 (17)	21 (20)	13 (12)
More than 60 years n (%)	10 (10)	6 (6)	6 (6)
Median age; years (IQR)	37 (31–49)	39 (32–46)	37 (31–42)
BMI range			
BMI < 18.5 n (%)	21 (20)	19 (18)	21 (20)
BMI > =18.5 & BMI < 25 n (%)	47 (45)	58 (55)	52 (49)
BMI > =25 & BMI < 30 n (%)	28 (27)	19 (18)	27 (26)
BMI > =30 n (%)	8 (8)	9 (9)	5 (5)
Median BMI; kg/m^2 (IQR)	22.6 (19.1–26.2)	22.4 (19.4–25.1)	22.4 (19.1–26.0)
Gender			
Male n (%)	57 (55)	62 (59)	64 (61)
Female n (%)	47 (45)	43 (41)	41 (39)
Marital status			
Not married n (%)	86 (83)	87 (83)	86 (82)
Married n (%)	18 (17)	18 (17)	19 (18)
Highest level of education attained			
Primary or lower n (%)	29 (28)	23 (22)	25 (24)
Secondary or higher n (%)	75 (72)	82 (78)	80 (76)
Employment			
Not employed n (%)	45 (43)	50 (48)	47 (45)
Employed n (%)	59 (57)	55 (52)	58 (55)
Financial status			
Median monthly income; ZAR (IQR)	4000 (3000–6500)	4300 (3000–5500)	4400 (3500–5500)
Median # supporting financially (IQR)	1 (0–2)	1 (0–3)	1 (0–2)
Time to clinic			
<= 30 min	72 (69)	73 (70)	70 (67)
> 30 min	32 (31)	32 (30)	35 (33)
Alcohol consumption			
No	59 (57)	62 (59)	60 (57)
Yes	45 (43)	43 (41)	45 (43)
Smoking			
No	70 (67)	58 (55)	63 (60)
Yes	34 (33)	47 (45)	42 (40)
TB knowledge			
None or little (<=2 correct answers)	39 (38)	36 (34)	41 (39)
Adequate (> = 3 correct answers)	65 (62)	69 (66)	64 (61)
Cough duration			
Less than 2 weeks	45 (43)	47 (45)	45 (43)
2 weeks or longer	59 (57)	58 (55)	60 (57)
Prior consultation			
No	85 (82)	79 (75)	84 (80)
Yes	19 (18)	26 (25)	21 (20)
Severity of TB symptoms			
Mild	82 (79)	84 (80)	85 (81)
Not mild	22 (21)	21 (20)	20 (19)

Table 1 (continued)

Sociodemographic Characteristics	SOC ($n=104$)	SMS ($n=105$)	WBOTs ($n=105$)
History of TB			
No	86 (83)	86 (82)	83 (79)
Yes	18 (17)	19 (18)	22 (21)
HIV status			
Positive	52 (50)	41 (39)	43 (41)
Negative	43 (41)	41 (39)	38 (36)
Unknown	9 (9)	23 (22)	24 (23)
On ART[b] *(n = 136)*			
No	33 (63)	24 (59)	21 (49)
Yes	19 (37)	17 (41)	22 (51)
Comorbidities			
Diabetes	6 (6)	4 (4)	6 (6)
CVS[a] problem	12 (12)	5 (5)	2 (2)
Epilepsy	2 (2)	1 (1)	0 (0)
Asthma	1 (1)	4 (4)	0 (0)
Comorbidities including HIV			
No	44 (42)	60 (57)	57 (54)
Yes	60 (58)	45 (43)	48 (46)

[a] *CVS* cardiovascular, [b]*ART* Antiretroviral therapy

Table 2 Treatment initiation in the different groups

	UNIVARIABLE FINDINGS $N=209$)			[a]MULTIVARIABLE FINDINGS ($N=209$)		
	Unadjusted IRR	**Confidence Interval**	***p*-value**	**Adjusted IRR**	**Confidence Interval**	***p*-value**
Treatment Initiation						
Allocation group						
SOC	Ref					
SMS	1.12	0.99–1.28	0.066	1.15	1.02–1.31	0.026
	Unadjusted HR	**Confidence Interval**	***p*-value**	**Adjusted HR**	**Confidence Interval**	***p*-value**
Time to Treatment Initiation (Day 29 censoring)						
Allocation group						
SOC	Ref					
SMS	2.77	2.03–3.77	< 0.001	3.29	2.36–4.58	< 0.001
Time to Treatment Initiation (Day 3 censoring)						
Allocation group						
SOC	Ref					
SMS	4.67	3.30–6.60	< 0.001	5.05	3.48–7.33	< 0.001

[a] Adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms

The total analysis time at risk and under observation of the patients was 1357 days. Patients in the SMS group had a shorter time to treatment initiation than those receiving standard of care (SMS-4 days, IQR: 3–5 versus SOC- 8 days, IQR: 5–13). This difference was significant ($P<0.001$). At least half of the patients who initiated treatment in the SMS group had done so by the 4th day while it took 8 days for those in the SOC group (Fig. 2).

Analysis of SOC and WBOTs groups

This section highlights results for SOC and WBOTs groups but restricted to the duration when paper slip reminders were implemented. The total number of patients analysed was 123 (SOC = 61 and WBOTs = 62).

Proportions initiated on treatment

Three of the 123 patients were transferred out while two died before treatment initiation. Treatment was

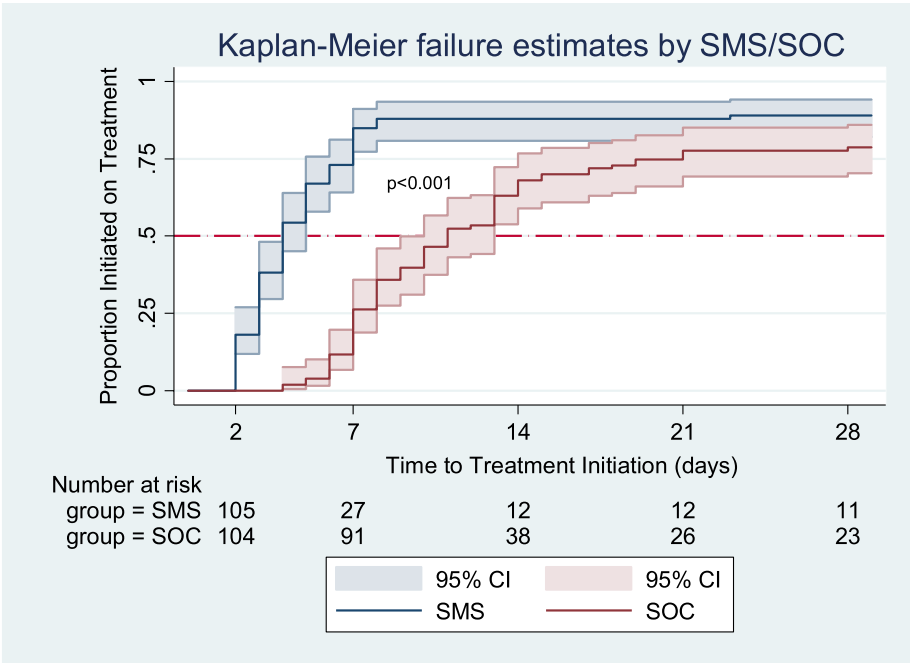


Fig. 2 Time to treatment initiation for the SMS and SOC groups

initiated in 72% (89/123) of them. The proportions in the SOC (44/61; 72%) and WBOTs (45/62; 73%) groups were similar ($P=0.956$). The chances of initiating treatment among patients in the 2 groups were also similar (IRR = 1.01; 95% CI: 0.81–1.25). This effect reduced slightly in the multivariable analysis (Table 3 and Table S3).

Time to treatment initiation

At any particular time, patients in the WBOTs group were 18% more likely to initiate treatment than those in the SOC group (HR = 1.18; 95% 0.78–1.79). When adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms, the effect size was similar (HR = 1.11; 95% CI: 0.70–1.77) (Table 3 and Table

Table 3 Treatment initiation in the different groups

	UNIVARIABLE FINDINGS (*N* = 123)			**[a]MULTIVARIABLE FINDINGS (*N* = 123)**		
	Unadjusted IRR	**Confidence Interval**	***p*-value**	**Adjusted IRR**	**Confidence Interval**	***p*-value**
Treatment Initiation						
Allocation group						
SOC	Ref					
WBOTs	1.01	0.81–1.25	0.956	0.97	0.76–1.25	0.830
	Unadjusted HR	**Confidence Interval**	***p*-value**	**Adjusted HR**	**Confidence Interval**	***p*-value**
Time to Treatment Initiation (Day 29 censoring)						
Allocation group						
SOC	Ref					
WBOTs	1.18	0.78–1.79	0.434	1.11	0.70–1.77	0.654
Time to Treatment Initiation (Day 3 censoring)						
Allocation group						
SOC	Ref					
WBOTs	1.59	1.04–2.43	0.033	1.64	0.98–2.73	0.059

[a] Adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms

S4). The estimates were increased when censoring was done at day 3.

The total analysis time at risk and under observation of the patients was 1809 days. Patients in the WBOTs group had a shorter time to treatment initiation (8 days, IQR: 6–29) than those in the SOC group (13 days, IQR: 7–29). This difference was significant (log-rank $P < 0.001$). At least half of the patients who initiated treatment in the WBOTs group had done so by the 8th day while it took 13 days for those in the SOC group (Fig. 3).

Analysis of SOC, SMS and WBOTs groups

This section highlights results from all three randomization groups (SOC, SMS and WBOTs) but restricted to the duration when paper slip reminders were implemented. The total number of patients analysed was 184 (SOC = 61, SMS = 61 and WBOTs = 62).

Proportions initiated on treatment

Five of the 184 patients were transferred out while three died before treatment initiation. Treatment was initiated in 77% (142/184) of them. There were 53/61 (87%) in the SMS group and 44/61 (72%) in the SOC group and 45/62 (73%) in the WBOTs group ($P = 0.087$).

