Exploring TB patient journeys and the emergence of MDR-TB in India and South Africa: A multi-methods study

Stephanie Law

Department of Epidemiology, Biostatistics and Occupational Health
McGill University, Montreal

December 2018

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Ph.D. in Epidemiology

Table of Contents

ABSTRACT

Background: Today, about 5% of all tuberculosis cases and 15% of all tuberculosis (TB) deaths are due to isolates that are multidrug-resistant (MDR), that is, resistant to isoniazid and rifampicin, the most potent TB drugs (WHO 2017a). The emergence of MDR-TB is largely due to incorrect and insufficient treatment. TB patient treatment journeys – from the onset of TB symptoms to completion of treatment, or death – include frequent encounters with multiple health care providers, over long periods of time, from six months to more than two years. Exploring these patient journeys could provide insight into potential interventions to prevent further emergence of drug resistance.

Objective: This dissertation used quantitative and qualitative methods to explore TB patient journeys in India and South Africa, two countries with a high burden of MDR-TB. These two countries served as case studies to investigate potential patient-, provider-, and systems-level interventions to improve patient retention-in-care and adherence, and their impact on TB and MDR-TB epidemics.

Methods: 1) A dynamic Markov model was constructed to represent India's TB epidemic, including a probabilistic framework reflecting complex TB treatment-seeking pathways. This model explored the impact of the different health care sectors (private, public and informal) on the emergence of drug-resistance. 2) A qualitative study was conducted to explore TB patient treatment journeys and potential strategies to improve patient retention-in-care in Cape Town, South Africa. 3) A systematic review was conducted to evaluate the effectiveness of psychosocial, educational and materials support interventions to improve MDR-TB treatment adherence and retention-in-care. 4) The dynamic Markov model constructed in part 1 was adapted to represent South Africa's TB epidemic, and used to explore the impact of strategies targeting different stages of the TB cascade of care on the emergence of drug-resistance and TB mortality.

Findings: In both India and South Africa, strengthening existing care for TB patients in the public

system - with a focus on reducing poor treatment adherence and losses to follow-up - would lead to greater reductions in drug resistance and mortality than other strategies, such as expanding access to new TB drugs. Strategies to promote treatment adherence and retention-in-care were suggested by the qualitative study in South Africa and the systematic review. The former study revealed the importance of establishing patient-provider trust. The latter study found that MDR-TB patients who received individual counselling or home visits by trained health workers, had lower rates of loss to follow-up than others who did not.

Conclusion: There is an urgent need to address patient-, provider- and systems-level issues affecting patient retention-in-care and treatment adherence, as these are major drivers of the global MDR-TB epidemic. This is particularly important to protect new drugs being introduced into routine treatment, such as bedaquiline and linezolid, to help prevent the development and further transmission of resistance to these drugs. Future research should develop and rigorously assess interventions that promote adherence and retention-in-care to prevent further worsening of the global DR-TB epidemic.

RÉSUMÉ

Contexte : Présentement, environ 5% de tous les cas de tuberculose (TB) et 15% de tous les décès dus à la TB sont causés par des isolats multirésistants (MR), c'est-à-dire résistants à l'isoniazide et à la rifampicine, les médicaments antituberculeux les plus puissants (WHO 2017a). L'émergence de la TB-MR peut être attribuée à des traitements inadéquats. Le parcours du patient, depuis l'apparition des premiers symptômes jusqu'à la fin du traitement ou le décès, comprend plusieurs rencontres avec de multiples prestataires de soins de santé, sur de longues périodes, de six mois à plus de deux ans. L'analyse de ces parcours pourrait donner un aperçu des interventions possibles visant à prévenir l'apparition ultérieure d'une résistance aux médicaments.

Objectif : Cette thèse a utilisé des méthodes quantitatives et qualitatives pour explorer le parcours de patients tuberculeux vivant en Inde et en Afrique du Sud. Ces deux pays servent d'études de cas pour évaluer les interventions potentielles au niveau des patients, des prestataires et des systèmes de santé visant à améliorer la rétention et l'adhésion au traitement des patients, ainsi que l'impact de ces interventions sur les épidémies de TB et de TB-MR.

Méthodes : Les méthodes utilisées pour les quatre études de cette thèse étaient : 1) l'élaboration d'un modèle de Markov dynamique représentant l'épidémie de TB en Inde, y compris un cadre probabiliste reflétant la complexité des parcours de traitements antituberculeux, afin d'évaluer l'impact des différents secteurs (privé, public et informel) sur l'émergence de la pharmacorésistance; 2) l'étude qualitative des parcours de traitement des patients tuberculeux et des stratégies potentielles pour améliorer la rétention des patients à Cape Town, en Afrique du Sud; 3) une revue systématique de l'efficacité des interventions psychosociales, éducatives et du soutien matériel ayant pour but d'améliorer l'adhésion au traitement et la rétention des patients atteints de TB-MR; et 4) l'adaptation du modèle de Markov, construit lors de la première étude, afin de représenter l'épidémie de TB en Afrique du Sud. Ce modèle adapté fût utilisé pour étudier l'impact des stratégies ciblant les différents stades de la cascade de soins sur l'émergence de la pharmacorésistance et sur la mortalité par

TB.

Résultats : En Inde et en Afrique du Sud, le renforcement des soins existants pour les patients tuberculeux dans le système public - en mettant l'accent sur le faible taux d'adhésion au traitement et de rétention - conduirait à des réductions plus importantes de la résistance aux médicaments et de la mortalité que d'autres stratégies, comme l'amélioration de médicaments. L'étude qualitative menée en Afrique du Sud et la revue systématique suggèrent des stratégies pour améliorer l'adhésion au traitement et la rétention. L'étude qualitative a révélé l'importance d'instaurer un climat de confiance précoce entre les patients TB et leurs prestataires. La revue systématique a démontré des taux de rétention supérieurs chez les patients ayant bénéficié de conseils individuels ou de visites à domicile par des intervenants en santé qualifiés.

Conclusion : Il est urgent d'adresser les enjeux qui affectent la rétention des patients et leur adhésion au traitement, tant au niveau des patients, des prestataires et des systèmes, puisque ces problèmes sont les principaux moteurs de l'épidémie mondiale TB-MR. Ceci est particulièrement important afin de protéger les nouveaux médicaments introduits dans le traitement de routine, tels que la bédaquiline et le linézolide, et de prévenir le développement et la transmission de TB résistantes à ces médicaments. Les recherches futures devraient développer et évaluer rigoureusement les interventions visant à promouvoir la rétention des patients et leur adhésion, afin d'empêcher une aggravation de l'épidémie mondiale de TB-MR.

ACKNOWLEDGEMENTS

I am forever grateful to everyone who supported me throughout my doctoral studies.

My sincerest thank-you to my supervisor Dick Menzies, for his guidance, mentoring and support (moral, emotional, tangible – in the form of cookies) throughout the last decade. Without him, I wouldn't have even started my PhD, let alone finish it.

I'd also really, truly, like to thank Amrita Daftary and Olivia Oxlade for putting up with all the many analyses and re-analyses, write and re-writes, and trial & tribulations throughout these past few years. And for being endlessly supportive. Also, I'd like to thank my coworkers – Nadya for putting up with my regular mental absence, and Josée for being supportive of my thesis work even if it took away from my real work, and for helping with my français. And of course, my partner Nnamdi, who has put up with my working through nearly all the weeknights and weekends in the past year, and who stuck around.

I would like to thank my thesis committee members Andrea Benedetti and Sam Harper for their comments and feedback along the way. I would also like to thank the United States Agency for International Development (USAID) for funding support, and the editorial guidance from Ms. Cheri Vincent (USAID) and Ms. Amy Piatek (USAID) during the drafting of the manuscript, for the research in India. Also, I'd like to thank Dr. Keertan Dheda at the University of Cape Town, and his entire team (particularly Dr. Ali Esmail, Sister Marietjie and Sister Wilson), for all the support (logistic and moral) during my extended stay in Cape Town.

Finally, I can't thank enough all the patients and providers in Cape Town who took time – and found courage – to sit down with me, and share their personal stories and experiences. I have learned so much from them, and will always be indebted to their kindness and generosity.

My doctoral research was made possible by funding from the Vanier Canada Graduate Scholarships program through the Canadian Institutes of Health Research (CIHR).

I dedicate this work to my late mentor, friend and comrade, Abby Lippman. I miss you.

CONTRIBUTION TO ORIGINAL KNOWLEDGE

This thesis makes the following novel findings to support growing global research efforts to stem the emergence of drug-resistant tuberculosis:

1. ***The public sector is the largest contributor to the emergence of drug-resistant TB in India, despite poorly regulated TB treatment practices in non-public sectors.***

This was the first modelling study to explore the impact of non-public providers on the emergence of drug-resistant tuberculosis in India, a country where patient treatment-seeking pathways are highly complex, and treatment for TB is readily available outside the public sector. Our findings showed although inappropriate TB treatment care provided in the non-public sectors does generate drug resistance, the majority of drug resistance is likely generated in the public sector. Thus, although treatment practices should be improved across all sectors, the priority should be to strengthen TB treatment and care - particularly by improving adherence - in the public sector.

2. ***Mutual trust between TB patients and their providers, which is an important determinant of patient adherence to treatment and retention-in-care, is constantly undermined by TB treatment practices that are premised on a lack of trust in patients.***

This was the first qualitative study to explore in-depth the treatment journeys of patients undergoing treatment for both drug-sensitive and drug-resistant TB in Cape Town, South Africa. The study highlighted the role patient-provider trust plays throughout treatment journeys, and found that mutual trust greatly affects patient adherence and retention-in-care, as well as patient and provider delays in accessing appropriate diagnostic tests and treatment. Yet despite this, current TB management practices limit the opportunities for building trust, and instead rely on paternalistic practices such as directly observed treatment, which often creates a foundation of mistrust between patient and providers. National TB programs and TB providers should implement strategies to build trust in TB care, thereby preventing the emergence of drug resistance through poor adherence.

3. ***Frequent and continuous access to individual psychosocial support from trained health workers reduces losses to follow-up during treatment for MDR-TB***

The systematic review on strategies to reduce losses to follow-up during MDR-TB treatment found psychosocial support (such as one-on-one counselling sessions or home visits by trained health workers) provided throughout treatment had the greatest impact on reducing treatment losses to follow-up. Other strategies compared included: financial support via reimbursement of travel, rent expenses and lost wages; nutritional support via food parcels and hot meals; peer support groups and group counselling; and psychosocial support provided over a limited time at the beginning of treatment. National TB programs should incorporate psychosocial support as part of routine MDR-TB care, and increase the opportunities for interaction and trust-building between TB patients and their providers. Furthermore, there is potential for counselling and home visits to replace directly observed therapy (DOT), which is resource-intensive and a burden on both providers and patients, as effective strategies to promote treatment adherence.

4. ***Efforts to reduce losses from the cascade of care during MDR-TB treatment will likely lead to the greatest reductions in drug-resistant TB in South Africa***

This was the first modelling study to directly compare several newly adopted global and national TB-related management strategies – including the introduction of a shortened 9 to 12-month MDR-TB treatment regimen endorsed by the WHO in 2016, and expanding access to bedaquiline-based MDR-TB treatment – and their potential impact on the emergence of drug-resistant TB in South Africa. Our study showed that although improving diagnostics and treatment for MDR-TB, as well as increasing coverage and adherence to antiretroviral therapy and isoniazid preventive therapy among people living with HIV, would greatly reduce mortality and further emergence of drug-resistance, none of these strategies were as effective as reducing pre-treatment (initial) and treatment losses to follow-up among TB patients. Thus, national TB programs should not neglect efforts to strengthen existing TB care, such as improving patient-provider relationships, when working towards other targets.

CONTRIBUTION OF AUTHORS

The contributions of authors to each manuscript included in this thesis are as follows:

1. ***Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study.***

Authors: Stephanie Law, Amy S. Piatek, Cheri Vincent, Olivia Oxlade, Dick Menzies.

I conducted the initial literature review to guide the study design, including comparing health care systems and TB treatment-seeking pathways in several countries where the private sector provides TB treatment. Together with the other authors, we finalized the study design. Thereafter, I performed all necessary literature searches and reviews to collect data needed for the model, analyzed the data to inform model development, designed and constructed a dynamic Markov-based decision analytic model to represent the TB epidemic and health system in India, interpreted the results with support from other authors, and drafted and submitted the final manuscript.

Dick Menzies and Olivia Oxlade provided mentoring support in all stages of the study, from study design to drafting of the manuscript. They helped with important decisions made in designing and constructing the model, and contributed to the interpretation of results and editing of the final manuscript.

Amy S. Piatek and Cheri Vincent, who are based at the United States Agency for International Development, came up with the idea for a TB modelling study that incorporates complex TB patient treatment-seeking pathways in a setting where patients can access TB care in non-public settings. They also contributed to interpreting the findings and editorial support in writing the manuscript.