Patients in the SMS group were 20% more likely to initiate treatment than those in the SOC group (IRR = 1.20; 95% CI: 1.00–1.45) while those in the WBOTs group were 1% more likely to initiate treatment than those in the SOC group (IRR = 1.01; 95% CI: 0.81–1.58). However, these findings were not significant and the effect sizes for both SMS and WBOTs interventions did not differ much in the adjusted analyses (Table 4 and Table S5).

Time to treatment initiation

At any particular time, patients in the SMS group were 3.3 times more likely to initiate treatment earlier than those in the SOC group (HR = 3.27; 95% CI: 2.17–4.93). Patients in the WBOTs group were 14% more likely to initiate treatment than those in the SOC group. However, this finding was not significant (HR = 1.14; 95% CI: 0.75–1.73). When adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms, the effect size for the SMS group increased slightly (HR = 3.53; 95% CI: 2.27–5.48) whilst that for WBOTs decreased (HR = 1.11; 95% CI: 0.71–1.72). The estimates were increased when censoring was done at day 3. Table 4 and Table S6 show the findings in the three group comparison.

The total analysis time at risk and under observation of the patients was 2242 days. Patients in the SMS group had a shorter time to treatment initiation than those receiving standard of care (SMS-4 days, IQR: 3–6 versus SOC - 13 days, IQR: 7–29). Patients in the WBOTs group also had a shorter time to treatment initiation compared to those in the SOC group (WBOTs – 8 days,

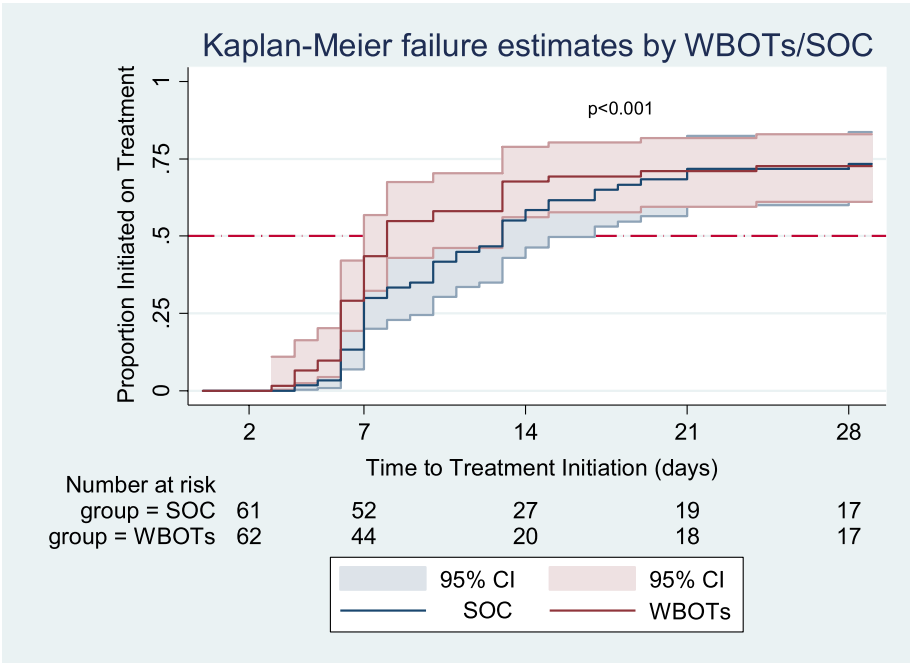


Fig. 3 Time to treatment initiation for the SOC and WBOTs groups

Table 4 Treatment initiation in the different groups

	UNIVARIABLE FINDINGS (*N* = 184)			[a]MULTIVARIABLE FINDINGS (*N* = 184)		
	Unadjusted IRR	**Confidence Interval**	***p*-value**	**Adjusted IRR**	**Confidence Interval**	***p*-value**
Treatment Initiation						
Allocation group						
SOC	Ref					
SMS	1.20	1.00–1.45	0.048	1.21	1.00–1.47	0.049
WBOTs	1.01	0.81–1.25	0.956	0.98	0.78–1.24	0.883
	Unadjusted HR	**Confidence Interval**	***p*-value**	**Adjusted HR**	**Confidence Interval**	***p*-value**
Time to Treatment Initiation (Day 29 censoring)						
Allocation group						
SOC	Ref					
SMS	3.27	2.17–4.93	< 0.001	3.53	2.27–5.48	< 0.001
WBOTs	1.14	0.75–1.73	0.531	1.11	0.71–1.72	0.657
Time to Treatment Initiation (Day 3 censoring)						
Allocation group						
SOC	Ref					
SMS	4.61	2.99–7.10	< 0.001	4.71	2.98–7.45	< 0.001
WBOTs	1.47	0.96–2.23	0.076	1.40	0.88–2.23	0.151

[a] Adjusted for age, gender, employment status, TB test disclosure, history of TB contact, travel time to clinic, HIV status and severity of TB symptoms

IQR: 6–29 versus SOC - 13 days, IQR: 7–29). At least half of the patients who initiated treatment in the SMS group had done so by the 4th day while it took 8 and 13 days for those in the WBOTs and SOC groups respectively (Fig. 4).

Discussion

We have some evidence that sending reminder messages to presumptive TB patients does ensure that patients diagnosed with TB are initiated on treatment. In the analysis of SMS group versus the SOC group, we found

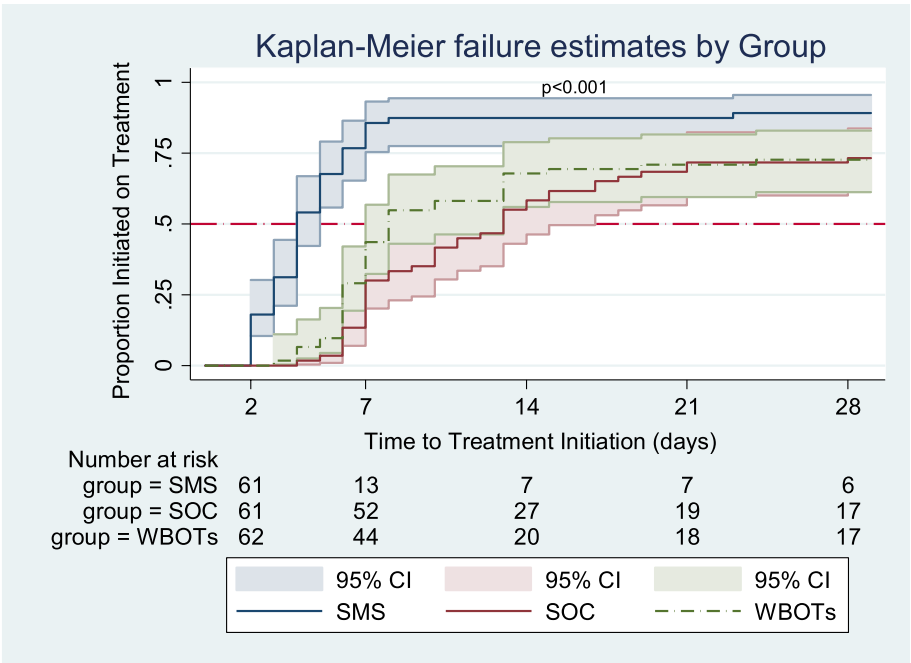


Fig. 4 Time to treatment initiation for the SMS, SOC and WBOTs groups

that the proportions of TB patients initiated on treatment in the two groups were similar. However, we found that the duration between sputum submission and treatment initiation across the three groups was shortest in the SMS group. Among the ones who initiated treatment in the groups, at least half of those in the SMS group had done so by the fourth day while it took 8 and 13 days for half of the participants in the WBOTs and SOC groups respectively to initiate treatment.

We found TB/HIV co-infection and ART coverage rates lower than what was reported for South Africa in the 2020 WHO Global TB Report (43% versus 58% TB/HIV co-infection rate and 43% versus 85% ART coverage rate) [1]. The low co-infection rate could be explained by the fact that a substantial proportion of patients (18% - 55/314) were not aware of their HIV status. If we suppose that at least half of these patients were actually positive, the total proportion of HIV positive patients would be similar to the national rate reported. The low ART coverage was possibly because some patients had recently been diagnosed with HIV (29% had been on ART for less than a month) and were being screened for TB before ART could be initiated.

SMS technology

Although there has been a tremendous increase in mobile cell phone usage over the past decade [11], we were cognisant of the fact that not everyone possessed a smartphone with messaging applications other than SMS such as WhatsApp, Hangout, etc. Therefore, we used the simple SMS messaging platform to cater for people who did not have smartphones. In addition, we opted to keep the process plain and simple by sending a notification message and patients would receive the results at the facilities. Sending actual results to patients and to keep results confidential, would have added some complexity (such as using pin numbers) to the study design process. This could potentially result in patients failing to access their results as was the case in the study by Maraba and colleagues where the majority of the 20% of patients who failed to receive their results reported a lack of understanding of the process [22].

Our findings on the effectiveness of SMS technology corroborate other studies [20–22]. The patients in the SMS group were more likely to initiate treatment than those in the SOC group. This was similar to what Wagstaff and colleagues found in their study where recipients of SMS messages were more likely to return to the clinic within the requested 2 days for results than the control group [20]. Although we found a reasonable proportion of patients in the SMS group initiated on treatment, the 12% loss to follow up before treatment initiation was still higher than the 5% national target [9]. Therefore, there is need for more effort (both on a patient level and on a healthcare facility level) to ensure that all patients diagnosed with TB are initiated on treatment appropriately.

WBOTs paper slips

Our results show similar proportions of patients initiated on treatment (73% versus 72%) and similar durations between testing and treatment initiation (8 days versus 13 days) in the WBOTs and SOC groups respectively. It is important to consider what the work of the WBOTs entails. The scope of TB program related work of the WBOTs puts emphasis on TB screening during household visits for possible sputum testing referral to respective facilities; and on treatment adherence for those already initiated on treatment [25, 30]. There is no explicit documentation in their scope of work that speaks to their role in ensuring treatment initiation among all patients diagnosed with TB. Their role is limited to referring symptomatic patients they find during home visits for testing and to ensuring treatment adherence among those already on treatment [25, 30]. A study conducted among WBOTs and TB program managers revealed that integration of the two programs through regular meetings could improve treatment initiation among TB patients [30].