2. ***"I really needed them to trust me, but they didn't": How patient-provider trust influences tuberculosis treatment outcomes***

Authors: Stephanie Law, Amrita Daftary, Ali Esmail, Keertan Dheda, Dick Menzies

I conceived the study idea to explore treatment journeys of TB patients in Cape Town, South Africa. I designed the study with support and guidance from Dick Menzies and Amrita Daftary. I collected and analyzed the qualitative data, and interpreted the findings with mentorship from Amrita Daftary. I drafted the manuscript, and received editorial support from all other authors.

Ali Esmail and Keertan Dheda provided logistical support during data collection, and editorial support for the manuscript.

3. ***Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review***

Authors: Stephanie Law, Amrita Daftary, Max O'Donnell, Nesri Padayatchi, Liviana Calzavara, Dick Menzies

I designed the study with guidance from Dick Menzies and Amrita Daftary. I developed the search strategy, conducted the search, screened the studies (with help from Amrita Daftary, who was the second screener for the review), and collected and analyzed the data. I interpreted the findings and drafted the manuscript, and received editorial support from all other authors.

Dick Menzies, Amrita Daftary, Max O'Donnell, Nesri Padayatchi and Liviana Calzavara all contributed to the interpretation of findings and provided editorial support for the manuscript. Liviana Calzavara and Amrita Daftary conceived the study idea.

4. ***Strengthening the tuberculosis cascade of care to reduce tuberculosis mortality and drug resistance: A dynamic modelling study***

Authors: Stephanie Law, Olivia Oxlade, Dick Menzies

I conceived the study idea, designed the study, analyzed the data to inform model development, designed and constructed a dynamic Markov-based decision analytic model to represent the TB epidemic and health system in South Africa, interpreted the results with support from other authors, and drafted and submitted the final manuscript.

Dick Menzies and Olivia Oxlade provided mentoring support in all stages of the study, from study design to drafting of the manuscript. They helped with important decisions made in designing and constructing the model, and contributed to the interpretation of results and editing of the final manuscript.

INTRODUCTION

Tuberculosis (TB) has been around for nearly 40,000 years (Wirth 2008). The main drugs used to treat TB today – isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin – were all discovered between the 1940s and 1960s. Yet despite decades of advancement in care and knowledge since then, there remains an estimated 10 million new TB cases and nearly 2 million TB-related deaths each year (WHO 2017a). One of the major threats to controlling the global TB epidemic is the emergence of multidrug-resistant TB (MDR-TB). Due to resistance to isoniazid and rifampicin, the two most effective TB drugs, MDR-TB is much more difficult and expensive to treat. Treatment for MDR-TB commonly lasts upwards of 20 months, requires daily injections for six months, and has low treatment success rates (54% globally), high mortality rates (16% globally), and severe side effects including permanent hearing loss (WHO 2017a).

Drug resistance can be transmitted (referred to as primary drug resistance) or acquired (referred to as acquired drug resistance). Primary drug resistance develops when someone with a drug-resistant strain of TB transmits the disease to an uninfected person (or a TB-infected person without drug-resistance to the same drugs). Thus, any patient or provider delays in initiating correct treatment, as well as any interruptions from treatment, increases the risk of primary transmission of disease. On the other hand, acquired drug resistance occurs when a TB patient is not taking appropriate or adequate treatment. This could be due to incorrect prescriptions, poor adherence to therapy, treatment interruptions, or malabsorption of drugs, among other reasons (WHO 2017a).

In most parts of the world affected by TB, TB is diagnosed via sputum smear microscopy, or more recently, via rapid diagnostics such as Xpert MTB/RIF (WHO 2017a). Depending on the test done, as well as the health systems infrastructure in place, there is a delay between the time of testing and when the results are available. This delay could range from a couple days to several weeks, during which time individuals with active TB disease remain contagious. In addition to long diagnostic delays, individuals with active TB disease might not always return promptly to care and initiate treatment, further increasing the risk of disease transmission. Finally, after initiating

treatment, barriers along the way – such as financial and personal problems, and issues with health care providers – could affect patient adherence to treatment, and thereby affect treatment success rates.

There are myriad factors contributing to the emergence of MDR-TB worldwide, many of which stem from sociopolitical, economic and institutional issues that lead to inadequate, inconsistent or inappropriate TB management and care, as well as under-resourced and over-burdened national TB programs (Kim 2005; Gandy 2002; Ogden 2003; Espinal 2003; Uplekar 2015). These systems-level issues are exacerbated by unregulated private health sectors, which have widely varying TB diagnostic and treatment practices (Uplekar 2015). Furthermore, the socioeconomic struggles faced by populations particularly affected by the disease create barriers to accessing and adhering to TB treatment. All these factors intersect to influence the quality of life of individuals and families affected by the diseases, global TB treatment success rates, and ultimately the dynamics of the TB and MDR-TB epidemics.

Treatment journeys for TB patients, as described by others (Loveday 2013; Rintiswati 2009), are often quite long: they start at the onset of symptoms, such as coughing, night sweats and weight loss; followed by taking action to seek care for the symptoms from different types of health care providers; then to receiving a diagnosis and starting treatment; and finally completing treatment, which could range from six months for drug-susceptible TB to over 20 months for MDR-TB. At each stage along the way, a wide range of barriers and facilitators at the patient-, provider- and health systems-level act in conjunction to affect the patient's chances of achieving cure. When there are delays or interruptions to treatment journeys, TB patients are at higher risk of acquiring drug resistance due to inappropriate or insufficient therapy, as well as transmitting the disease to others around them.

Globally, nearly 40% of incident (new or relapse) TB patients are not reported to national TB programs and are likely receiving improper TB treatment, or none at all (WHO 2017a). This proportion is even higher among MDR or rifampicin-resistant (RR) TB cases at nearly 80%. Most of these patients either delay, are unable to, or do not seek care for their symptoms, or they seek

care from providers in the private (or informal) sectors, who are not consistently trained to diagnose and treat tuberculosis. Of new TB and RR/MDR-TB patients who are enrolled in TB treatment, 83% and 54% successfully complete treatment, respectively. Nearly half of the RR/MDR-TB patients who do not complete treatment are lost to follow-up (i.e. interrupted treatment for at least two consecutive months), or their treatment outcomes are not evaluated. Adding all this together, merely 50% and 12% of incident TB and RR/MDR-TB patients, respectively, successfully complete the entire TB treatment journey and have hopes of cure.

A careful exploration of issues that affect TB treatment journeys could reveal important time points and targets for interventions to improve access and adherence to treatment, and also elucidate their potential impact on the emergence of drug resistance. This could have implications on not only the MDR-TB epidemic, but also on the development of resistance to new and developing TB drugs, including bedaquiline, delamanid, pretomanid and sutezolid (WHO 2017a). There is a growing body of evidence examining health-seeking patterns (i.e. where individuals seek and receive care for their symptoms) among TB patients (e.g., Sreeramareddy 2014, Meintjes 2008, Van Wyk 2011), as well as risk factors associated with poor adherence and patient losses to follow-up (e.g., Sarpal 2014, Vijay 2010, Kigozi 2017, Marx 2012). However, there is limited research exploring how those issues in turn affect the MDR-TB epidemic. For example, how much do delays in initiating treatment or non-adherence to treatment contribute to the global emergence of drug resistance? Furthermore, there is a paucity of evidence on strategies to improve adherence and retention-in-care during MDR-TB treatment (Toczek 2013; WHO 2017b), despite several reviews on this topic for treatment of drug-susceptible TB (e.g., Lutge 2015, M'Imunya 2012). This thesis seeks to address those knowledge gaps.

My thesis research seeks to explore TB treatment journeys and their relationship to the MDR-TB epidemics. Two countries were selected as case studies to study the global MDR-TB epidemic: South Africa and India. Both countries have well-established national TB programs that provide TB testing and treatment free-of-charge, and both have high burdens of TB and MDR-TB (WHO

2017a). However, their health systems and potential issues affecting TB patient treatment journeys differ in important ways, for example: India has a substantial private sector where patients can receive unregulated TB treatment containing isoniazid and rifampicin, whereas South Africa does not (WHO 2017a; Wells 2011); and South Africa has a large HIV co-epidemic, where 60% of TB patients are HIV-positive (WHO 2017a), and India does not. These differences provide an opportunity to compare TB treatment journeys in different contexts, and an exploration of various factors that contribute to the emergence of drug resistance.

Research objectives

The overarching goal of this research is to examine TB patient journeys in India and South Africa, and to estimate the effects of possible interventions targeted at different points along their journeys on the emergence of drug resistance.

The specific research objectives are:

1) In India, to estimate the impact of seeking and receiving TB care from different health sectors (public, private and informal), as well as the potential impact of improving different elements of TB care in the different sectors, on MDR-TB incidence, prevalence and mortality. This will be addressed with decision analytic modeling;

2) In South Africa, to explore TB treatment journeys, as well as issues affecting adherence and retention-in-care, among patients with drug-susceptible and drug-resistant TB. This will be studied using qualitative methods;

3) To systematically review the effectiveness of psychosocial, educational and material support interventions in improving treatment adherence and retention-in-care among MDR-TB patients. This will be a systematic review; and

4) In South Africa, to estimate the impact of strategies targeting different stages of the cascade of TB care to reduce the incidence and mortality due to drug-susceptible and drug-resistant TB in South Africa. This will be addressed using decision analytic modeling.

BACKGROUND

Introduction

From a disease that was once untreatable, causing death in up to 70% of those infected (Tiemersma 2011), TB is now treated with a global average treatment success rate of 83% using a WHO-standardized six-month regimen. With the scaling-up of effective treatment and diagnostics worldwide over the past few decades, the global TB mortality rate has fallen by over 45% since 1990 (WHO 2017a). Yet still, worldwide, there are an estimated 5,500 TB deaths occurring each day, and the TB treatment success rate has remained more or less unchanged since it first surpassed the 85% mark in 2007 (WHO 2009). The World Health Assembly, the decision-making body of the WHO, adopted a new post-2015 Global TB Strategy in May 2014 (WHO 2014). The strategy aims to reduce TB deaths by 95% and new cases by 90% between 2015 and 2035, and to ensure no individual or family suffers catastrophic costs due to TB. To achieve these goals, the post-2015 strategy lays out three pillars: 1) to provide patient-centred care and prevention that "puts patients at the heart of service delivery"; 2) to implement supportive systems and policies that would increase cooperation between the different health sectors, governments and communities; and 3) to intensify TB research and innovation.

One of the major threats to achieving the post-2015 goals is the emergence of MDR-TB. Due to resistance to the two most potent anti-TB drugs on the market – isoniazid (INH) and rifampicin (RIF) – MDR-TB is much more difficult and costlier to treat than drug-susceptible TB (WHO 2017a). This thesis research touches on a few aspects of the first two pillars of the post-2015 Global TB Strategy in relation to the emergence of drug resistance. Specifically, the thesis research objectives were in part guided by the following questions:

1) How would increasing cooperation between the public and non-public sectors affect the MDR-TB epidemic?

2) What are specific strategies that might improve the quality of care provided to patients, and encourage better treatment outcome, among both drug-susceptible and drug-resistant TB patients?
3) How would improving the quality of care, through a patient-centred approach, affect treatment outcomes and thereby the MDR-TB epidemic?

Emergence of drug resistance

Drug resistance in TB is not a new phenomenon. When the first anti-TB agent, streptomycin, was introduced in 1945, resistance emerged within the first few years (Crofton 1948). By the early 1950's, para-aminosalicylic acid (PAS) and isoniazid (INH) were added to streptomycin in a new regimen that successfully cured nearly all TB cases, and showed that taking two or more drugs in combination could prevent the development of drug-resistance to any single drug (Medical Research Council 1952). Rifampicin (RIF), which has the highest sterilizing activity amongst first-line TB drugs, was introduced in the late 1960s, and by adding it to a regimen containing INH, ethambutol and pyrazinamide, treatment was shortened from 18-24 months to 6-9 months and with much less toxicity (Enarson 1995). This combination continues to be used today as the WHO-recommended standardized regimen for drug-susceptible TB.

In any infected individual, TB bacteria can spontaneously mutate and confer resistance to anti-TB agents (Canetti 1965). The estimated frequency (per replication) of conferring resistance to INH is 3.5×10^{-6} and to RIF is 3.1×10^{-8} (Johnson 2006), thus the probability of double spontaneous mutation to both INH and RIF is very low – even in patients harbouring extensive pools of TB bacteria – occurring roughly once per 10^{13} replications (Iseman 1993). When someone harbouring mutant bacteria with drug resistance is not treated effectively with active agents to which the bacteria are susceptible, the drug-resistant mutants will selectively survive and continue to replicate, leading to acquired drug resistance.

For example, if someone with drug-susceptible TB harbouring a small number of INH-resistant mutants is treated with INH-monotherapy, the INH will kill all the bacteria except the INH-

resistant mutants. These mutants eventually dominate the TB bacteria population, and the patient now has disease due to a mono-INH-resistant strain. If RIF is then added to the INH regimen, all the bacteria would be killed except RIF-resistant mutants, leaving only INH and RIF-resistant bacteria and the patient now has MDR-TB disease. Thus, proper treatment with a sufficient number of drugs at adequate dosages is crucial in the prevention of MDR-TB.