WBOTs have the potential to play a key role in ensuring treatment initiation among TB patients in communities. In some settings, this cadre of healthcare staff has been pivotal in taking healthcare services to the community level and has contributed tremendously to reduction in infant mortality as well as to general good health status of the population through improved access to healthcare services [23, 24].

Although we relied on and utilized the schedule of the WBOTs to send out the paper slip reminders, we tried to emphasize the importance of the study. We also conducted a revision session on the basics of TB since gaps in TB knowledge among community healthcare workers have been found [31, 32] and scores in TB clinical knowledge and skills do worsen with an increase in the time since last training [33]. A South African study showed that community healthcare workers are willing to conduct TB related work but they do require ongoing tailor-made training and access to TB information materials [34]. With adequate capacity building, empowerment and support, the WBOTs can hugely contribute to the success of the TB program.

The SMS and WBOTs interventions are applicable to settings similar to ours. They are also relevant and may be applicable to other settings. They focus on addressing some of the patient-related and healthcare system-related reasons for failure to initiate TB treatment such as lack of communication and forgetfulness.

Conclusion

Reminder messages to patients do play an important role in TB treatment initiation. SMS messaging is an affordable, feasible option that national TB programs can use. There is need for further research to show effect of WBOTs since implementation of this intervention was suboptimal (fewer patients than planned were exposed to the intervention in this trial). With proper integration of TB and WBOTs programs, WBOTs have the potential to contribute to improved treatment initiation.

Limitations

The WBOTs' work schedule was not managed by the study but rather that the teams followed their daily routine schedule. This meant that despite efforts to emphasize the importance of the study, implementation of the paper slip reminder messages was compromised. In addition, it was during the last 6 months of the data collection period that the COVID 19 pandemic started and this further made it impossible to use the WBOTs to deliver the paper slips.

Another limitation in the study was that there was no way of ascertaining if the messages reached the targeted people. It is also possible that some patients might not have gone to collect their test results at the facility where the TB test was done but went elsewhere. If positive, there was no way of knowing whether they initiated treatment especially if they changed cell phone numbers where they could be reached to ascertain this. Checking treatment registers in the facilities within inner-city Johannesburg as well as the ETR.net/TIER.net was not as easy we had anticipated due to the lack of real-time data capturing into these electronic databases. Some patients might have left the region making tracing even more impossible practically.

Although the sample size was not large and each TB patient was individually checked for in the data sources available, it is possible to have missed some TB positive participants and thereby potentially under-ascertaining treatment initiation. Re-interviewing a sample of participants would have guaranteed optimal quality assurance of the data linkage.

We recognize that sometimes phone sharing can have an impact whether or not the patient sees the message in that the person opening the message may not be the intended recipient and they may forget to convey the message.

We are unable to ascertain the impact of our interventions on treatment completion as we did not follow up with patients for the duration of their respective treatment courses.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-022-12736-6.

Additional file 1: Table S1: Treatment initiation in SMS and SOC groups. **Table S2**: Time to treatment initiation in SMS and SOC groups. **Table S3**: Treatment initiation in WBOTs and SOC groups. **Table S4**: Time to treatment initiation in WBOTs and SOC groups. **Table S5**: Treatment initiation in SMS, WBOTs and SOC groups. **Table S6**: Time to treatment initiation in SMS, WBOTs and SOC groups.

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Authors' contributions

JMK and CM conceptualized the study. JMK and CC were involved in the design of the study. JMK and JL conducted the data analysis. JMK drafted the manuscript. CM, CC, JL and NI reviewed the manuscript. Final manuscript was read and approved by all authors.

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Availability of data and materials

The data has patient identifying information and therefore is not publicly available due to confidentiality agreements with the participants. However, contact with corresponding author can be made for data access.

Declarations

Ethics approval and consent to participate

Permission to conduct this study was granted by the University of Witwatersrand Human Research Ethics Committee (M170651) and the Johannesburg District Research Committee (DRC 2017-08-0001). It was also registered with the South African National Health Research Database (GP2017 GP_201708_24). Informed consent was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations. There were no harms observed in any of the intervention groups.

Consent for publication

Not applicable.

Competing interests

None declared.

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RESEARCH NOTE

Open Access

Initial loss to follow up among tuberculosis patients: the role of Ward-Based Outreach Teams and short message service (SMS) technology (research proposal)

Judith R. M. Mwansa-Kambafwile[1,2,3*], Charles Chasela[1], Nazir Ismail[2,4,5] and Colin Menezes[5,6]

Abstract

Introduction: Tuberculosis (TB) is a problem in South Africa. Initial loss to follow up (LTFU) among TB patients is high varying between 14.9 and 18%. Some of the reasons for this are: lack of proper communication between patient and staff on next steps after testing, not aware that results are ready; and other competing priorities. Receiving reminder messages that result is ready is an intervention that can be explored to reduce initial LTFU. This can be through either receiving a note from the Ward-Based Outreach Teams (WBOTs) or via short message service (SMS) advising the patient to collect test result at the facility. This proposal aims to assess the effectiveness of WBOTs or SMS technology in reducing TB initial LTFU.

Methods: This will be a mixed methods approach. In depth interviews with WBOT Managers and TB Program Managers will be conducted. Focus group discussions with WBOT members will also be conducted. Two interventions (enhanced WBOTs/SMS technology) will be tested using a 3 arm randomized controlled trial (standard of care, SMS technology or enhanced WBOTs). The WBOTs will deliver paper note reminders while SMS intervention will entail sending reminder SMS messages to patients as soon as TB results are ready.

Keywords: TB, Initial LTFU, WBOTs, SMS, Messaging

Introduction

Tuberculosis (TB) is a deadly communicable disease, killing approximately 1.6 million of the global 10 million people who developed the disease in 2017. South Africa's TB incidence is currently 567/100,000 population whilst the HIV prevalence among these incident cases is 60% [1]. Although the mortality due to TB in South Africa has been declining, the disease still tops the list of the "ten leading underlying natural causes of death, 2014–2016" [2].

Patients whose TB test results are positive but never get initiated on treatment are known as initial loss to follow up patients.

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There are different reasons why patients diagnosed with TB do not start treatment. Some of the reasons documented are those written in registers such as "transfer out" or "died". In a Malawian study, critical narrative interviews with 19 of 23 patients not initiated on treatment revealed that lack of education and poverty were the main characteristics of these patients [3]. A later study conducted in Pakistan corroborates these findings and in addition found that not having someone to go with to the clinic, consulting traditional healers, social stigma and religious beliefs contributed to initial LTFU [4].

Apart from the patient centred factors highlighted above, Botha et al. found that more frequent causes for initial LTFU are those to do with the quality of the healthcare services rendered to these patients. They found that at least 56% of the TB patients they interviewed after tracing them gave reasons for LTFU directly linked to the services at the facilities [5]. The

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long pathways to diagnosis, characterized mainly by health system structural barriers were also a cause for initial LTFU in the Malawian study [3]. Lack of proper recording and reporting in facilities can result in an overestimate of initial LTFU as was found in a study conducted in India [6].

A systematic review which assessed the magnitude of the initial LTFU rate in smear-positive or culture-positive TB patients found that this rate varies between 4 and 38% with weighted values for African studies of 18% and for Asia of 13% [7]. A more recent study conducted in South Africa reported pre-treatment LTFU rates of 14.9 and 17.0% for Xpert and smear microscopy respectively; this was despite telephonic or home visit contact by study investigators at week 1 and 1 month into the trial [8]. Another South African study conducted in Kwa Zulu Natal province found an initial LTFU rate of 17.9% from retrospective review of TB case identification registers for the year 2007 [9].

TB patients already on treatment have been a focus of TB control programs in many countries. The emphasis has mostly been on ensuring that patients take their treatment. This has been evidenced from the implementation of Directly Observed Therapy Short-Course (DOTS). In addition, the scope of work for the Ward-Based Outreach Teams (WBOTs) of the re-engineered primary healthcare model includes adherence support to TB patients on treatment. However, not much attention has been paid to the patients who test positive for TB but never get initiated on treatment. TB patients who are lost before treatment is initiated continue to transmit infection in communities. This is an important group of people as they contribute to the burden of TB in communities. Treatment initiation is a way of infection control because a patient on treatment stops being infectious within 2 weeks of starting treatment [10, 11].

Sending reminders to patients to inform them that their results are ready at the facility where they tested could help increase the number of TB patients initiating treatment. Two ways these reminders could be sent are through short message service (SMS) messaging to patients or through paper notes delivered to patients by the WBOTs. This study intends to assess the effectiveness of WBOTs and SMS technology to reduce initial LTFU among TB patients. More detail about the WBOT and SMS is provided below.

Table 1 Scope of work for CHW on the WBOTs. Source: Provincial guidelines for the implementation of the three streams of PHC re-engineering [15]

Improve the quality of life of community members by mobilizing for improved access to and delivery of Primary Health Care at local level within the context of an inter-sectoral environment	
1	Promote health and prevent illness
2	Conduct community assessments and mobilize around community needs
3	Conduct structured household assessment to identify their health needs
4	Provide psychosocial support to community members
5	Identify and manage minor health problems
6	Support screening and health promotion programmes in schools and Early Childhood Development (ECD) centers
7	Promote and work with other sectors and undertake collaborative community based interventions
8	Support continuum of care through service coordination with other relevant service providers

Ward-Based Outreach Teams (WBOTs)

Within the structure of South Africa's re-engineered PHC model are WBOTs. These work within specific geographical areas of PHC facility total catchment areas. The WBOTs consist of a team leader (often a Professional Nurse) and 6 community healthcare workers (CHWs) including a health promoter (HP) and an environmental health officer (EHP) where these exist [12]. The WBOT is linked to a PHC facility through the Outreach Team Leader who is usually a Professional Nurse based at a PHC facility. The objective of this stream of the PHC model is to provide PHC services at household and community levels. In Brazil, the model of taking healthcare services to the communities resulted in improved access to healthcare among the people and consequently healthier communities [13]. The findings of an evaluation of Brazil's Family Health Program on infant mortality rate show a decline from 49.7/1000 live births in 1990 to 28.9/1000 live births in 2002 [14]. The WBOTs refer clients to appropriate PHC facilities when necessary thus linking them to healthcare. The scope of work is centred on health promotion and prevention of disease (Table 1 [15]). With regards to TB services, the WBOTs' work is to identify, support and follow-up TB patients and their contacts [12]. They are supposed to ensure that TB patients adhere to treatment once initiated [16]. An exploratory research assessing TB/HIV-related training, knowledge and attitudes of CHWs conducted in both urban and rural parts of the Free State Province of South Africa revealed that at least a third of the CHWs had not been trained on basic TB/DOTs and over half of them had no formal training on HIV counselling and testing [17]. An earlier study conducted in Papua New Guinea on CHW clinical competency showed that CHW obtained low scores on clinical knowledge/skills and these scores worsened with duration of time since last training. The authors recommended closer on-site supervision as well as semi-annual trainings to ensure optimal healthcare service delivery by this cadre of healthcare workers [18].