In an effort to improve TB treatment success rates and prevent the development of drug resistance, the WHO launched a global strategy in 1995 to standardize treatment and management of TB. This strategy, known as DOTS (Directly observed therapy – short course), involves the use of directly observed therapy (DOT) – where an observer (who could be a health care worker, or a community health worker, or even a family or friend) watches the patient take each dose of treatment – and standardized therapy (Raviglione 2002). The reasons for standardizing TB treatment include: to reduce the burden on health care resources such as laboratory testing requirements and human resources; to reduce the consultation and medical follow-up time necessary, thereby reducing the burden on patients and physicians; and to produce lower wastage of drugs by allowing for estimations of drug needs. Additionally, standardizing treatment has the potential of protecting patients against drug resistance by reducing prescription errors, as well as sporadic prescriptions when patients switch providers. However, if standardized regimens are not designed properly, there is a risk of introducing inappropriate or inadequate therapy to millions of TB patients treated by national TB programs around the world. In time, this could amplify drug resistance through inadequate therapy, and increase disease transmission through inappropriate therapy for patients infected with drug-resistant strains.

In fact, this did happen: a long-standing recommendation for an eight-month standardized regimen for all previously treated TB patients (those returning from relapse, lost to follow-up or failure) was eliminated in 2017 from WHO treatment guidelines (WHO 2017b). This now-obsolete regimen, known as the 'category II' regimen, had been recommended since 1991 (Rouillon 1991). It was nearly identical to the initial (category I) treatment for new TB patients, except it extended

the use of three first-line drugs (isoniazid, rifampicin and ethambutol) to eight months, with pyrazinamide given for three months, and streptomycin, a first-line injectable drug, in the first two months. This regimen was no longer recommended due to two main reasons: 1) unacceptable average treatment success rates of 68% among previously treated patients; and 2) the regimen was driving the development of drug resistance, particularly among previously treated TB patients with confirmed isoniazid resistance (WHO 2017b). Instead, the WHO now recommends that all previously treated TB patients to undergo drug-susceptibility testing so that appropriate, effective treatment can be provided as to not fuel the drug-resistant TB epidemic, and improve treatment outcomes.

A history of poorly managed and under-resourced national TB programs around the world, as well as discrepancies and inconsistencies in TB treatment across health sectors and across countries, allowed MDR-TB to emerge globally. Today, approximately half a million cases of MDR-TB emerge globally each year, nearly half of which are found in China, India and the Russian Federation (WHO 2017a), as well as 110,000 cases of RIF-resistant (RR)-TB, which like MDR-TB requires treatment with second-line drugs. The increased global use of Xpert MTB/RIF – a rapid molecular test that simultaneously detects both TB and resistance to rifampicin (but not to INH) – has led RR-TB to be regarded as a proxy for MDR-TB, as a large proportion of RR-TB patients also harbor resistance against INH (Caws 2006; Ramaswamy 1998; Rieder 2007; Aziz 2004; Sam 2006). Mortality rates remain high among RR/MDR-TB patients, there were nearly 240,000 deaths from RR/MDR-TB in 2016. Currently, RR/MDR-TB cases make up approximately 4.1% of new cases and 19% of previously treated cases worldwide, and these proportions are continuing to rise. Furthermore, another 8.5% of all TB cases are resistant to INH, which are at risk of acquiring further resistance to RIF and developing MDR-TB (WHO 2017a; Stagg 2017).

While the MDR-TB epidemic continues to hinder global progress in the fight against TB, extensively drug-resistant TB – a form of MDR-TB with additional resistance to the two most potent classes of second-line drugs - fluoroquinolones and second-line anti-TB injectables – has emerged in at least 123 countries (WHO 2017a; WHO 2010). XDR-TB makes up over 6% of all

MDR-TB cases, and poses a serious threat to global control of TB and all the progress made thus far. It is imperative to improve detection and treatment of MDR-TB in order to avert further emergence of XDR-TB.

TB detection and treatment coverage

In 2016, an estimated 4.1 million incident TB cases were missed by national TB programs, representing a treatment coverage gap of 39% (WHO 2017a), and are at risk of receiving inappropriate TB therapy, or none at all. This gap could be largely attributed to under-diagnosis, wherein infected individuals are not being diagnosed correctly due to the lack access to healthcare, lack of laboratory infrastructure and accurate diagnostic testing, as well as factors associated with delays in seeking health care, among others. Furthermore, the gap also results from under-reporting, wherein detected cases are not being reported to national surveillance programs, including those detected in private health sectors). According to WHO (2017a) estimates, the ten countries with the largest gap between notified cases and estimated TB incidence are India, Indonesia, Nigeria, the Philippines, South Africa, Pakistan, Bangladesh, the Democratic Republic of Congo, China and the United Republic of Tanzania.

The gap is even larger among RR/MDR-TB cases. As recently as a decade ago, in many low and middle-income countries, drug-susceptibility testing was performed only on patients who had previously failed treatment (Stop TB Partnership, 2006). In 2008, among 27 high MDR-TB burden countries, drug-susceptibility testing was performed on 1% of new TB cases and 3% of previously treated TB cases (WHO 2010). Left undetected, infected patients are often treated ineffectively with drugs to which they are resistant and continue to transmit the disease. The low rates of drug-susceptibility testing in the past could be largely attributed to the high labour and laboratory requirements and costs of the diagnostic tools (Canetti 1969; Kim 2005). This however has shifted with the advent of rapid diagnostic tools that use molecular techniques to detect TB and drug resistance, the most prevalently used being Xpert MTB/RIF® assay (Cepheid, U.S.A.) which simultaneously tests for presence of TB and RIF resistance if TB is found. Since the introduction of Xpert in 2010, drug-susceptibility testing coverage, at least for RIF-resistance,

increased to 33% for new patients and 60% for previously treated patients in 2016 (WHO 2017a). The use of Xpert has shown to reduce treatment delays for RR/MDR-TB patients (Cox 2017), and thereby also reduce transmission. Today, approximately 26% of the estimated 600,000 annual incident RR/MDR-TB cases are detected and started on treatment worldwide. Greater roll-out and uptake of rapid diagnostics globally is required to increase RR/MDR-TB treatment coverage.

Treatment of Drug-Resistant Tuberculosis

Given the low detection rates, many MDR-TB patients are left undiagnosed and often receiving inappropriate therapy. Among those who are notified to national TB programs and initiate second-line treatment, approximately 54% are successfully treated and the remainder fail treatment (8%), die (16%), are lost to follow-up (15%) or have no reported outcome (7%). Similar to the trend with the global treatment success rate of incident TB cases, the treatment success rate among MDR-TB has remained largely unchanged – and in fact decreased – since the first WHO reported estimate of 60% in 2008 (WHO 2010).

Treatment for RR/MDR-TB should be individualized based on results from drug susceptibility testing, such that at least five effective drugs are included in the regimen (WHO 2016). Therapy containing an insufficient number of effective second-line drugs may lead to acquired drug resistance to additional drugs, and XDR-TB (Mukherjee 2004; Han 2005). There are four groups of drugs used in RR/MDR-TB treatment: 1) fluoroquinolones (e.g. levofloxacin, moxifloxacin and gatifloxacin); 2) second-line injectables (e.g. amikacin, capreomycin and kanamycin); 3) other core second-line agents (i.e., ethionamide/prothionamide, cycloserine/terizidone, linezolid and clofazimine); and 4) add-on agents that are not part of the core regimen, such as first-line drugs (high-dose INH, ethambutol and pyrazinamide), new anti-TB drugs, bedaquiline and delamanid, which often require special application and approval to use, and other agents like para-aminosalicylic acid or meropenem (WHO 2016).

RR/MDR-TB treatment, which varies in duration from nine months to over 20 months, requires close monitoring to manage side effects and amplified drug resistance (WHO 2016). Although

MDR-TB was largely treated in centralized hospitals in the past, requiring lengthy hospitalization usually for the six-month period while the patient is receiving the second-line injectable, WHO now recommends a decentralized model of care where treatment is provided in the patient's community through local health centres and, in some settings, supported by trained community health workers (WHO 2017b). Decentralized care for MDR-TB has been found to reduce demand on hospital beds, increase access to treatment and care for patients, decrease risk of nosocomial transmission, and improve patients' productivity and overall quality of life (Mitnick 2008, WHO 2017b).

TB Treatment journeys

In most parts of the world, patients are able to seek care from diverse types of healthcare providers, including public system providers, private practitioners and traditional healers or practitioners of alternative medicines. It is common for TB patients to seek care from multiple providers before being diagnosed, and upon diagnosis, patients also seek treatment from different providers (Sreeramareddy 2014). Health-seeking patterns and treatment pathways are particularly relevant when a strong non-public healthcare sector exists alongside the public system. The non-public sector is unregulated and unmonitored in most countries, thus, if TB treatment is provided, it may be inadequate, leading to an increased risk of failure or relapse with amplified drug resistance (WHO 2017a).

When patients change from one provider to another, particularly between providers in different health sectors, this movement can affect the MDR-TB epidemic in two main ways: 1) lengthy treatment-seeking pathways where care is sought from multiple providers increase the likelihood of delayed diagnosis, which increases the duration of the contagious period (Sreeramareddy 2014); and 2) patients who seek care from non-public healthcare providers, or who move around between different providers, may be more likely to interrupt therapy, or be treated with incorrect or inadequate regimens (Uplekar 2001). These problems increase the risk of primary transmission as well as acquired drug resistance and poor treatment outcomes.

There are many reasons for TB patients to seek care from non-public providers, even though treatment is provided free-of-charge in the public sector. These include: belief in other healing systems such as traditional and alternative medicines; a perception of better quality of care from non-public providers; convenience of non-public providers and pharmacists, such as shorter queues or more flexible operating hours; and poor past experiences or opinion of public providers and facilities (Smith 2001). In order to reduce the treatment coverage gap, as well as improve treatment outcomes for TB patients, it is important to address the factors that lead patients to seeking care outside the public sector, as well as to increase coordination efforts between public and non-public sectors.

Moreover, although most patients who enter the public sector receive correct treatment, some struggle with adherence or are lost to follow-up from treatment. Factors that affect adherence and treatment completion rates vary widely, and are context dependent, but include health service factors (such as quality of care and facilities, convenience, and wait-times), personal factors (such as access to food and transport, comorbidities, and use of alcohol or drugs), structural factors (such as poverty and gender discrimination), and the sociocultural context (Munro 2007). As such, the WHO recommends the use of directly observed therapy (DOT) – preferably community- or home-based DOT, rather than health facility-based or unsupervised treatment – as well as patient care and support interventions to improve adherence and retention-in-care (WHO 2017b). These interventions include health education and counselling on TB and adherence, material and psychological support, home visits and digital reminders, and staff education. However, the evidence supporting the selection and use of interventions remain weak (WHO 2017b), as has been found by other systematic reviews on TB adherence interventions: on patient education and counselling (M'Imunya 2012); on material incentives and enablers (Lutge 2012); on reminder systems (Liu 2014); and particularly for treatment of drug-resistant TB (Toczek 2013).

MDR-TB Case studies: India and South Africa

This thesis research uses South Africa and India as case studies to explore the global MDR-TB

epidemic. Specifically, the research explores: 1) how increasing referral rates from non-public providers, and increasing public-private coordination of care, could affect TB and MDR-TB incidence and mortality in India and South Africa; 2) the effectiveness of psychosocial, educational and material support to improve retention-in-care and treatment adherence in MDR-TB treatment; and 3) the potential impact of improving TB diagnostics and treatment management, as well as retention-in-care and treatment adherence, on TB and MDR-TB outcomes in India and South Africa.

Current state of TB and the healthcare system in India

India has the highest burden of TB and MDR-TB in the world, it accounts for over a quarter of the total number of incident TB cases and of TB deaths globally (WHO 2017a). Each year in India, there are over 2 million incident TB cases, nearly 150,000 incident MDR-TB cases, and close to half a million TB deaths. Furthermore, only 63% of the estimated incident TB cases are reported to the national TB program, making up nearly 20% of the total 4.1 million missed TB cases in the world (WHO, 2017a). One major factor contributing to this high proportion of missed cases is the complex nature of the health care system in India.

TB control in India is complicated because of the involvement in different aspects of TB care of large and popular private and informal sectors, which include allopathic and non-allopathic doctors and clinics, laboratories and pharmacies. TB diagnosis and treatment are provided for free in the public sector. There have been numerous studies conducted in India over the past few decades attempting to understand how TB patients access the health system in India, and to map out complicated treatment pathways. Between 27% to 50% of TB patients visit a public healthcare provider as their first contact, and the remaining patients visit private or informal providers, as well as pharmacists. According to a systematic review looking at the delays in diagnosis and treatment of pulmonary tuberculosis in India (Sreeramareddy 2014), between 11% to 82% (median of 48%) of TB patients first consulted the private or informal sector, and the median number of healthcare providers visited prior to diagnosis was 2.7 (range 1.9-12.3).

There are fewer studies examining where patients go, after being lost to follow-up from TB treatment. According to a study by Dandona, et al. (2004), 10.9% of TB patients registered with the national TB program (RNTCP) were lost to follow-up during the diagnosis process or before starting treatment. Of those who were lost to follow-up during diagnosis, 8.6% reported starting treatment with another doctor, and of those who were lost to follow-up after diagnosis but before starting treatment, 8.5% reported starting treatment at a private facility. According to two studies in India (Dandona 2004; Jaggarajamma 2007), between 19.4% to 20.3% of TB patients in the public sector were lost from treatment, of which 11% to 13% reported taking treatment elsewhere. In summary – the great majority of patients (over 80%, and in many studies over 90%) who are lost to follow-up never start, or never complete treatment. There are no similar studies conducted with patients receiving TB treatment in the private or informal sector, as such as less clear where patients go after being lost to follow-up in private or informal care. However, studies done in the public sector found that 8% to 20% of TB patients in the public sector were diagnosed or had previously received treatment in the private sector (Jaggarajamma 2009; Satyanarayana 2011), and a large majority of these patients left the private sector due to financial reasons (Jaggarajamma 2009).

Several studies have attempted to quantify the extent of the use of inappropriate drug regimens for the treatment of TB in the private and informal sector (e.g.: Achanta 2013; Anandhi 2002; Bate 2013; Charles 2010; Kapoor 2012; Satyanarayana 2011; Uplekar 1998). The most recent study on TB management by private practitioners, which included both allopathic and non-allopathic doctors, found that only six out of 106 private practitioners wrote a prescription with a correct TB regimen (Udwadia 2010). In addition, these 106 doctors prescribed 63 different drug regimens. Incorrect regimens could contribute to emergence of drug resistance in India.

To date, no studies have examined the impact of diagnosis and treatment delays, initial losses to follow-up (occurring after diagnoses but before initiating treatment), and improper treatment in the different health sectors on the emergence of drug resistance in India.

Current state of TB and the healthcare system in South Africa

South Africa has the highest TB incidence rate in the world, at an estimated 781 per 100,000 population. TB is the leading cause of death in the country, accounting for nearly 10% of all deaths annually (Statistics South Africa 2014). Including those who are co-infected with HIV, there were an estimated 124,000 deaths due to TB in 2016 (WHO 2017a). Although the overall TB incidence rate has been slowly decreasing over the past decade, the RR/MDR-TB incidence rate has been increasing steadily, currently estimated to be approximately 34 per 100,000 population (WHO 2017a). There were an estimated 19,000 incident RR/MDR-TB cases in 2016, of which half were notified and initiated on treatment with second-line drugs.

South Africa has a high burden of HIV. About 60% of all TB cases are co-infected with HIV (WHO 2017a), this makes up 30% of the global incident cases of TB-HIV co-infection (Creswell 2014). People living with HIV, particularly those who are not treated with antiretroviral therapy (ART) or have very low CD4 cell counts, are at an estimated 20 to over 30 times higher risk of developing active TB disease after becoming infected, compared to HIV-uninfected individuals (WHO 2009). ART became publicly available in South Africa, free-of-charge, beginning in 2004 (Simelela 2014). By that time, the HIV prevalence among antenatal women had reached 30% (National Department of Health, 2017), and the estimated overall HIV prevalence in the total population was over 10% (Statistics South Africa 2016). At initial roll-out, guidelines recommended therapy initiation when the person's CD4-cell count was below 200 cells/μL or had WHO Stage IV illness, with a minimum two-week delay among newly diagnosed TB patients who have not yet commenced ART (Department of Health 2004). This was later updated in 2010 to increase the CD4 threshold to 350 cells/μL in HIV-positive pregnant women and TB-HIV co-infected patients, and to expand therapy to all M/XDR-TB patients regardless of CD4 cell count (Department of Health 2010). By the end of 2010, an estimated 55% of eligible adults were receiving ART. Finally, in the 2013 update, the CD4 threshold was removed for all TB-HIV co-infected individuals (Department of Health, 2013). The adult antiretroviral therapy guidelines were updated in 2017 (Meintjes 2017); these reflect current WHO recommendations to initiate ART with minimal delay, for all individuals diagnosed with HIV, regardless of their CD4 cell count.

A delay of two to eight weeks is recommended for tuberculosis patients who have yet to initiate ART, this is to reduce the risk of shared toxicity of simultaneous therapy, and of immune reconstitution inflammatory syndrome.

South Africa adopted the WHO DOTS strategy in 1996, and in line with this strategy, diagnosis and treatment for TB has been provided free-of-charge in the public system (Department of Health 2004). Despite the availability of free TB treatment, over a quarter of TB patients seek care from non-public providers at the onset of symptoms (Meintjes 2008; Van Wyk 2011). There is a wide variation in care-seeking patterns between rural and urban settings. Patients in rural settings seek care from the public sector more often than those in urban settings, where there is a stronger presence of private healthcare providers (Department of Health 2007; van der Hoeven 2012). There are no published studies examining whether non-public providers treat TB patients, nor what sort of care they provide to potential TB patients. There is however published evidence that seeking care from private doctors and traditional healers is associated with longer treatment delays, poorer adherence rates and worse treatment outcomes (Barker 2006; Edginton 2002; Meintjes 2008; Van Wyk 2011). Furthermore, one study in rural South Africa found 18.9% of new TB patients who were lost to follow-up from treatment reported seeing a traditional healer (Finlay 2012). Qualitative research support this finding that TB patients may interrupt treatment in the public sector and seek care from traditional healers (Daftary 2012).

Existing qualitative research has found reasons for long treatment-seeking pathways, including: mistrust of the public system; feeling that one's privacy and confidentiality is better ensured by private providers; stigma associated with HIV, and by extension with TB; and poor perception of the quality of care in the public system; financial hardship; lack of patient support and counselling; and stronger trust in traditional medicine (Daftary 2012; Edginton 2002; Finlay 2012; Foster 2015; Møller 2012; Naidoo 2009; Skordis-Worrall 2010). Furthermore, among patients who are diagnosed in the public sector, up to a quarter are lost to follow-up before initiation of treatment (Classens 2013, Naidoo 2017), and over 17% are lost to follow-up during treatment (Naidoo 2017). There is a great need to examine the impact of treatment delays, and

patient losses to follow-up during the different stages of the cascade of TB care, on the emergence of drug-resistance in South Africa, and to explore potential strategies to address them.

METHODS AND METHODOLOGY

To address the objectives of this thesis, qualitative and quantitative methods were used. The first and fourth research objectives were addressed using decision analysis, via dynamic Markov modelling. The second objective was addressed using constructivist grounded theory qualitative methodology, and a systematic review of quantitative evidence was used for the 3rd objective. The following details on the methods and methodology for each objective supplement those found in the published, submitted or prepared manuscripts.

Dynamic Markov modelling of the TB and MDR-TB epidemics in India and South Africa (Objectives 1 and 4)

Both objectives 1 and 4 involved development of a dynamic Markov model to project the TB and MDR-TB epidemics in India and South Africa, respectively. Thus, the methods for the model development are described together in this section.

Aim & objective

The overall goal was to develop cohort-based, decision analytic Markov models for South Africa and India that represent the framework of TB care covering all relevant healthcare sectors, as well as TB dynamics within the populations in each setting. Development of these models allowed us to investigate how different changes to the health systems (such as limiting the availability of anti-TB drugs in the private sector, or improving adherence and retention-in-care in the public sector) might affect the TB dynamics and emergence of drug resistance in those two settings.

Overview of decision analysis

Decision analytic modelling is founded on statistical decision theory (Raiffa & Schlaifer 1959). Decision analysis models synthesize risks, probabilities, costs and clinical data obtained from multiple sources, which could include cohort studies, systematic review and meta-analyses, and cost studies, in order to estimate numerous outcomes. In summary, decision analysis utilizes

inputs from multiple sources in order to model (or simulate and predict) outcomes from different "decisions" or strategies over long periods of time. These models could be easily modified and used to compare different interventions and decisions. Furthermore, by performing extensive sensitivity analyses in decision analytic modelling, it is possible to examine how changes in certain parameters in treatment management, which are felt to be critical determinants, or whose values are most uncertain, may affect treatment outcomes (Spiegelhalter & Best 2003).

Decision analysis is potentially useful for the objectives of this thesis due to the complex nature of the questions, as well as the large amount of uncertainty involved. Although observational studies can answer questions such as whether patient movement could affect rates of acquired drug resistance over a few years, they cannot explore the long-term effects (over 20 years or more, for example) at the population level. Whereas observational studies can look at effects within a patient cohort, decision analysis can be used to look at effects within a population – where are patients going to seek care, what happens after that, how is disease being spread, etc. Furthermore, cohort studies are much costlier to conduct. Thus, decision analysis – which uses secondary data sources – could provide the needed evidence to support, or refute, the need to conduct a long-term cohort study, or a randomized trial in the future. Decision analysis has been used in TB research to evaluate many questions including: the impact of different TB-related interventions in Indonesia, Kazakhstan and Mozambique on epidemiologic outcomes and costs (Oxlade 2015); the cost-effectiveness of an infant TB vaccine in South Africa (Channing 2014; Ditkowsky 2014); and the cost-effectiveness of TB screening and prophylactic treatment with isoniazid for HIV-infected people in Rio de Janeiro (Azadi 2014).

In our study, a cohort-based Markov model was chosen rather than individual-level state-transition (microsimulation) models. The primary difference between a cohort-based Markov model and an individual-based model is that the Markov model assumes transition probabilities do not depend on history (also known as the Markov assumption). That is, every person in any given state has the same probability of transitioning into other states – this is the average transition probability. However, despite this assumption, it is possible to integrate patient

history into Markov models by defining states that include history. For example, previously untreated drug-sensitive TB patients seeking care are defined to be in a different state than drug-sensitive TB patients who have already received one round of treatment. In this way, the important elements of patient history can be incorporated while still retaining the basic Markov model approach.

The main advantages of cohort-based Markov models over individuals-based ones are that they are easier to debug, less computationally intensive, and easier to communicate to non-experts (Siebert 2012). The main disadvantage is the Markov assumption. However, for the purposes of this study – which is to inform policy development – important patient history characteristics was incorporated into different Markov states in order to account for some degree of individual-level (first-order) uncertainty, that is the variability in probabilities of different state transitions and outcomes. Furthermore, probabilistic sensitivity analysis was done to account for parameter (second-order) uncertainty, that is the statistical uncertainty around the estimated probabilities themselves. This is in accordance with the recommendation of the ISPOR-SMDM (International Society for Pharmacoeconomics and Outcomes Research-Society of Medical Decision Making) Modeling Good Research Practices Task Force in their 2012 report: "If the decision problem can be represented with a manageable number of health states that incorporate all characteristics relevant to the decision problem, including the relevant history, a cohort simulation should be chosen [rather than an individual-level state-transition model] because of its transparency, efficiency, ease of debugging, and ability to conduct specific value-of-information analyses" (Siebert et al., 2012).

Development of dynamic cohort-based Markov models

The dynamic cohort-based Markov models described the clinical progression of TB disease, patient trajectories through the health care system, as well as the transmission of disease from infected to uninfected individuals among the population in each setting. In the models, a patient's health was characterized by mutually exclusive states, and the progression of the disease and patient trajectories were summarized by the possible transitions between these

states (schematics of the models are found in the respective chapters).

At the first cycle of the model, the population was distributed amongst the different health states based on initial probabilities identified in the literature (described in more detail in later chapters). The time frame (cycle length) of the model was one-year. This means that during each year, a person could either remain in the present health state or transition into another health state. In the model, treatment could be sought repeatedly from any type of healthcare provider. The number of times somebody could re-seek treatment before entering a chronic state was determined from ethnographic evidence and literature reviews.

At the end of each year, the different health outcomes were accrued in each health state for the whole population, and these outcomes affected the distribution of the population among the Markov states in the new year. How patients transitioned between states from year to year depended on numerous probabilities. All of these probabilities determined how patients moved through the model within each yearly cycle, and were derived from published sources (single or multiple studies, with a preference for use of systematic reviews if found), and expert clinical judgement when no published studies could be found (the search method is described in the next section). The movement of patients within the healthcare sectors determined how long patients remained contagious, and affected the treatment outcomes, which have different probabilities based on which sectors were visited. For example, if a patient sought care from four different providers in the cycle, without being diagnosed or treated, then they would be contagious during that time. If a patient never succeeded in getting diagnosed and receiving treatment, then they would be contagious for the whole year. Uncertainty in parameters was accounted for in sensitivity analyses (described later).

The Markov models used a dynamic population whereby new births or immigrants in the population replaced people who died, such that the population remained stable and the susceptible population did not become depleted over the modeling time horizon.