Short message service (SMS) Technology

Globally, mobile cellular phone usage has grown tremendously over the past decade. By 2015, there were over 7 billion mobile cellular subscriptions [19]. Use of short message service (SMS) technology in patient healthcare has resulted in favourable outcomes particularly with regards to adherence to various chronic medications [20–23]. This technology is also acceptable among patients who use it [16, 24]. A systematic review which looked at interventions used to promote adherence to ART among HIV infected individuals found that there was a 65% increased chance of adherence to ART (confidence interval = 1.25–2.18) when SMS messages were used compared to no SMS [25].

SMS messaging has also been used to improve adherence to treatment among patients TB patients. Different companies have developed techniques to improve adherence to TB treatment. One of these techniques (SIMpill technique) involves the packaging of TB drugs in a special bottle that has a sim card in it. Once this bottle is opened, a message gets sent to a central server which stores the unique information for that medication bottle. This is linked to the patient's name and contact details. If the bottle is not opened, an SMS reminder gets sent to the patient's phone number. If the bottle is still not opened, another SMS is then sent to the patient's alternative number (relative's phone number). This SIMpill was piloted among 155 TB patients between July 2006 and April, 2007. The findings show improvement in both adherence and treatment success rate of 86–92% and 94% respectively [26]. Sending SMS messages to TB suspects who test positive asking them to go to the clinic could potentially contribute to reduction in initial LTFU among TB patients.

A study conducted in Cambodia which looked at active TB case finding in communities used SMS technology to send positive test results from the laboratory to TB workers. The TB workers would then inform the respective patients either telephonically or through Community Health Volunteers who conducted home visits. The researchers found that 94.6% (741/783) of the patients diagnosed with TB were initiated on treatment and at a median time of 3 days (IQR 1–6) [27].

Although linkage to care has been a favorable outcome of using SMS intervention in healthcare, there have also been instances of unresponsiveness to SMS messages. A study to understand the factors which influence adolescents' non-responsiveness to text messaging was conducted by Irons et al. [28]. This was a sub-study of a trial that evaluated the feasibility, acceptability and effectiveness of a text messaging reminder system to improve clinic attendance at family planning appointments among 5 young women using Depo-Provera contraception. The researchers found that personal conflicts such as school or work were a main cause for non-responsiveness. Findings from this study, however, cannot be generalized. The sample was drawn from the intervention arm of a small feasibility and acceptability family planning trial. The sample size may have limited ability to further stratify to identify differences between non-responders [28].

Problem statement

According to the South African National TB guidelines, treatment success rate is the proportion of new smear positive TB patients cured plus the number completed treatment but not meeting the criteria for "cure" or "failure". The denominator for this is the total number of new smear positive pulmonary TB patients registered [29]. However, the number of patients starting treatment is only a proportion of the ones eligible [7, 30]. There is a possibility that the success rate of the TB control program is an overestimate due to the assumption that the initial LTFU rate is negligible and so not factored in. Initial LTFU rates in South Africa range between 14.9 and 18% [8, 9]. These rates are much higher than the national target of "less than 5%" for the South African TB Control Program [29]. Long pathways to diagnosis, characterized mainly by health system structural barriers, have been found as one of the reasons for initial LTFU [3]. There is need to have ways that will help reduce this rate so as to achieve the national target.

Study justification

Adherence support to TB treatment in patients already initiated on treatment is covered in the scope of work of the WBOTs. However, following up patients diagnosed with TB but not initiated on treatment is not. TB treatment in a patient rapidly decreases infectivity, decreases transmission and is vital for TB control [10, 11]. Delaying TB treatment initiation or losing bacteriologically confirmed TB patients before treatment is initiated contributes to on-going TB transmission in communities and to poor patient outcomes. Strategies to reduce initial LTFU are needed in order to reduce on-going transmissions in communities. WBOTs are an important cadre of workers who make it possible for healthcare services to be delivered at the family and community levels. The concept of community level healthcare has been shown to work in reducing infant mortality rate [14]. Treatment adherence to chronic medication such as TB and HIV treatment is also done by the WBOTs [16]. However, ensuring that TB patients are initiated on treatment is not part of their scope of work. Having WBOTs involved in ensuring treatment initiation among TB patients is one way of reducing initial LTFU. SMS technology has also been shown to work in different programs [26]. Sending SMS messages to patients testing positive for TB is another way.

Conceptual framework

The conceptual framework for this study (Fig. 1) is based on a combination of 2 conceptual models. The Health Belief Model of the 1950s and later modified by Rosenstock et al. gives possible concepts to explain health behaviour [31]. The model by Krishnan et al. looks at individual and provider/system barriers/delays to TB diagnosis and treatment at various time points along the continuum of TB care [32]. The framework above takes into account the fact that there are both patient and health system factors that can prevent a patient from starting treatment. SMS and paper note reminders will address both patient and health system factors. Both methods will remind a patient that he/she needs to find time to go and collect the test results at the clinic. With regards to health system factors, WBOTs are a cadre of staff that can be utilized to ensure that patients return to the clinic for their results. This will reduce the proportion of patients diagnosed with TB but not initiated on treatment thereby reducing the TB transmission in communities.

Aim

The main aim is to assess the effectiveness of WBOTs and/or SMS technology in reducing initial LTFU among TB patients.

Objectives

1. To determine reasons for initial LTFU from the perspective of TB Program Managers and WBOT Managers.
2. To understand the nature of the work of WBOTs (spread, their reach, potential limitations they foresee with TB follow up work).
3. To assess the effectiveness of WBOTs in reducing initial LTFU among TB patients.
4. To assess the effectiveness of SMS technology in reducing initial LTFU among TB patients.
5. To describe the implementation process of distribution of paper note and SMS reminders to patients testing for TB from the perspectives of TB patients and of WBOTs.

Methods

The current cascade for patients with presumptive TB (TB suspects) in South Africa is as shown in Fig. 2 [29]. A patient feeling sick and presenting to a primary healthcare (PHC) facility is screened for TB symptoms. If productive cough is among the presenting symptoms, the patient is asked to produce sputum on the spot. This sputum is sent to the laboratory for testing. In the laboratory, the sputum is tested using the Xpert MTB/Rif (Xpert)

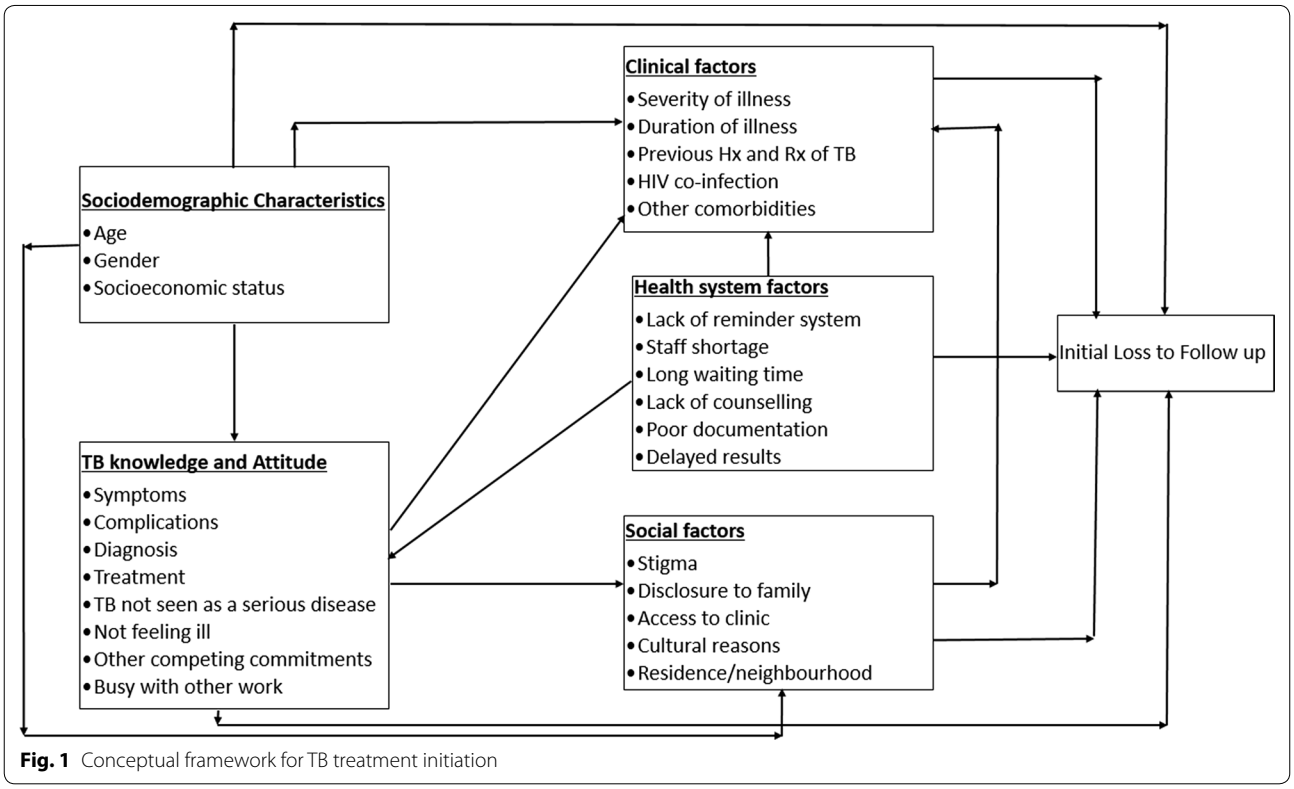


Fig. 1 Conceptual framework for TB treatment initiation

machine if available. If not available, smear microscopy is the diagnostic test used. Laboratory turnaround time for a test using the Xpert machine is 2 h. The patient is asked to come back after 2 days to cater for transportation time and delivery of result to the PHC facility. When the patient returns and if TB test result is positive, treatment is initiated same day or within 5 days. If diagnosis was done using Xpert, the patient is asked to submit another sputum sample for smear microscopy. This second sample is needed as a baseline for monitoring treatment progress when changing from intensive phase to continuation phase of treatment and at time of treatment completion. Xpert is not used for monitoring as it tends to pick up dead TB bacilli and would therefore give a positive test result even after 2 months of treatment [29].