The models also specifically measured and reported on any INH-resistance because patients

with INH-resistance are at increased risk of acquiring MDR-TB (Gegia 2017). Furthermore, any resistance to RIF was considered as MDR-TB because RIF-resistance is considered a surrogate marker for MDR, and has significantly worse outcomes than other types of drug resistance (Siddiqi et al., 2002; Telenti et al., 1993; Van Rie et al., 2001).

Estimating model parameters

Model parameters included those identified in the systematic review done as part of this thesis research (Study 3), as well as those identified in other systematic reviews and published literature. In cases where there were no existing reviews available from which to extract relevant model parameters, limited searches were conducted. Although these searches were not systematic, and therefore may not have included all eligible studies, they were done in a standardized manner. All limited searches were done on MEDLINE (using Pubmed) only. Studies identified through electronic searches were screened for their titles and abstracts, followed by full text. For eligible studies, data were extracted using a standardized form for each parameter which included: effect estimate and precision, information for assessing quality (see next paragraph), and any additional notes on why the study was included.

The parameter estimates were obtained in a manner that conforms to evidence-based medicine principles: they were extracted from systematic reviews whenever possible; when no systematic review existed, all eligible studies for each parameter were included and incorporated; studies were assessed for their quality, including the risk of bias; and when there were multiple sources for a single parameter, acceptable methods were used to synthesize the evidence (Briggs et al., 2012). There was no *a priori* exclusion criteria based on study quality.

Calibration of models

The Markov models were calibrated against drug-resistant and drug-susceptible TB mortality and incidence rates estimated in South Africa and India. In order to do this, each model ran for 500 to 1,000 years to allow for the models to reach equilibrium, at which point the incidence of drug-susceptible TB has plateaued. These equilibrium numbers should be similar to the values

estimated in the start year of the models. If not, pathogenic parameters (e.g. reactivation rate, or contagiousness) would be modified (Oxlade 2011).

Drug-resistance was introduced into the models differently in India and in South Africa, according to the availability of reliable historical data on drug resistance in each setting (see respective chapters for more detail).

Estimating uncertainty in sensitivity analyses

Probabilistic sensitivity analysis was done to incorporate statistical or sampling variability in input parameter estimates. In probabilistic sensitivity analysis, variability in all parameters were considered simultaneously through Monte Carlo simulations (Briggs et al., 2012). The variability of parameters was determined based on meta-analyses results, published sources, clinical experience and expert opinion. In each iteration, parameter values were sampled from predefined probability distributions:

Table 1. Specification and estimation of parameter distributions*		
Type of parameter	**Corresponding distribution**	**Method of estimating distribution****
Probability (binomial data)***	Beta distribution	Method-of-moments estimates using sample mean and variance
Right skew parameter (e.g.: costs, delays, number of providers visited); relative risks or hazard ratios	Log-normal distribution	The shape parameter is the standard deviation of the log of the distribution; the scale parameter is the median of the distribution
Odds ratios	Logistic distribution	The location parameter is the mean (the point estimate) and variance estimated from the 95% confidence interval on the log scale.

*Sources used for this table: Briggs, 2012; Acharya , 2003

** Means, medians, and variances obtained from meta-analyses will be used for estimating the distributions. For parameters elicited through consultations with experts, the expected ranges constitute the 95% confidence interval from which the variance will be estimated.

*** For probability nodes in the model with multiple branches (e.g. the probabilities of visiting the different types of providers, which cannot be set to be conditional on each other), the dirichlet distribution will be used (Briggs, 2003).

After a pre-defined number of simulations, the results from all the simulations were averaged to estimate the means and variances of the outcomes (Claxton et al., 2005). Thus, although the Markov model itself is deterministic and its base-case analysis offers a point estimate, by performing probabilistic sensitivity analysis, both the point estimate and its variance were estimated.

Certain parameters used in the Markov models were not independent and this had to be accounted for in the probabilistic sensitivity analyses. For example, receiving inadequate treatment affected treatment outcome probabilities compared to receiving the correct treatment. In this case, the probabilities did not come from independent distributions. However, the probabilities associated with correct treatment were considered as the baseline probability, and a relative risk reduction or increase was assigned to those baseline probabilities for receiving inadequate treatment. In this manner, the baseline probabilities and the relative risk were independent, and were assigned distributions in the probabilistic sensitivity analysis. By defining parameters in our model this way, mutual independence was induced (Briggs et al., 2012).

Linking patient movement to emergence of drug resistance

In the state-transition Markov models, patient movement was linked to the development of MDR-TB through patient and/or provider (or system) errors. As described earlier, drug resistance is acquired after a patient fails, relapses or stops treatment early. The probabilities of having

those treatment outcomes are increased as a result of: receiving a wrong regimen as a result of provider errors, patient adherence issues, and system or dispensing errors. In the base case analyses, the models assumed a status-quo scenario based on existing (average) practices in the different sectors considered in each country.

Then, the model parameters were varied according to expected effects of setting-specific interventions identified for South Africa and India, in order to compare the potential impact of those interventions on the epidemiology of DS-TB, INH-resistant TB and RR/MDR-TB. The interventions compared were determined based on the qualitative findings from Study 2 (for South Africa), on findings from the systematic review in Study 3, as well as discussions with TB experts from each setting (including collaborators at USAID and University of Cape Town). Interventions considered included: increasing the implementation of public-private mix models; limit drug stock-outs and shortages; and implementing widespread support and counselling for TB patients.

In the decision analysis comparing different interventions, the probabilities of provider, patient and system errors were varied based on the specific aims and effects of each intervention. For example, an intervention that involves the scaling-up of public-private mix programs would increase the diagnosis rate among private providers, increase the referral rate among private providers to the public system, and also increase patient adherence in the private sector as a result of improved patient monitoring – in turn, this intervention would decrease the contagious period of patients as diagnosis was achieved sooner, and decrease the risk of receiving incorrect regimens, thereby decreasing both primary transmission of any form of TB and acquired drug resistance.

How each intervention changed model parameters was based on the systematic review conducted in Objective 3, a rapid review of the literature (on care and management on other infectious diseases in low and middle-income settings), and on expert opinion (with extensive sensitivity analyses).

Limitations

There were several limitations to this part of the study. The main limitation was the considerable uncertainty for several parameters that were used, for example: proportion of patients who visit the different types of healthcare providers; how often patients move between providers; treatment regimens provided by non-public providers; treatment non-completion and non-adherence rates; and the impact of different potential interventions, among others. In order to address this limitation, extensive sensitivity analyses were conducted (as discussed above) to observe how much impact the uncertainty had on projected outcomes.

Furthermore, the Markov models assumed a homogeneous population, where probabilities reflected the average person in the population. This means that the model would not, for example, reflect what would happen if the distribution of a certain characteristic in the population related to the outcome of interest – that is not explicitly modelled – were to change. For instance, if older people were associated with a higher risk of a poor treatment outcome, and the age distribution in the population were to skew older in the future, the model would underestimate poor outcomes (assuming the model transition probabilities were not stratified or adjusted by age). Additionally, we assumed steady-state populations in the model, which did not reflect the annual population growth of 1.3% and 1.2% in South Africa and India, respectively (World Bank, 2015). This was done in order to avoid adding too much complexity to the model, which could lead to an over-estimation of the proportions of infected individuals.

Qualitative study of patient treatment journeys in Cape Town, South Africa using a constructivist grounded theory approach (Objective 2)

Aim & objectives

The general aim of the qualitative study was to examine how patient-provider interactions in the public, private and informal/traditional sectors in Cape Town, South Africa, influence TB patient journeys, with special attention to how these experiences contribute to the emergence of drug resistance. The study explored society or health system level barriers and facilitators for

retention-in-care, which included individual-level factors that cause or are affected by system-level problems.

More specific objectives included: 1) ascertain TB treatment practices in the non-public sectors; 2) gain an understanding of how patient-provider interactions in different sectors may affect treatment delay, retention-in-care, and movement between healthcare providers; 3) compare patient and provider perceptions of TB care in the public system; 4) explore differences in care provided in different healthcare sectors, with an emphasis on issues of privacy, confidentiality, empowerment, and trust and 5) identify relevant health systems interventions for preventing drug resistance (to inform Study 4).

Theoretical Orientation: Constructivism

Knowledge is understood to be constructed relative to an interpreter (e.g., the researcher), according to their social, political, cultural, ethnic and gender background (Guba 1994). That is, there is not one, single objective truth, but rather multiple realities, which are constructed through the lens of researchers, whose worldviews are shaped by their histories and sociocultural contexts. Thus, there can be multiple constructions and understanding of a given phenomenon or reality, that is a product of both human intellect and human interactions. The creation of knowledge is a result of the interaction between the researcher and the participants, and the values of both participants and researchers are not separate from this construction, nor the interpretation of findings and the inquiry outcomes. The constructivist paradigm sees realities as highly context-specific, and are influenced by social, historical, cultural and economic structures.

This study used a constructivist grounded theory approach, as proposed by Charmaz (1995). Following this method, researchers seek meaning in data by considering the implicit values, beliefs and ideologies underlying the data. There is an understanding that the data is produced through the interactions between researcher and participants, and "therefore the meanings that the researcher observes and defines" (Charmaz 1995b, p. 35). The data is collected and analyzed

in a systematic and iterative fashion, and the researcher often reads, and re-reads, codes and re-codes the data numerous times, each time posing new questions to the data to find new analytic points and core codes or themes (Charmaz 2000). During analysis, researchers stay close to the data and uses active language when coding the data, often preferring to use participants' own words, in order "to keep that life in the foreground" (Charmaz 2000, p. 526). This ensures that participants' voices and meaning are retained and embedded in the final research outcome.

Setting

This study was located in Cape Town, South Africa. Tuberculosis is the fifth leading cause of death in the city, accounting for five per cent of all reported deaths in 2013 (Statistics South Africa, 2014). TB treatment is provided mostly as ambulatory care through public primary care clinics, which adhere to the WHO DOTS protocol. These clinics are supported by a large TB laboratory and nearby tertiary hospitals. Cape Town provides ample opportunity to study patient movement because its healthcare context is highly pluralistic, with treatment options offered by public clinics, private doctors, as well as traditional and faith healers. In a 2011 cross-sectional study of adult patients at a TB clinic in Cape Town, Van Wyk (2011) found 27% of 210 patients reported visiting a non-public healthcare provider first.

Sampling and Recruitment

This study involved in-depth and focus group interviews with: 1) adult TB patients within and without the public system (18 years old or older); and 2) public, private and traditional healthcare providers. Purposive sampling was done to recruit participants into the study. This is a non-probabilistic sampling method that selects participants based on certain characteristics (Patton 1990). Specifically, maximum variation sampling was used, "which allows researchers to explore the common and unique manifestations of a target phenomenon across a broad range of phenomenally and/or demographically varied cases" (Sandelowski 2000). Characteristics on which TB patients were selected included, but were not limited to: HIV status, gender, age, type of TB (drug-susceptible or drug-resistant), previous history of TB treatment, and health care providers' perception of the patient's level of adherence to treatment. Diverse healthcare

providers were interviewed, including doctors, nurses, community healthcare workers and traditional healers. The goal was not to obtain a representative sample, as commonly done in quantitative research, but to select participants who would offer insight to the diversity of experiences had by TB patients and healthcare providers.

Data collection

In total, 69 in-depth, open-ended, semi-structured interviews were conducted between December 2016 and May 2017. The interview guide (appendix) was derived from the five specific objectives. Recruitment and interviews occurred until data saturation (Strauss & Corbin 1990), which meant no new themes were identified through additional interviews of several new participants (Speziale & Carpenter 2007).

Methodological rigour

Steps were taken to ensure the credibility, dependability, and transferability of the research (Guba 1985). Member checking was done by reporting study findings back to the relevant stakeholders after preliminary analyses, which helped to ensure interpretations of findings were valid and appropriate (Carspecken 1996; Guba 1985). This included: feedback sessions conducted at monthly drug-resistant TB meetings hosted by all the sub-districts in the Western Cape province; meetings with managerial staff at the City of Cape Town's Department of Health; and meetings with managerial and training staff at a national NGO, TB/HIV Care Association, which oversees the recruitment and management of community health workers in Cape Town. Investigator triangulation (Denzin 2005) was done by having Dr. Amrita Daftary review a sample of interviews and texts independently. Reflexivity (Guba 1985) was practiced by staying actively and consciously reflexive throughout the entire research process, and recording reflections in a journal from beginning to end of the study. Constant reflection was done to limit assumptions and beliefs from biasing interpretations of patients' and providers' responses.

Ethical Considerations & Confidentiality

The study was conducted according to the ethical principles stated in the World Medical

Association's Declaration of Helsinki (2013). Ethics approval was obtained from the Research Ethics Office (Institutional Review Board) at McGill University, the Human Research Ethics Committee (Faculty of Health Science) at the University of Cape Town, and the City of Cape Town (appendix). Site permissions were obtained from authorities at TB clinics in order to access patient data for recruitment purposes, and also to conduct interviews in the clinics.