The methods are described in detail below based on respective objectives.

Objective 1: To determine reasons for initial LTFU from the perspective of TB Program Managers and WBOT Managers

Study design: In depth interviews with TB Program Managers and WBOT Managers.

Study setting: City of Johannesburg.

Study population: TB Program Managers and WBOT Managers.

Sample size and data collection: In-interviews using a structured interview guide will be employed. Purposive sampling for maximum variation will be employed until saturation is reached. The interviewers will be researchers with experience in conducting in-depth interviews and with no relationship with potential participants. The interviews will be audio-recorded and then transcribed in readiness for analysis. To ensure reliability of the coding framework, the transcripts will be reviewed by 2 people so as to agree on the framework.

Outcomes: An understanding of the problem of initial LTFU of TB patients from the perception of managers. Thematic analysis in Nvivo 11 software will be used to analyse the data.

Objective 2: To understand the nature of the work of WBOTs (spread, their reach, potential limitations they foresee with TB follow up work)

Study Design: In depth interviews/Focus group discussions with WBOT members.

Study setting: City of Johannesburg.

Study population: Members of the WBOTs.

Sample size and data collection: Members of the WBOTs in the study area will be approached for participation. Purposive sampling for maximum variation will be employed until saturation is reached. A structured interview guide will be used.

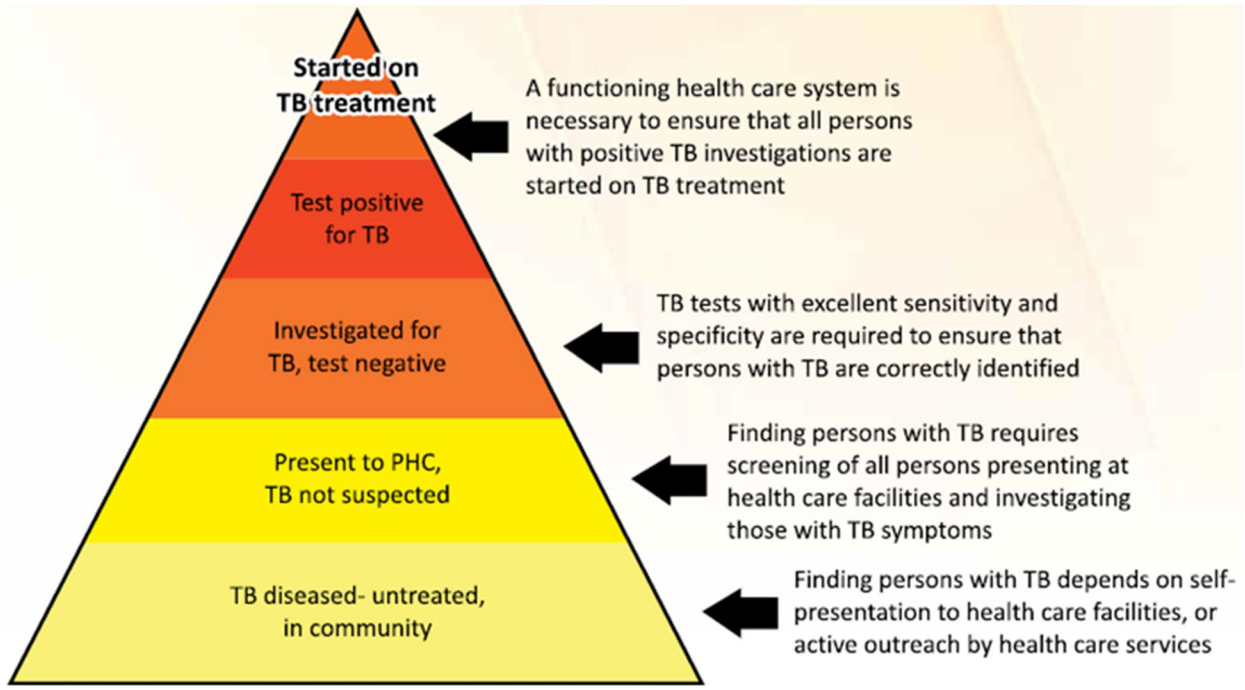


Fig. 2 Steps required for the diagnosis of TB (Source: SA National Tuberculosis Guidelines 2014 [29])

Outcomes: An understanding of the nature of the work of WBOTs. Thematic analysis in Nvivo 11 software will be used to analyse the data.

Objectives 3 and 4: To assess the effectiveness of SMS messaging or WBOTs on initial LTFU among TB patients

These 2 objectives are covered under the same methods.

Study design: This will be an Individual Randomised Controlled Trial. Two interventions (enhanced WBOTs and SMS technology) will be tested using the same population. Therefore, there will be 3 arms at the different sites/facilities (each site implementing all 3 arms of the study). The intervention "Enhanced WBOTs" refers to WBOTs conducting delivering paper note reminders to patients whose test results are ready in addition to their current scope of work [12]. SMS intervention will entail sending reminder SMS messages to TB patients as soon as results are received at the facility.

Arm A: Standard of care (no SMS technology and no enhanced WBOTs).

Arm B: SMS technology.

Arm C: Enhanced WBOTs.

A summary of the protocol is shown in Table 2.

Study setting: Inner-city Johannesburg metropolitan area in South Africa occupies an area of 1645 km^2 and has a population of 4.4 million [33]. WBOTs focus on health promotion, disease prevention and adherence support [12, 16]. Enhanced WBOTs will not only focus on those 3 areas, but they will also ensure that patients diagnosed with TB are initiated on treatment.

Study population: Patients with presumptive TB accessing healthcare services from the PHC facilities.

Inclusion criteria for TB suspects: Patients aged 18 years old and above not yet diagnosed with TB who present with productive cough of more than 24 h.

Exclusion criteria for TB suspects: Children less than 18 years old; patients already on TB treatment.

Sampling and sample size calculation

Eight high burden facilities with functional WBOTs linked to them will be conveniently selected from the health facilities in the district.

Patients meeting the inclusion criteria at the selected facilities will be allocated to any of the 3 arms. This will be by permuted block randomization. Patients who test positive for TB will be allocated any of the three letters from A to C depending on a pre-run block randomization sequence. The letter on the paper indicates the arm to which the patient is allocated to.

Due to lack of literature on SMS messaging and use of WBOTs to reduce initial LTFU in TB services, it will be assumed that the initial LTFU in this study will decrease from the 18% upper limit reported in South African studies to 5% in each of the arms with an intervention (with either SMS technology or with enhanced WBOTs). Sample size calculation will be calculated for either intervention versus control (standard of care). With a power of 80% and a level of significance of 0.05, the sample size required will be 94 TB patients in each arm. This gives a total sample of 282 for the 3 arms together. Accounting for 10% LTFU, the total minimum sample size of 311 TB patients will be required. Therefore, a sample size of 312 with 104 in each arm will be taken.

Interventions

The interventions are described below in detail for the different arms of the study.

Arm A: Standard of care (No enhanced WBOTs and no SMS technology)

As per current standard of practice, patients with presumptive TB submitting sputum will be asked for their contact details including mobile phone numbers. This information will be entered in the TB Case Identification Register as well as in the study book. The patients will submit sputum and asked to collect test result after 2 days. The TB Case Identification Register at the clinic will be checked regularly to check the results of the patients enrolled in the study. The names of those with a positive result will be checked for in the TB Treatment initiation register. The TB patients will be allocated to this arm if they are allocated the letter "A" from the randomization block. After 4 weeks, the ones with positive TB test result but not initiated on treatment will be noted.

Arm B: SMS technology

This group will have the SMS technology as the intervention. As per current standard of practice, patients with presumptive TB submitting sputum will be asked for their contact details including mobile phone numbers. This information will be entered in the TB Case Identification Register as well as in the study book. The patients will submit sputum and asked to collect test result after 2 days. Patients with positive test results will receive SMS messages telling them that their results are ready at the facility. The TB patients' names will be allocated to this arm if they are allocated the letter "B" from the randomization block. The TB treatment initiation register at the clinic will be checked regularly for names of the patients randomized to this arm for a period of 4 weeks. The ones with positive TB test but not initiated on treatment will be noted.