A systematic review of interventions and strategies to improve retention-in-care during MDR-TB treatment (Objective 3)

The overall aim of the systematic review was to identify studies of interventions to improve adult MDR-TB patient retention in the public setting. Reporting of this systematic review and its meta-analyses followed the PRISMA statement (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). Details of the methods used in this objective are found in the manuscript.

STUDY 1: EMERGENCE OF DRUG RESISTANCE IN PATIENTS WITH TUBERCULOSIS CARED FOR BY THE INDIAN HEALTH-CARE SYSTEM: A DYNAMIC MODELLING STUDY

This study explores the potential contribution of the different health sectors in India to the emergence of drug-resistant TB, and the findings are discussed in the following published manuscript.

Manuscript 1: Law S, Piatek AS, Vincent C, Oxlade O, Menzies D. (2017). Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study.

The following text is a duplicate of the following published manuscript:

Law S, Piatek AS, Vincent C, Oxlade O, Menzies D. (2017). Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study. Lancet Public Health. 2(1): e47-55. doi: 10.1016/S2468-2667(16)30035-4. PMID: 29249480.

Summary

Background

India has the highest number of patients with tuberculosis and multidrug-resistant tuberculosis in the world. We used a transmission model to project the emergence of drug resistance in India due to incorrect tuberculosis management practices in multiple sectors, including public and private providers, chemists, and non-allopathic practitioners.

Methods

We constructed a dynamic Markov model to represent India's tuberculosis epidemic, including a probabilistic framework reflecting complex treatment-seeking pathways. Underlying drug resistance and the acquisition of drug resistance during treatment were included. India-specific epidemiological data, including tuberculosis management practices, were obtained from published literature. Outcomes, which included annual risk of infection, incidence of new disease, prevalence of untreated tuberculosis, and tuberculosis-related mortality, were

stratified by underlying drug resistance, as well as by health sector to understand how each sector contributes to the emergence of drug resistance.

Findings

If tuberculosis management practices across sectors in India remain unchanged over the next 20 years, we estimated a 47% increase in the incidence of isoniazid resistance, a 152% increase in multidrug-resistant tuberculosis incidence, a 242% increase in prevalent untreated multidrug-resistant tuberculosis, and a 275% increase in the risk of multidrug-resistant tuberculosis infection. By 2032, an estimated 85% of multidrug-resistant tuberculosis will be primary multidrug-resistant tuberculosis compared with only 15% in 2012. The public sector contributed 87% of acquired multidrug-resistant tuberculosis, related to irregular adherence; the remainder came from the private sector, related to treatment non-completion. Chemists and non-allopathic practitioners do not treat with rifampicin, but because of the high rates of inappropriate isoniazid-containing regimens, and treatment non-adherence, this would generate isoniazid resistance.

Interpretation

We predict a gradual transformation from the current epidemic of drug-susceptible tuberculosis to a drug-resistant epidemic. Evidence-based strategies to improve provider practices and patient adherence across health sectors are urgently needed to prevent this.

Funding

United States Agency for International Development and the Canadian Institutes for Health Research.

Introduction

The emergence of drug-resistant tuberculosis has the potential to reverse progress made to reduce tuberculosis-related morbidity and mortality over the past 20 years. Of particular concern are multidrug-resistant strains resistant to isoniazid and rifampicin, the two most

effective tuberculosis drugs. Drug resistance emerges as a result of inadequate tuberculosis treatment, which might be an incorrect combination of tuberculosis drugs, inadequate dose or duration, or irregular drug-taking. These problems can occur in any setting, but are particularly prevalent in poorly regulated non-public sectors. To date, only a few studies have examined how patient and health-care provider behaviour within non-public sectors contributes to the drug-resistant tuberculosis epidemic.

India had the largest estimated burden of tuberculosis (2·8 million cases) and rifampicin-resistant or multidrug-resistant tuberculosis (130 000 cases) in the world in 2015.[1] India has a complex health-care system with at least three non-public sectors, including private allopathic providers (ie, private practitioners of western medicine), chemists (pharmacists), and informal health-care providers. Informal providers, or non-allopathic providers, refer to all practitioners of alternative medicine, which include ayurvedic and homoeopathic practitioners. Inappropriate tuberculosis care practices have been documented in all sectors, including prescription of inadequate tuberculosis regimens, low doses or reduced duration, and high rates of treatment non-completion or poor adherence by patients.[2–5] Thus, both public and non-public sectors might contribute to India's drug-resistant tuberculosis epidemic.

Computer simulation models offer a method to quantify how inappropriate practices in the different sectors might contribute to the development of drug-resistant tuberculosis. The primary objective of our study was to estimate the effect of different inappropriate management practices overall and in different health sectors on the emergence of drug resistance in India. Our secondary objective was to estimate the benefit of correcting these practices in each sector.

Research in context

Evidence before this study

We reviewed published literature (without restrictions on publication date or language) by searching MEDLINE (PubMed) using the search terms "India" and "tuberculosis" for studies done in India relevant to tuberculosis treatment and diagnostic practices across different sectors, treatment-seeking and treatment-taking behaviours among patients with tuberculosis, and factors associated with drug-resistant tuberculosis. Our searches identified considerable published evidence on the situation of tuberculosis treatment (current practice including regimens, adherence, and outcomes) in India. We also identified several systematic reviews on the effect of various regimens and treatment outcomes on the emergence of drug resistance. Random-effect meta-analyses were done to produce estimates for all model variables from studies identified in our search. Furthermore, we re-analysed data from our own published systematic reviews to obtain more accurate estimates for the effect of different drug regimens on treatment outcomes, stratified by underlying drug resistance. Our primary objective was to provide an estimate of the effect of inappropriate management practices, in multiple health sectors, on the overall tuberculosis epidemic and multidrug-resistant tuberculosis epidemic in India, as this has not been done before. No other studies have been published on this topic.

Added value of this study

There have been several modelling studies published in recent years examining the tuberculosis epidemic in India. One study found that improving non-multidrug-resistant tuberculosis cure rates would decrease overall incidence and mortality from tuberculosis, but have little effect on multidrug-resistant tuberculosis rates. Another found that national scale-up of universal rapid drug susceptibility testing could greatly reduce the numbers of multidrug-resistant tuberculosis cases between 2015 and 2025. However, this study only focused on the public sector. A third study modelled how different health-care system interventions might affect patient care-seeking pathways and the tuberculosis epidemic in

India, but did not examine the emergence of drug resistance. By contrast, our study examined the complex health system-related issues across all sectors, and how these issues—including lengthy delays in care-seeking—affect the emergence of drug resistance in India.

If the state of tuberculosis care in India remains unchanged over the next 20 years, our model projected a modest increase in isoniazid-resistant tuberculosis and a nearly two-fold increase in rifampicin-resistant tuberculosis or multidrug-resistant tuberculosis, and a substantial shift from a treatment-generated multidrug-resistant tuberculosis epidemic to one that is transmission-generated. The public sector was the largest contributor to drug-resistant tuberculosis, because the most patients with tuberculosis were treated in this sector, and because all patients received rifampicin as part of standard therapy, whereas non-public providers were less likely to prescribe rifampicin. We found the main driver of acquiring drug resistance during treatment in the public sector was irregular adherence (ie, patients were not taking medication regularly, but did complete the treatment), whereas in the non-public sector it was treatment non-completion.

Implications of all the available evidence

Concerns about quality of tuberculosis care in non-public health sectors are common in many low-and-middle-income countries. This study suggests that although non-standard or inappropriate tuberculosis management treatment practices by providers and patients in all sectors—public and non-public—contribute to the emergence of drug resistance, correcting issues in the public system will probably have the largest effect on the multidrug-resistant tuberculosis epidemic. Furthermore, the issues affecting each sector are not identical. For example, irregular adherence is a larger problem in the public sector, whereas high treatment non-completion rates are found in the non-public sectors. Evidence-based strategies to improve provider practices and patient adherence in all health sectors are urgently needed to arrest an emerging multidrug-resistant tuberculosis epidemic in India.

Methods

Model design

We constructed a dynamic tuberculosis transmission Markov model using decision analysis software (TreeAge Professional, 2014), as described in detail elsewhere[6] and in the appendix. The model represented India's tuberculosis epidemic, which included a probabilistic framework reflecting complex treatment-seeking pathways (appendix). Model variables related to the natural history of tuberculosis were derived from published studies (appendix). India-specific epidemiological data, including tuberculosis management practices, were also obtained from published literature (table 1). Several key pathogenetic variables were refined through model calibration (appendix). We adjusted these key variables until the model predicted a drug-susceptible tuberculosis epidemic that matched the 2012 WHO-estimated tuberculosis incidence and prevalence rates in India (appendix).[8] Drug resistance was then incorporated by stratifying the initial population—representing the full population of India—by underlying drug resistance (drug susceptible, isoniazid resistant [but not multidrug resistant], and rifampicin resistant or multidrug resistant).[9] We did not calibrate variables associated with development of drug-resistant tuberculosis because of the absence of robust historic data regarding drug-resistant tuberculosis trends in India. However, we incorporated transmission variables for drug-resistant tuberculosis estimated through calibration in a tuberculosis modelling study by another group using India-specific data.[37] HIV was not explicitly considered because of the low and declining percentage of patients with tuberculosis co-infected with HIV (roughly 4%) in India.[1]

People with active tuberculosis in our model could seek care in public (the Revised National Tuberculosis Control Program) or non-public health sectors; non-public sectors were divided into private allopathic doctors, chemists (those who dispense tuberculosis drugs), and informal providers (appendix). Information regarding how individuals initially access the health system was obtained from a large general population sample from India[11] and supplemented with data from another source (table 1, appendix).[12] The probability that individuals with active

tuberculosis were treated varied by sector (table 1). If no tuberculosis drugs were given, an individual could seek care from another provider, with up to a maximum of three attempts, after which they would no longer seek care and remain untreated. We used three attempts since it was the average number of health-care providers consulted by patients with tuberculosis before diagnosis in India according to a systematic review.[10] Full details on the probabilities of seeking care at the end of three health-seeking attempts are provided in the appendix. Patients made a maximum of three attempts to receive tuberculosis treatment. After up to three attempts at diagnosis (or first round of treatment), 17·3% (95% CI 13·3–18·4) of individuals ended up in the private sector, of which 91·8% (79·6–96·2) were diagnosed with tuberculosis; 64·1% (64·1–68·4) of individuals were in the public sector, of which 96·4% (94·5–98·8%) were diagnosed; 3·3% (2·3–4·4) were treated by chemists, of which 34·1% (28·2–43·9) received tuberculosis drugs; and 15·4% (10·9–17·9) were in the informal sector of which 97·5% (91·4–99·5) did not receive tuberculosis drugs (table 1, appendix). Those who were diagnosed and treated were assigned a total delay of 57·5 days between onset of symptoms and starting tuberculosis treatment, during which time they were infectious to others (table 1).[10] This delay applied to all sectors since sector-specific data for these delays was not identified in published literature.

A correct tuberculosis regimen for initial treatment consisted of at least three drugs in the initial phase (containing both isoniazid and rifampicin); rifampicin for at least 6 months; and correct dose of rifampicin. Patients receiving tuberculosis drugs from any type of provider could be prescribed or dispensed incorrect regimens, and could also take treatment irregularly or incorrectly (table 1). These errors in turn affected the risk of treatment failure, relapse, and acquired drug resistance during treatment (appendix).

If a patient did not respond to treatment, relapsed, or did not complete their first treatment, our model assumed patients treated in the public sector remained in the public sector for re-treatment, and were re-treated correctly (appendix). However, patients treated in non-public sectors could switch providers after initial treatment for their second round of treatment. The probabilities for seeking re-treatment with the different types of provider, and the probabilities of treatment errors in non-public sectors remained unchanged as initial treatment. Patients who

received a second round of treatment always received tuberculosis drugs, regardless of which sector they visited. A maximum of two rounds of treatment with tuberculosis drugs could be given.

In the initial year of analysis, individuals in latent and active tuberculosis states could have drug-susceptible, isoniazid-resistant, or rifampicin-resistant or multidrug-resistant tuberculosis, based on WHO estimates of the prevalence of drug resistance in new and previously treated patients with tuberculosis.[9] Some individuals could acquire drug resistance during treatment, and some could become infected with a drug-resistant strain of tuberculosis. Untreated drug-resistant cases generated secondary drug-resistant infections, but with a slight reduction in transmission (appendix) based on several published studies[38–41] that have found drug-resistant tuberculosis to be less infectious (appendix). Not all individuals were diagnosed or received treatment with tuberculosis drugs when they sought care (table 1). If they received no tuberculosis drugs, they could spontaneously be cured or die, but could not acquire drug resistance (appendix).

Outcomes

The base case analysis began in 2012 and assumed no changes in provider or patient behaviours, and projected epidemiological outcomes for India in 2032. Outcomes were stratified by underlying drug resistance and included annual risk of infection, incidence of new disease, prevalence of untreated tuberculosis, and tuberculosis-related mortality. Patients with drug resistance were stratified according to whether this was primary (from transmission) or acquired (during treatment) resistance. Outcomes were also stratified by health sector to understand how each sector contributes to the emergence of drug resistance.