Arm C: Enhanced WBOTs

As per current standard of practice, patients with presumptive TB submitting sputum will be asked for their

Table 2 Research protocol summary

Objective	Study design	Study population, sample and sample size	Data collection tools/method	Main outcome variables/ construct	Data analysis technique
To determine reasons for initial LTFU from the perspective of service providers	In-depth interviews	TB Program Managers/WBOT Managers (min 6)	Structured interview guide	Knowledge of the TB program; reasons for initial LTFU	Thematic analysis
To understand the nature of the work of WBOTs (spread, their reach, potential limitations they foresee with TB follow up work)	In-depth interviews/Focus group discussion	WBOT members from facilities with functional WBOTs (min 4)	Structured interview guide	Knowledge of the work of the WBOTs	Thematic analysis
To determine the effectiveness of WBOTs in reducing initial LTFU among TB patients	Randomized controlled trial	Patients testing for TB TB positive patients (312)	Data from TB case identification register and from TB treatment initiation registers to a study data abstraction form	Treatment initiation within 4 weeks of submitting sputum for diagnosis	Descriptive analysis Chi square statistics regression analysis (cox and multinomial)
To determine the effectiveness of SMS technology in reducing initial LTFU among TB patients	Randomized controlled trial	Patients testing for TB TB positive patients (312)	Data from TB case identification register and from TB treatment initiation registers to a study data abstraction form	Treatment initiation within 4 weeks of submitting sputum for diagnosis	Descriptive analysis Chi square statistics regression analysis (cox and multinomial)
To describe the implementation process of distribution of paper note and SMS reminders to patients testing for TB from the perspectives of TB patients and of WBOTs	Descriptive case study	TB patients (min 6) WBOTs (min 6)	In-depth interviews	Perceptions of TB patients and those of WBOTs of the process of distribution of reminder messages	Thematic analysis

contact details including mobile phone numbers. This information will be entered in the TB Case Identification Register as well as in the study book. The patients will be informed that results of the test will be ready after about 2 days when they can go to the clinic to collect them. The patients' names who test positive for TB and allocated to this arm will be given to the WBOTs. The patients will be allocated to this arm if they are letter "C" from the randomization block. The WBOTs will then deliver a paper note advising the patient to go to the clinic to collect TB results. In the event that the WBOTs do not find the patient at the named address, they will leave the paper note. Treatment initiation registers at the clinics will be checked regularly for a period of 4 weeks. The ones with positive TB test result but not initiated on treatment will be noted.

Outcome: The primary outcome is the proportion of TB patients not initiated on treatment within 4 weeks of submitting sputum for diagnosis among patients accessing services from the 3 study arms. A secondary outcome will be the time to treatment initiation.

Analysis: Descriptive analysis to determine the initial LTFU for the different study arms will be run and comparisons across the different arms will be done using Chi square statistics and regression analysis (cox and multinomial) to determine associations and predictors of initial LTFU.

Objective 5: To describe the implementation process of distribution of paper note and SMS reminders to patients testing for TB from the perspectives of TB patients and of WBOTs

Study design: Focus group discussions and/or in-depth interviews with WBOT members and In-depth interviews with some of the TB patients who received reminder messages.

Study setting: City of Johannesburg.

Study population: Members of the WBOTs at the study sites and also TB patients who received reminder messages.

Inclusion criteria: WBOT members at the study sites and TB patients who were part of the study.

Exclusion criteria: WBOT members from facilities not from the study sites and TB patients not enrolled in the study.

Sample size and data collection

All available members of the WBOTs at the study sites will be approached for participation in a focus group discussion or in-depth interviews will be conducted if the WBOT members are not available at the same time for a focus group discussion. Focus group discussion/interview guide will be used. In-depth interviews with TB patients using a structured interview guide will be employed. Purposive sampling for maximum variation will be employed until saturation is reached. The interviewers will be researchers with experience in conducting in-depth interviews and with no relationship with potential participants. The interviews will be audio-recorded and then transcribed in readiness for analysis. To ensure reliability of the coding framework, the transcripts will be reviewed by 2 people so as to agree on the framework. Outcomes: Perceptions of the implementation process by implementers (WBOTs) and the by the users (TB patients). Thematic analysis in Nvivo 11 software will be used to analyse the data.

Limitations

A main limitation with sending SMS messages will be that there will be no way of ascertaining if the messages reach the targeted people.

Some patients might not go to collect their test result at the facility where the TB test was done. They might test elsewhere and actually get initiated on TB treatment. To overcome this, contact details of participants will be collected so that after the 1 month period, it will be possible to know if the patients are indeed LTFU by checking treatment registers in the facilities within inner-city Johannesburg as well as the ETR.net/TIER.net.

Abbreviations

TB: tuberculosis; LTFU: loss to follow up; WBOT: Ward-Based Outreach Team; SMS: short message service; WHO: World Health Organization; DOTS: Directly Observed Therapy Short-Course; ART: antiretroviral therapy; Xpert: Xpert MTB/Rif; PHC: primary healthcare; CHWs: community healthcare workers; HP: health promoter; EHP: environmental health officer.

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Authors' contributions

JRMM-K and CM conceptualized the study. JRMM-K and CC were involved in the design of the study. JRMM-K drafted the manuscript. CM, CC and NI reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
This article is a research proposal. The data collected thus far has not yet been analysed.

Ethics approval and consent to participate
Permission to conduct this study has been granted by the University of Witwatersrand Human Research Ethics Committee (M170651) and the Johannesburg District Research Committee (DRC 2017-08-0001) and registered with the South African National Health Research Database (GP2017 GP_201708_24). Informed consent will be sought from all the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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8.5. Appendix 5: Study Approvals

R14/49 Dr J Mwansa-Kambafwile et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170651

NAME: Dr J Mwansa-Kambafwile et al
(Principal Investigator)
DEPARTMENT: School of Public Health
Medical School

PROJECT TITLE: Initial lost to follow-up and contact tracing amongst tuberculosis patients: the role of ward-based outreach teams (WBOT's) and short message service (SMS) technology

DATE CONSIDERED: 30/06/2017

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Professor C Menezes

APPROVED BY: _____
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 23/10/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

_____ _____
Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Joburg
a world class African city

JOHANNESBURG HEALTH DISTRICT

11th Floor, Central- west wing
Residence, Chris Hani Baragwanath
Academic Hospital,Chris Hani Road
Soweto, South Africa
judy.mwansa@gmail.com

Enquiries: Dr EM Ohaju
Tel: 011 694 3888 Cell: 076 8831659
Email: Elizabeth.Ohaju@gauteng.gov.za
Hillbrow CHC: Administration Building
Cr Smith Str. & Klein Street
Private Bag X21, Johannesburg
South Africa, 2017

DRC Ref: 2017-08-001

NHRD Ref no: GP_201708_024

Dear: Dr Judith Mwansa-Kambafwile

Re: INITIAL LOSS TO FOLLOW UP AMONG TUBERCULOSIS PATIENTS: THE ROLE OF WARD-BASED OUTREACH TEAMS AND SHORT MESSAGE SERVICE (SMS) TECHNOLOGY

Your application for Research Approval refers

The District Research Committee has reviewed your application. This letter serves as an in-principle approval to interview managers/staff of the TB program and of the Ward-based Outreach program as well as to access the Districts Health facilities (mentioned below) for the above project subject to following conditions:

- The facility to be visited: **Glenanda Clinic, Rosettenville Clinic, South Hills Clinic, Yeoville Clinic, Hillbrow clinic, Witkopen Clinic, Lenasia South CHC, Lenasia Clinic, Zola Clinic, Senaone Clinic, Itireleng Clinic, Joubert Park Clinic, Randburg clinic, Hikhensile clinic, Malven Clinic, and freedompark clinic.**
- This facility will be visited from 28/05/2018 to 28/05/2019
- The research can only commence after you submit an ethics clearance certificate from a recognized institution.
- You will report to the Facility Manager before initiating the study.

Region	Regional Health Manager	Contact No.	Cell phone
A	Nelly Shongwe	011 237 - 8010	082 467 9276
B	Paulinah Maepa	011 718 - 9656	082 551 5804
D	Mabel Ngcobo	011 986 - 0164	082 467 9316
F	Oupa Montsioa	011 681 - 8130	082 467 9423
G	Hlubi Ntamehlo	011 211 - 8936	083 286 0388
ABEF	Ms Matlala	011 440 - 1259	082 307 0267

- Participants' rights and confidentiality will be maintained all the time.
- No resources (Financial, material and human resources) from the above facilities will be used for the study. Neither the District nor the facility will incur any additional cost for this study.
- The study will comply with Publicly Financed Research and Development Act, 2008 (Act 51 of 2008) and its related Regulations.
- You will submit a copy (electronic and hard copy) of your final report. In addition, you will submit a six-monthly progress report to the District Research Committee.
- Your supervisor and University of South Africa will ensure that these reports are being submitted timeously to the District Research Committee.
- The District must be acknowledged in all the reports/publications generated from the research and a copy of these reports/publications must be submitted to the District Research Committee.

We reserve our right to withdraw our approval, if you breach any of the conditions mentioned above.

Please feel free to contact us, if you have any further queries. On behalf of the District Research Committee, we would like to thank you for choosing our District to conduct such an important study.

Regards,

Dr EM Ohaju
Chairperson: District Research Committee
Johannesburg Health District
Date 28/05/2018

Acting

Mrs M. Morewane
Chief Director
Johannesburg Health District
Date: 30/05/2018

8.6. Appendix 6: Study Tools

MANAGERS' IN-DEPTH INTERVIEW

I want to thank you for taking the time to meet with me today. My name is _____ and I would like to talk to you about your initial loss to follow up of TB patients. We are aiming to determine your understanding of Ward-based outreach teams as a Manager. The interview should take less than an hour. I will be recording the session because I don't want to miss any of your comments. Although I will be taking some notes during the session, I can't possibly write fast enough to get it all down. Because we're on tape, please be sure to speak up so that we don't miss your comments. All responses will be kept confidential. This means that your interview responses will only be shared with investigator team members and we will ensure that any information we include in our report does not identify you as the respondent. Remember, you don't have to talk about anything you don't want to and you may end the interview at any time. Are there any questions about what I have just explained? Are you willing to participate in this interview?

Contact details of researcher/s – The person who is finally in charge of this study is Dr Judith Mwansa 071 073 3406. If you believe that we have not cared for you correctly, or you have other complaints, please call the person in charge of the Wits Ethics Committee. The administrator (secretary) of the committee is Ms Zanele Ndlovu. Her telephone number is 011-717-1252.

Name: _____
Sign: _____
Date: _____

Witness: _____
Sign: _____
Date: _____

Name:
D.O.B/Age: _____
Gender: male / female

Job Title: _____

Duration worked in above position: _____

What do you know about procedure for patients starting TB treatment?
_____
_____
Do you think there is a problem with starting patients on TB treatment (Explain your answer)?
_____
_____
What do you think are the reasons why TB patients are loss to follow up before treatment initiation?
_____
_____

What would be your suggestion with regards to ensuring that all TB patients are started on treatment?
_____
_____
_____
Do you think Ward-based outreach teams could be used to assist with ensuring all TB patients are started on treatment (Elaborate)?