Sensitivity analysis

We considered scenarios where a single inappropriate tuberculosis management practice or barrier in each sector was corrected within the model, while keeping all other variables constant, and sequentially removed each type of error in each sector from the model until there was no

more acquired drug resistance. By doing so, we were able to estimate the benefit of correction of each error.

Due to the insufficient published evidence for the effect of multiple errors, the base case analysis did not estimate the effect of sequential errors (ie, a provider error followed by a patient error). In sensitivity analysis, we investigated the effect of combining provider errors with patient errors on projected outcomes—overall and by sector. In another sensitivity analysis, we estimated the outcomes that would result if only one sector provided treatment for all tuberculosis cases. These additional scenarios were first modelled with existing non-standard treatment practices and then modelled to correct the most important inappropriate management practice causing acquired drug resistance. Although published evidence suggests informal doctors and chemists do not prescribe rifampicin in India,[25] we considered an alternative scenario in sensitivity analysis where all patients with tuberculosis went to these providers and were prescribed rifampicin. Finally, a probabilistic sensitivity analysis reporting 95% uncertainty ranges (UR), generated from 10 000 Monte Carlo simulation trials, was done to quantify the combined uncertainty when key variables were varied simultaneously. Distributions were defined with reported or calculated CIs around point estimates obtained from the literature. All values reporting ranges in table 1 and the appendix were defined as distributions and used in the probabilistic sensitivity analysis. Probability variables were defined by β distributions and non-probability variables were defined by normal distributions.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, and data interpretation, or writing of the report. All authors had full access to the data and the corresponding author had final responsibility for the decision to submit for publication.

Results

Without any changes to patient behaviours or existing treatment practices, the model projected a 76% increase in isoniazid-resistant tuberculosis and a doubling of the multidrug-resistant

tuberculosis incidence over the 20-year period (table 2). The annual risk of tuberculosis infection would also slightly increase, with a slight drop in risk of drug-susceptible tuberculosis infection, and an increase in risk of drug-resistant infections (table 2). The increase in multidrug-resistant tuberculosis incidence was associated with a 242% increase in prevalence of untreated multidrug-resistant tuberculosis, and a 275% increase in risk of multidrug-resistant tuberculosis infection, so that by 2032, we predicted that 85% of multidrug-resistant tuberculosis infections would be from primary transmission, compared with only 15% in 2012. The relative contributions to acquired isoniazid-resistant and multidrug-resistant tuberculosis in patients who did not respond to treatment, relapsed, did not complete treatment, or had irregular treatment adherence, by health sector are summarised in table 3 and the appendix. The public sector accounted for most of the multidrug-resistant tuberculosis cases because most patients treated with rifampicin were treated by public sector providers, and many had irregular treatment adherence. The two most important factors associated with acquired multidrug-resistant tuberculosis were no response to initial treatment and irregular adherence. The risk of acquired isoniazid resistance was much higher in patients treated by chemists or informal providers, and slightly higher in those treated in the private sector than in the public sector (table 3). However, the risk of acquired multidrug-resistant tuberculosis was higher in the public sector than in all other sectors.

Changes with the largest effect on projected outcomes are shown in table 4 (see appendix for all secondary analyses). The biggest reduction in mortality would occur if all patients were diagnosed and treated during the first encounter, although this would have little effect on drug resistance. The biggest reduction of isoniazid resistance would occur if all patients with tuberculosis were treated in the public sector—this would also reduce mortality, but would increase multidrug-resistant tuberculosis because of the consistent use of rifampicin. Correction of irregular adherence in patients treated in the public sector would have the largest effect on multidrug-resistant tuberculosis incidence. In other sectors, increased completion of treatment by patients treated by private providers would reduce mortality and isoniazid resistance, but have little effect on multidrug-resistant tuberculosis incidence. The largest reduction of

tuberculosis morbidity and mortality in patients treated by chemists, and by informal providers, would occur if these providers referred all patients with tuberculosis to public or private allopathic providers. However, if informal providers and chemists stopped treating patients with tuberculosis drugs (even non-standard treatment), there would be greater mortality with a small decrease in isoniazid resistance.

When the effect of patient treatment adherence factors were combined with incorrect provider treatment practices in all sectors, the incidence and mortality rates due to drug-susceptible tuberculosis and isoniazid-resistant tuberculosis increased slightly, but the mortality rates due to multidrug-resistant tuberculosis increased substantially (table 5). Results from hypothetical scenarios where all patients sought care from only one sector (eg, all patients seen by the public sector only) are shown in the appendix. The findings from these scenarios suggest that if more patients were treated by chemists or informal providers, the emergence of drug resistance would be much greater than in the base-case scenario, particularly if these sectors use rifampicin.

Discussion

Our tuberculosis transmission model projected minor changes in overall risk of infection, incidence, or prevalence of tuberculosis in India over 20 years, given current use, and frequency of inappropriate management practices by patients and providers within the different health sectors. However, if these practices are not corrected, we project the tuberculosis epidemic will shift gradually from one that is predominantly drug susceptible to one with increasing drug resistance. In particular, multidrug-resistant tuberculosis in India will shift from being mainly acquired during treatment to being mainly acquired through primary transmission. Our study is not alone to find such a substantial transition; Suen and colleagues[42] also projected that by 2035, over 60% of new multidrug-resistant tuberculosis cases will result from transmission rather than be acquired during treatment.

This is the first study, to our knowledge, to examine the effect of tuberculosis management and

patient adherence on emergence of drug resistance in all major health-care sectors in India. One strength of this study is that the major health-care sectors involved in the treatment of tuberculosis in India were accounted for, with a comprehensive analysis of how various treatment practices in these sectors might affect acquired and transmitted drug resistance. An additional strength was that many variables used in the modelling were based on an extensive review of the scientific literature, including a recent systematic review,10 and were India-specific.

This study had several limitations. The health-care system in India is complex, and despite the development of a comprehensive model to reflect this, capturing all options for patients seeking care for tuberculosis was difficult. Furthermore, the health-care landscape in India is highly heterogeneous and is variable at a subnational level; for example, there is stronger presence of informal practitioners in rural settings compared with urban settings, where the presence of private allopathic doctors is more prevalent. Our model aimed at representing the average landscape across India, and thus simplified the experiences of patients with tuberculosis across the country. In our base case analysis, patients were assumed to have only one barrier or error, but in reality, patients can have multiple barriers, or errors. This limitation was explored in our sensitivity analysis, but interpretation should be cautious as no evidence for how compounded errors truly affect treatment outcomes has been published.

Several modelling studies have been published in the past few years examining the tuberculosis epidemic in India. Suen and colleagues[42] found that improving non-multidrug-resistant tuberculosis cure rates would decrease overall incidence and mortality from tuberculosis, but have little effect on multidrug-resistant tuberculosis rates. Sachdeva and colleagues[43] found that national scale-up of universal rapid drug-susceptible tuberculosis could greatly reduce the numbers of multidrug-resistant tuberculosis cases between 2015 and 2025. However, their study only focused on the public sector. Mandal and colleagues[44]modelled how different health-care system interventions might affect patient care-seeking pathways and the tuberculosis epidemic in India but did not examine the emergence of drug resistance. By contrast, our study examined

the complex health system-related issues across all sectors, and how these issues affect the emergence of drug resistance in India.

Our modelling study suggests that tuberculosis treatment in the public sector contributes substantially to acquired multidrug-resistant tuberculosis in India. One possible reason for this finding is the use of a thrice weekly intermittent schedule of treatment, which is associated with a high rate of irregular adherence (estimated at 39% in published studies, table 1). Other studies have suggested the reasons for poor adherence in India are multifactorial, including but not limited to poor provider–patient interactions, inaccessibility to treatment centres (eg, operating hours, distance), insufficient social support, increased financial strain, comorbid conditions, and social stigma.[45–47]

Another important finding was the contribution of pre-existing isoniazid mono-resistance to the emergence of multidrug-resistant tuberculosis because the standardised WHO regimens for new and previously treated patients have high rates of failure and relapse with amplification to multidrug resistance.[48] This finding emphasises the need for routine drug susceptibility testing for all individuals diagnosed with tuberculosis, regardless of their treatment history, to ensure drug resistance is identified and an appropriate regimen is prescribed. The finding that non-public health-care services might substantially contribute to isoniazid-resistant tuberculosis suggests that barriers in all health sectors must be addressed to prevent further emergence of multidrug-resistant tuberculosis in India.

The landscape of tuberculosis care has changed enormously in India over the past two decades, with rapid expansion of diagnosis and treatment, especially the use of rifampicin in the public sector. A large number of studies have described important barriers to existing treatment practices in both public and private health sectors in India—many of which could generate drug resistance. Our aim was to assemble these estimates and use them to project the effect of inappropriate management practices on overall epidemiological trends and the potential benefit of their correction. The next step will be to analyse the effect of interventions to improve inappropriate tuberculosis management practices and adherence issues that we have identified

as important contributors to the epidemic of drug resistance. Potential interventions include scaling up effective public–private strategies to improve tuberculosis management,[49] implementing local initiatives to increase tuberculosis case notification from private and informal sectors to ensure diagnosed patients receive appropriate treatment,[50] and introducing patient-centred strategies (eg, reminder systems) to improve treatment adherence.[51] Evidence-based strategies to improve provider practices and patient adherence, and ultimately reduce the burden of drug-resistant tuberculosis in all relevant health sectors are urgently needed.

Contributors

ASP and CV conceived the study idea. SL, OO, ASP, CV, and DM contributed to the study design. SL, OO, and DM did the literature reviews and data analysis. All authors contributed to data interpretation, writing the manuscript, and approved the final version of the paper.

Declaration of interests

CV and ASP are employed by the United States Agency for International Development. All other authors declare no competing interests.

Acknowledgments

SL was funded in part by a doctoral fellowship from the Canadian Institutes for Health Research. This study was funded by the United States Agency for International Development (USAID). The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of USAID.

Table 1: Key input parameters that are specific to India

	Value	95% CI*	Source(s)
General Epidemiologic parameters for India			
Background Mortality (non-TB causes)	0·8%/year	n/a	The World Bank, 2016[7]
Initial TB incidence rate in 2012 (per 100,000 population)	176	n/a	World Health Organization [WHO], 2013[8] (adjusted during model calibration)
Proportion pulmonary TB of all TB patients	80%	n/a	WHO, 2013[8]
Proportion smear-positive of all pulmonary TB patents	66·5%	n/a	Ibid
Proportion of new TB patients with any non-MDR INH-resistance	10·1%	6.2-15.2%	WHO, 2008[9]
Proportion of previously treated TB patients with any non-MDR INH-resistance	19·4%	17.1-21.9%	Ibid
Proportion of new TB patients with any RIF-resistance or MDR-TB	2·6%	2.3-3.6%	Ibid
Proportion of previously treated TB patients with any RIF-resistance or MDR-TB	18·1%	15.9-20.6%	Ibid
All Sectors			
Average total delay (patient delay plus health system)	57·5 days	36-118 days	Sreeramareddy, Qin, Satyanarayana, Subbaraman, & Pai, 2014[10]
Proportion seeking care at each health sector (per attempt)†			
Public	34.8%	n/a	IIPS, 2007; Vijayan et al., 2014[11, 12]
Private	12.3%	n/a	Ibid
Chemists	19.3%	n/a	Ibid
Informal	33.6%	n/a	Ibid
Public Sector			
Proportion treated on first encounter	73·1%	69·6-84·6%	Ananthakrishnan, Jeyaraju, Palani, & Sathiyasekaran, 2012; Selvam et al·, 2007; Suganthi et al·, 2008[13-15]

Treatment with 3+ drugs and over 6 months of RIF	100%	n/a	Assumed
Substandard dose of RIF prescribed	32·4%	23.8-42.3%	Mishra & Mulani, 2013[2]
Poor quality RIF dispensed (e.g., due to poor storage conditions, or past expiry)	6·5%	4.5-9.2%	Ramachandran et al·, 2013[16]
Private Sector			
Proportion treated on first encounter	53	34·4-62·7	Achanta et al·, 2013; Baxi & Shah, 2006; Datta, Bhatnagar, & Murhekar, 2010; Krishnan et al·, 2009; Roy et al·, 2005; Singla, Sharma, Singla & Jain, 1998; Uplekar et al·, 1996; Vandan, Ali, Prasad, & Kuroiwa, 2009 [5,17-23]
No TB drugs given	0	n/a	Mishra & Mulani, 2013; Singla et al·, 1998; Udwadia, Pinto, & Uplekar, 2010; Yadav et al·, 2012 [2-5]
Monotherapy (INH and RIF not given)	0·5%	0-1.6%	Ibid
Treatment with Two drugs	2.7%	1.7-4.6%	Ibid
INH + RIF	59.0%	19.0-86.7%	Ibid
INH + non-RIF	15.0%	0-39.3%	Ibid
RIF + non-INH	26.0%	12.8 -59.3%	Ibid
Treatment with 3+ drugs	97.0%	n/a	Ibid
Correct doses, but duration of RIF < 6 months	1.7%	0-2%	Ibid
Correct duration but low dose of RIF	25.3%	12-38%	Ibid
Correct dose and duration	72%	52-88%	Ibid
Informal sector			
Refer to public or private providers	66.2%	54.2-76.5	Anandhi, Nagaraj, & Kumar, 2002[24]
Proportion treated with TB drugs on first encounter, among those who are not referred out**^**	80%	58.7-92.4	Ibid
Chemist Prescribing#			
Refer to other providers (any type)	25%	n/a	Assumed
Proportion treated with TB drugs on first encounter	5%	n/a	Assumed based on findings from Satyanarayana S, Kwan A, Daniels B, et al.[25]
Chemist dispensing errors ## (if correct prescription given by private/informal doctors)			
Poor quality RIF	8.9%	4.5-15.1%	Bate, Jensen, Hess, Mooney, & Milligan, 2013[26]