_____
_____
_____
Do you think SMS messages could be used to assist with ensuring all TB patients are started on treatment (Elaborate)?
_____

WBOTS PAPER NOTE/SMS MESSAGE FOR TB PATIENTS

English
Date of note issue/SMS sent: _____
Good day, your results for the TB test are ready at the clinic for your collection. You are advised to collect your results as soon as possible.
Best regards
Clinic TB Team

IsiZulu
Usuku lokukhishwa kombhalo _____
Sawubona _____ (igama lesiguli)
Imiphumela yakho yokuhlolwa seyikhona emtholampilo ungeza uzoyithatha. Uyacelwa ukuthi ufike uzothatha imiphumela yokuhlolwa ngokushesha. Veza lo mlayezo uma ufika emtholampilo.
Ozithobayo
Abasebenzi baseMtholampilo

INFORMATION DOCUMENT and INFORMED CONSENT (Enrolment)

Study title: Initial Loss To-Follow Up among TB patients
Greeting: Good day; thank you for your time.
My name is: _____
Introduction:
We are conducting a research to determine if using SMS messaging and/or using Ward-based Outreach Teams (WBOTs) helps to ensure that patients diagnosed with TB start taking TB treatment. Research is a word which means the things we do to learn the answer to a question. Finding, diagnosing people who have TB early and putting them on treatment will mean that these people will not infect other people they live with or spend time with and therefore they won't spread TB in the community.
Invitation to participate: We are inviting you to take part in this research study.
What is involved in the study –
As a participant in the study, you will be allocated to a group that will receive one of the following: SMS message; a paper note from WBOTs; both SMS and paper note; or neither SMS nor paper note from WBOTs.
Risks: There are no risks to participants in terms of your personal health.
Benefits: We will be able to know if the interventions we are proposing can help increase the number of TB patients starting treatment. Consequently we will reduce TB transmission in communities.
Participation is voluntary, As a person you have rights to health, and if you chose not to be a part of this study, nothing can take away your rights to health. You can be sure that if you do not wish to participate, you will not suffer in any way. You will still receive the services you need.
Confidentiality: Your personal and contact information will be kept confidential when presenting our study findings. Your name or information that will give away your identity will not be shared outside the research team. Any publications from this work will not identify participants in any way.
Contact details of researcher/s – The person who is finally in charge of this study is Dr Judith Mwansa 071 073 3406. If you believe that we have not cared for you correctly, or you have other complaints, please call the person in charge of the Wits Ethics Committee. The administrator (secretary) of the committee is Ms Zanele Ndlovu. Her telephone number is 011-717-1252.

INFORMED CONSENT
I, _____, have voluntarily agreed to take part in this research study to determine if using SMS messaging and/or using Ward-based Outreach Teams (WBOTs) helps to ensure that patients diagnosed with TB start taking TB treatment. I have read this consent form (or had it read to me by the research study staff member, and have had an opportunity to discuss this with him/her. All questions have been answered to my satisfaction and I fully understand my participation in this study. I will be given a copy of the consent form to keep.

_____	_____	_____
Name & Signature of Patient	Date	Time
_____	_____	_____
Name & Signature of Witness	Date	Time

Specimen Barcode: _____

INITIAL LOSS TO FOLLOW UP AMONG TUBERCULOSIS PATIENTS: THE ROLE OF WARD-BASED OUTREACH TEAMS AND SHORT MESSAGE SERVICE (SMS) TECHNOLOGY					*Return visit
1	Facility Name:				
2	Study Number:				
3	Date submitted sputum for TB test:	DD MMM (words) YYYY			
*4	Date TB treatment started:	DD MMM (words) YYYY			
	Sociodemographic Characteristics				
*5	Weight (kg):				
*6	Height (m):				
7	Date of Birth:	DD MMM (words) YYYY			
8	Gender:	Male		Gender:	
9	Marital status	Never married	Currently married	Separated	
		Divorced	Widowed	Other: Specify	
10	What is the highest level of education attained?	None	Primary	Secondary	Tertiary
11	Occupation:				
12	Are you currently employed?	Yes		No	
13	What is your average monthly income? (rands)				
14	How many people do you take care of financially?				
	Clinical Factors				
15	For how long were you feeling sick this time before you came here to get tested?	< 2 weeks	2-4 weeks	> 4 weeks	
16	Did you go to the clinic for this cough before coming here to be tested?	Yes		No	
17	If Yes, how many times?				
18	Have you ever had TB before this time?	Yes		No	

Specimen Barcode: _____

19	If Yes, how many times?					
20	If Yes, how long ago most recent TB episode?	<1 year ago	1-2 years ago	>2 years ago		
21	What other diseases do you suffer from?	Diabetes	High blood pressure	Epilepsy	Heart problem	Other: specify
22	What is your HIV status?	Positive	Negative	Don't know		
23	If Positive, are you on ART?	Yes		No		
24	For how long have you been on ART?	< 1 month	1-12 months	> 12 months		
25	What ART drugs are you taking?					
	Social Factors					
26	Do you take alcohol?	Yes		No		
27	Do you smoke cigarette?	Yes		No		
28	Did you tell anyone you were going to test for TB?	Yes		No		
29	If No why?	No time	Not necessary	Scared		
30	Did you tell anyone you were going to get results for TB?	Yes		No		
31	If No why?	No time	Not necessary	Scared		
32	Have you spent at least 8 hours with someone with TB in the last 1 year?	Yes		No		
33	If Yes, how long ago?	<3 months ago	3-6 months ago	>6 months ago		
34	Do you live in Johannesburg?	Yes		No (specify town or province or country)		
35	How far is your place of residence from the clinic (time by transport)?	Less than 5 mins	5-30 mins	30 mins - 1 hour	More than 1 hour	
	TB Knowledge and Attitudes					

Specimen Barcode: _____

36	Before testing this time, had you heard about TB?	Yes		No	
37	Before testing this time, did know how one can get TB?	Yes		No	
39	Before testing this time, did you know symptoms of TB?	Yes		No	
40	Before testing this time, did you know TB be can be cured?	Yes		No	
* 41	What made you come back to the clinic after testing?	I was told to come back by nurse	I received SMS reminder	I received paper note reminder	Other: specify
* 42	If you received any reminder (SMS/Paper note), how long after that did you come?	< 1 day	1-3 days	> 3 days	
	THANK YOU FOR YOUR PARTICIPATION				

WBOTs' IN-DEPTH INTERVIEW

I want to thank you for taking the time to meet with me today. My name is _____ and I would like to talk to you about your experiences with regards to the implementation of the paper note and SMS reminders project. We are aiming to determine your experiences – both negative and positive. The interview should take less than an hour. I will be recording the session because I don't want to miss any of your comments. Although I will be taking some notes during the session, I can't possibly write fast enough to get it all down. Because we're on tape, please be sure to speak up so that we don't miss your comments. All responses will be kept confidential. This means that your interview responses will only be shared with investigator team members and we will ensure that any information we include in our report does not identify you as the respondent. Remember, you don't have to talk about anything you don't want to and you may end the interview at any time. Are there any questions about what I have just explained? Are you willing to participate in this interview?

Contact details of researcher/s – The person who is finally in charge of this study is Dr Judith Mwansa-Kambafwile 071 073 3406.If you believe that we have not cared for you correctly, or you have other complaints, please call the person in charge of the Wits Ethics Committee. The administrator (secretary) of the committee is Ms Zanele Ndlovu. Her telephone number is 011-717-1252.

Name: _____
Sign: _____
Date: _____

Witness: _____
Sign: _____
Date: _____

Name:

D.O.B:_____ Gender: male / female

For how long were you involved in the project? _____

What were your most memorable moments of the implementation?
_____
_____
_____
What challenges did you face?
_____
_____
_____
What do you think were the causes of your challenges?

_____
_____
_____

How would you suggest the challenges can be overcome?

_____
_____
_____

How would you describe the attitude of the patients when you gave them the paper note reminders?

_____
_____
_____

Would you say that the project achieved its objectives?

_____
_____
_____

Is there anything else you would like to add on in terms of suggestions on the way things are done at the facilities or on patients diagnosed with TB? *(Probe on healthcare system recommendations and advice to newly diagnosed TB patients etc.)*

_____
_____
_____

INFORMATION DOCUMENT and INFORMED CONSENT

Study title: Initial Loss To-Follow Up among TB patients

Greeting: Good day; thank you for your time.

My name is: _____

Introduction:

We are conducting a research to determine if using SMS messaging and/or using Ward-based Outreach Teams (WBOTs) helps to ensure that patients diagnosed with TB start taking TB treatment. Research is a word which means the things we do to learn the answer to a question. Finding, diagnosing people who have TB early and putting them on treatment will mean that these people will not infect other people they live with or spend time with and therefore they won't spread TB in the community.

Invitation to participate: We are inviting you to take part in this research study.

What is involved in the study –

As a participant in the study, you were allocated to a group received one of the following: SMS message; a paper note from WBOTs; or neither SMS nor paper note from WBOTs. We now would like to hear from you your experience during the study

Risks: There are no risks to participants in terms of your personal health.

Benefits: We will be able to know your experiences and how you felt about the being the study. This is helpful in knowing if the interventions can be rolled out or not.

Participation is voluntary, As a person you have rights to health, and if you chose not to be a part of this study, nothing can take away your rights to health. You can be sure that if you do not wish to participate, you will not suffer in any way. You will still receive the services you need.

Confidentiality: Your personal and contact information will be kept confidential when presenting our study findings. Your name or information that will give away your identity will not be shared outside the research team. Any publications from this work will not identify participants in any way.

Contact details of researcher/s – The person who is finally in charge of this study is Dr Judith Mwansa 066 301 1725. If you believe that we have not cared for you correctly, or you have other complaints, please call the person in charge of the Wits Ethics Committee. The administrator (secretary) of the committee is Ms Zanele Ndlovu. Her telephone number is 011-717-1252.

INFORMED CONSENT

I, _____, have voluntarily agreed to take part in this research study to share my experiences during my participation in the study. The study aimed to determine if using SMS messaging and/or using Ward-based Outreach Teams (WBOTs) helps to ensure that patients diagnosed with TB start taking TB treatment. I have read this consent form (or had it read to me by the research study staff member, and have had an opportunity to discuss this with him/her. All questions have been answered to my satisfaction and I fully understand my participation in this study. I will be given a copy of the consent form to keep.

_____	_____	_____
Name & Signature of Patient	Date	Time
_____	_____	_____
Name & Signature of Witness	Date	Time

TB PATIENTS' IN-DEPTH INTERVIEW (English)

I want to thank you for taking the time to meet with me today. My name is _____ and I would like to talk to you about your experiences with regards to the implementation of the paper note and SMS reminders project. We are aiming to determine your experiences as a TB patient who received a reminder message – both negative and positive experiences. The interview should take less than an hour. I will be recording the session because I don't want to miss any of your comments. Although I will be taking some notes during the session, I can't possibly write fast enough to get it all down. Because we're on tape, please be sure to speak up so that we don't miss your comments. All responses will be kept confidential. This means that your interview responses will only be shared with investigator team members and we will ensure that any information we include in our report does not identify you as the respondent. Remember, you don't have to talk about anything you don't want to and you may end the interview at any time. Are there any questions about what I have just explained? Are you willing to participate in this interview?
Contact details of researcher/s – The person who is finally in charge of this study is Dr Judith Mwansa 066 301 1725. If you believe that we have not cared for you correctly, or you have other complaints, please call the person in charge of the Wits Ethics Committee. The administrator (secretary) of the committee is Ms Zanele Ndlovu. Her telephone number is 011-717-1252.

Name: _____
Sign: _____
Date: _____

Witness: _____
Sign: _____
Date: _____

Name:
D.O.B:_____
Gender: male / female

For how many months were you on TB treatment?
_____
_____
_____
What type of reminder message did you receive? _____
How did you feel after receiving the message?
_____
_____
_____
What can you say about the way in which you received the message?
_____
_____
_____

Would you say that the message made a difference to your action (Elaborate)?

_____
_____
_____

Would you prefer receiving the message differently and if so how?

_____
_____
_____

Do you think receiving the message is good or bad (Elaborate)?

_____
_____
_____

Is there anything else you would like to add on in terms of suggestions on the way things are done at the facilities or on patients diagnosed with TB? *(Probe on healthcare system recommendations and advice to newly diagnosed TB patients etc.)*

_____
_____

INCWADI YOLWAZI NEMVUME (IsiZulu)
Isihloko socwaningo: Izizathu zeziguli zokungabuyeli ukuyothatha umshwanguzo wesifo sofuba ngemva kokwaziswa.
Imikhonzo: Sawubona, ngiyabonga isikhathi sakho.

Igama lami ngu:

Isingeniso:

Senza ucwaningo ukuze sithole ukuthi ingabe ukuthumela umlayezo ngocingo (SMS) kumbe ukusebenzisa i- Ward-based Outreach Teams (WBOTs) kungasiza yini ukuqinisekisa ukuthi abantu abahaqwe isifo sofuba (TB) bayaqala ukuthatha imishwanguzo yabo ngokushesha. Ucwaningo yigama elisho ukuthi ukuthola ulwazi ngombuzo othile. Ukuthola kanye nokuxilonga abantu abanesifo sofuba nokubakhuthaza ukuthi bathathe imishungwazo ngokukhulu ukushesha kusho ukuthi ngeke basathelela abantu abahlala nabo noma abantu abachitha isikhathi nabo ngakho-ke lesifo ngeke sichayeke sigcwale kakhulu.

Isimemo: Sikumema ukuba ubeyingxenye yalolucwaningo.

Yini ehlanganisa lolucwaningo –

Njengengxenye yalolucwaningo, ungabe ungomunye wabantu abathole lokhu okulandelayo: Umlayezo wocingo (SMS); ipheshana elibuya kwi-WBOTs ; noma awutholanga i-SMS kanye nepheshana. Okwamanje singathanda ukuzwa ngokuhlangenwe nakho kwakho.

Ubungozi: Abukho ubungozi obuhlangene nokuphepha kwempilo yakho.

Izinzuzo: Sizokwazi ukuthola ukuthi waphatheka kanjani noma indlela ozizwé ngayo ngokuba yingxenye yalolucwaningo. Lokhu kuyasiza ukuze sazi ukuthi loluhlelo lungasetshenziswa yini noma cha.

Ukuba yingxenye akuphoqelelwa kodwa ukwenza ngokuzithandela. Njengomuntu unamalungelo ezempilo, ngaleyo ndlela uma kwenzeka ukhethe ukungabi yingxenye yalolucwaningo akukho okuzothatha ilungelo lakho ngezempilo. Ungaqiniseka ukuthi uma ukhetha ukungabi yingxenye angeke uhlukumezeke nganoma iyiphi indlela. Usazothola usizo lokwelashwa oludingayo.

Okuyimfihlo yakho: Imininingwane yakho nenombolo yakho yocingo kuzogcinwa kuyimfihlo lapho sethula esikutholile ngocwaningo. Igama lakho kanye nokunye okungase kuveze ukuthi ungubani, kuzobonwa kuphela ngabayingxenye yethimba lwocwaningo. Esizokusakazela emphakathini mayelana nalokhu esikuthole kulocwaningo ngeke kuveze abayingxenye yalolucwaningo nganoma iyiphi indlela.

Imininingwane yabacwaningi ─ Umuntu ophethe ithimba labacwaningi nguDokotela u-Judith Mwansa, inombolo yakhe ithi 066 301 1725. Uma ukholelwa ukuthi asizange sikukhathalele kahle kumbe unezinye izikhalo, sicela ushayele ophethe i-Wits Ethics Committe. Unobhala wekhomishi nguNksz Zanele Ndlovu, inombolo yakhe ithi 011-717-1252.

IMVUME

Mina,_____, ngivume ngokuzithandela ukuba yingxenye yalolucwaningo ukuze nginazise ngokuhlangenwe nakho kwami. Inhloso yalolucwaningo ukucacisa ukuthi ingabe ukusebenzisa i-SMS kumbe ukusebenzisa i-Ward-based Outreach Teams (WBOTs) kuyasiza ukuqinisekisa ukuthi iziguli ezinesifo sofuba ziqala ukuthatha amapilisi wesifo sofuba. Ngiyifundile lemvume (kumbe ilunga lethimba lalolucwaningo lingifundele yona futhi nginikwe ithuba lokuxoxa ngalolucwaningo naye). Yonke imibuzo ebenginayo iphenduliwe ngokwaneliseka futhi ngiyaqonda ubungxenye bami kulolucwaningo. Ngizonikwa ikhopi yalemvume ukuze ngiyigcine.

Igama nokusayina Usuku Isikhathi

Igama nokusayina Usuku Isikhathi

INGXOXO EJULILE NEZIGULI ZESIFO SOFUBA

Ngithanda ukukubonga ngokuthatha isikhathi sakho uhlangana nami namhlanje. Igama lami ngu,_____, futhi ngingajabula kakhulu ukukhuluma nawe ngendlela ozizwe ngayo mayelana nomkhankaso wokuthumela umlayezo nge-SMS kumbe ngepheshana. Inhloso yethu ukuthola ukuthi uye waphatheka kanjani njengesiguli sesifo sofuba (TB) ngesikhathi uthola umlayezo – lokhu kuhlanganisa okuhle nokubi. Ingxoxo yethu izothatha isikhathi esingaphansi kwehora elilodwa. Ngizobe ngirekhoda ingxoxo yethu ukuze kungasali lutho ozokuphawula. Nakuba ngizobe ngibhala phansi okunye ozokusho kungenzeka ngingakwazi ukukubhala konke. Njengoba sirekhoda lengxoxo ngicela ukhulume uzwakale ukuze kungasali lutho. Yonke imibono yakho izogcinwa njengemfihlo. Lokhu kusho ukuthi zonke izimpendulo zakho zizofinyelela ithimba locwaningo kuphela futhi sizoqinisekisa ukuthi imininingwane yakho njengengxenye yalolucwaningo ayaziwa. Khumbula ukuthi akudingeki ukuthi ukhulume ngezinto ongathandi ukukhuluma ngazo futhi ungayinxamula ingxoxo nganoma isiphi isikhathi uma uzizwa ungakhululekile. Ingabe unemibuzo mayelana nalokhu esengikuchazile? Ingabe uzimisele ukuba yingxenye yalengxoxo?

Imininingwane yabacwaningi ─ Umuntu ophethe ithimba labacwaningi nguDokotela u-Judith Mwansa, inombolo yakhe ithi 066 301 1725. Uma ukholelwa ukuthi asizange sikukhathalele kahle kumbe unezinye izikhalo, sicela ushayele ophethe i-Wits Ethics Committe. Unobhala wekhomishi nguNksz Zanele Ndlovu, inombolo yakhe ithi 011-717-1252.

Igama:

Sign:

Usuku:

Ufakazi:

Sign:

Usuku:

Igama:

Usuku lokuzalwa:

Ubulili: owesilisa / owesifazane

Sekuyizinyanga ezingaki uthatha umshwanguzo wesifo sofuba (TB)?

Yimuphi umlayezo wesikhumbuzo owutholile?
Uzizwe kanjani emva kokuthola lomlayezo?

Yikuphi ongakusho mayelana nendlela othole ngayo umlayezo?

Ucabanga ukuthi umlayezo wenze umehluko ngendlela osabalele ngayo? Chaza.

Ubungathanda ukuthola lomlayezo ngendlela ehlukile? Uma kunjalo iyiphi leyondlela?

Ucabanga ukuthi ukuthola umyalezo kuhle noma kubi? Chaza.

Ingabe kukhona okunye ofisa ukwengeza okuyiziphakamiso mayelana nendlela izinto ezenziwa ngakhona ezindaweni zokwelashwa noma ngabantu abantu abatholwe banesifo sofuba? (Ukuthuthukiswa uhlelo lokwezokunakekelwa kwezempilo kanye neseluleko kulabo abasanda kuthola ukuthi banesifo sofuba)

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