Dispensing on a daily or weekly basis (increased probability of short treatment)	50.0%	50-64%	Rajeswari, Balasubramanian, Bose, Sekar, & Rahman, 2002[27]
Patient-level behaviours (only arise when a correct Tx is given)			
Take monotherapy (any sector)	4.7%**	1.9-10.3%	Uplekar, Juvekar, Morankar, Rangan, & Nunn, 1998[28]
Take 2 drugs (any sector)	9.3%***	5.1-16.0%	Ibid·
Treatment not completed			
Public providers	6%	5.9-6.1%	Central TB Division, 2014[29]
Non-public providers	40%	39-44%	Ambe et al·, 2005; Reed, McCausland, & Elwood, 1990; Tandon, Gupta, Tandon, & Gupta, 2002; Uplekar et al·, 1998 (assumed patients had self-administered therapy)[28, 30-32]
Take therapy irregularly			
Public providers	39%	37.0-40.7%	Gopi et al·, 2007 (Assumed as partial adherence to DOT) [33]
Non-public providers	10%	8-10%	Kulkarni et al·, 2013; Zaman, Sheikh, Das, Zaman, & Pal, 2014 [34,35]

*****95% CIs were estimated using the DerSimonian and Laird random effects method for meta-analysis when there were two or more studies.[36] When there was only one study present, the 95% CI was derived from the study sample data. These estimates and their associated 95% CI (when available) were used to specify the beta distributions used in the probability sensitivity analysis.

†Patients made a maximum of three attempts to get TB treatment. After up to three attempts at diagnosis (or first round of treatment), 17·3% (95% CI 13.3-18.4%) of individuals ended up in the private sector, of which 91·8% (95% CI 79.6-96.2%) were diagnosed; 64·1% (95% CI 64.1-68.4%) in the public sector of which 96·4% (95% CI 94.5-9.8%) were diagnosed; 3·3% (95% CI 2.3-4.4%) in the chemists of which 34.1% (95% CI 28.2-43.9%) received TB drugs; and 15·4% (95% CI 10.9-17.9%) in the informal sector of which 97.5% (91.4-99.5%) did not receive TB drugs (For details on how these were estimated, see Appendix Tables S3 and S4).

^When patients were treated with TB drugs in the informal sector, 55% received monotherapy with Streptomycin alone. The remainder (45%) got INH with either Streptomycin or Ethambutol.[23]

#When patients were treated with TB drugs by chemists, 55% received Streptomycin only, and 45% receive INH with either Streptomycin or Ethambutol (assumed same as informal providers).

When TB patients presented to private chemists with a TB prescription, 5% were assumed to be referred to public sector for dispensing.

** Of these, we assumed: a third received INH, a third received RIF, and a third received some other drug (e.g.: Streptomycin or Ethambutol).

*** Of these, we assumed: a third received INH and RIF, a third received either INH or RIF in combination with some other drug (e·g·: Streptomycin or Ethambutol).

Table 2: Main findings from model projection over 20 years – annual risk of infection, incidence, prevalence and mortality, by underlying drug resistance, in 2012 and 2032*

	DS-TB (95% uncertainty range)	INH-resistant TB (95% uncertainty range)	MDR-TB (95% uncertainty range)	All TB (95% uncertainty range)	% of all cases due to DR-TB (95% uncertainty range)
ANNUAL RISK OF INFECTION (%)					
2012	1.7 (1.6-1.8)	0.2 (0.2-0.3)	0.08 (0.07-0.09)	2.0 (1.9-2.2)	14.0 (12.3-20.5)
2032	1.5 (1.4-1.7)	0.4 (0.3-0.5)	0.3 (0.2-0.4)	2.2 (1.9-2.6)	31.8 (19.2-47.4)
INCIDENCE (per 100,000)					
2012 – Total incidence	156.4 (150.0-161.9)	15.1 (9.9-21.1)	3.9 (3.1-4.8)	175.4 (163.1-187.8)	10.8 (6.9-15.9)
2012 – Incidence Acquired DR	-	3.8 (2.4-5.5)	3.9 (2.7-5.4)	-	-
2032 - Incidence	136·7 (128.6-145.8)	26·6 (18.8-34.8)	14.1 (11.2-16.0)	177.4 (158.5-196.6)	22.9 (15.3-32.1)
2032 - Incidence Acquired DR	-	3.3 (2.2-4.9)	4.6 (3.3-6.1)	-	-
PREVALENCE (per 100,000)					
2012 Untreated	350.3 (334.3-364.3)	42.2 (28.3-58.1)	14.0 (11.9-16.3)	406.5 (374.5-438.7)	13.8 (9.2-19.9)
2032 Untreated Prevalence	320.6 (300.6-340.5)	59.0 (43.2-77.0)	48.0 (38.8-58.4)	427.6 (382.6-475.9)	25.0 (17.2-35.4)
MORTALITY (Deaths per 100,000)					
	Due to DS-TB	**Due to INH-resistant TB**	**Due to MDR-TB**	**Total (DS-TB & DR-TB)**	**% of deaths due to DR-TB**
2012	24·6 (23.2-25.8)	3.0 (2.0-4.1)	1.7 (1.5-1.9)	29.3 (26.7-31.8)	16.0 (11.0-22.5)
2032	21·2 (19.0-23.5)	5.9 (4.3-7.4)	7·5 (5.8-8.9)	34.6 (29.1-39.8)	38.7 (25.4-56.0)

*The 95% uncertainty range gives the 5th-percentile and 95th-percentile of the range of estimated outcomes from 10,000 Monte Carlo simulations done in probability sensitivity analysis (see text for details on the probability sensitivity analysis).

Table 3. Acquired drug resistance projected after 20 years under base case scenario, by health sector (all numbers per hypothetical population of 100,000 persons)*

Health Sector (% of all TB patients treated with TB drugs in the sector)	**Number of DS-TB patients who received treatment (95% uncertainty range)**	**Number of DS-TB patients who acquired INH-resistant TB during treatment (95% uncertainty range)**	**% of DS-TB patients who acquire INH-resistant TB during treatment (95% uncertainty range)**	**Overall - % of all acquired INH-resistance - due to TB treatment in each sector**	**Total number of DS-TB and INH-resistant TB patients who received treatment (95% uncertainty range)**	**Number of DS-TB and INH-resistant TB patients who acquired MDR-TB during treatment (95% uncertainty range)**	**% of DS-TB and INH-resistant TB patients who acquired MDR-TB during treatment (95% uncertainty range)**	**Overall - % of all acquired MDR - due to TB treatment in each sector**
Public (68.2%)	99 (92-107)	1.7 (1.1-2.5)	1.7 (1.2-2.3)	51.5%	123 (109-137)	4.0 (2.9-5.4)	3.3 (2.7-3.9)	87%
Private (15.3%)	24 (21-27)	0.6 (0.5-0.9)	2.5 (2.4-3.3)	18.2%	29 (24-34)	0.6 (0.4-0.8)	2.1 (1.7-2.4)	13%
Chemist** (2.3%)	3 (3 - 4)	0.1 (0.07-0.2)	3.3 (2.3-5)	3.0%	4 (3-5)	0	0	0
Informal** (14.2%)	22 (19-26)	0.9 (0.5-1.4)	4.1 (2.6-5.4)	27.3%	27 (22-32)	0	0	0
Total	148 (135-164)	3.3 (2.2-5.0)	2.2 (1.6-3.0)	100%	183 (158-208)	4.6 (3.3-6.2)	2.5 (2.1-3.0)	100%

*The 95% uncertainty range gives the 5th-percentile and 95th-percentile of the range of estimated outcomes from 10,000 Monte Carlo simulations done in probability sensitivity analysis (see text for details on the probability sensitivity analysis).

**Assumed chemists and informal providers do not prescribe RIF (see Table 1).

Table 4a: Secondary analysis - Projected TB incidence and Mortality after 20 years, following correction of major problems identified in each health system sector

(Corrections with greatest epidemiologic impact shown – by major category of drug resistance)

		Incidence (per 100,000 person)			Mortality (per 100,000 persons)		
Health sector targeted	**Type of Health System Change**	**DS-TB**	**INH-resistant TB**	**MDR-TB**	**Due to DS-TB**	**Due to INH-resistant TB**	**Due to MDR-TB**
	No change (base case)	136·7	26·6	14·1	21·2	5·9	7·5
ALL SECTORS	All patients seek care in the public sector	131·0	22·4	14·7	14·1	3·5	7·8
	All patients diagnosed and start treatment on first diagnostic attempt*	132·3	26·7	13·7	18·1	5·9	7·3
PUBLIC SECTOR	All patients treated in the public sector complete treatment (100% adherence)	136·2	26·3	14·0	20·6	5·7	7·4
	No Irregular adherence in patients treated in the public sector	136·7	26·6	13·3	20·8	5·8	6·8
PRIVATE SECTOR	All patients treated in the private sector complete treatment	135·3	25·5	14·0	19·5	5·3	7·4
CHEMISTS	Chemists refer all TB suspects to private and public providers for diagnosis and treatment	134·0	25·5	14·3	18·3	5·2	7·6
INFORMAL SECTOR	Informal practitioners refer all TB suspects to private and public providers for diagnosis & Treatment	136·3	24·6	14·6	19·6	4·7	7·8

*Total delay prior to treatment initiation is only 38·1 days (reflects health system delay only).

Note: Correction of the following problems made very little difference in these outcomes compared to the base case analysis: (1) Drug quality improved at a regulatory level; (2) Private Allopathic doctors prescribe correct TB drugs; (3) Chemists who fill private doctors prescriptions dispense only monthly drug doses (ie· no daily/weekly dispensing); (4) Patients treated in the private sector do not selectively take drugs (ie· no monotherapy or taking only two of the prescribed drugs); (5) When chemist dispense without a prescription, they dispense all correct TB drugs.

Table 4b: Sensitivity analysis - Projected TB incidence and Mortality after 20 years: combined inappropriate provider and patient treatment practices

		Incidence (per 100,000 person)			Mortality (per 100,000 persons)		
Health sector targeted	**Type of Health System Change**	**DS-TB**	**INH-resistant TB**	**MDR-TB**	**Due to DS-TB**	**Due to INH-resistant TB**	**Due to MDR-TB**
	Base case scenario (single inappropriate practice)	136·7	26·6	14·1	21·2	5·9	7·5
ALL SECTORS	Combined inappropriate provider and patient –treatment practice*	134.2	27.5	19.9	21.6	6.5	11.9
PUBLIC SECTOR only		135.1	27.0	17.3	21.2	6.2	9.9
PRIVATE SECTOR only		136.2	26.9	15.2	21.2	6.1	8.4

*Assumed that one provider substandard treatment practice (RIF for less than 6 months; RIF dosage less than standard; monotherapy; or only 2 drugs) can be combined with one patient treatment adherence factor (selectively taking only one or two drugs; irregular adherence; or non-completion). The probability of having a specific combination of errors is the product of the independent probabilities of the two errors. We assumed the probability of the treatment outcomes (death, failure, relapse, non-completion, and acquiring drug resistance) was simply the sum of the respective probabilities from each error. For example, if a patient received RIF for less than 6 months *and* had irregular adherence, then the probability of treatment failure would be the sum of the probability of treatment failure of receiving a short regimen *and* having irregular adherence.

References

1 WHO. Global Tuberculosis Report 2016. Geneva: World Health Organization, 2016.

2 Mishra G, Mulani J. Tuberculosis prescription practices in private and public sector in India. Natl J Integr Res Med 2013; 4: 71–78.

3 Yadav A, Garg SK, Chopra H, et al. Treatment practices in pulmonary tuberculosis by private sector physicians of Meerut, Uttar Pradesh. Indian J Chest Dis Allied Sci 2012; 54: 161–63.

4 Udwadia ZF, Pinto LM, Uplekar MW. Tuberculosis management by private practitioners in Mumbai, India: has anything changed in two decades? PLoS One 2010;

5: e12023. 5 Singla N, Sharma PP, Singla R, Jain RC. Survey of knowledge, attitudes and practices for tuberculosis among general practitioners in Delhi, India. Int J Tuberc Lung Dis 1998; 2: 384–89.

6 Oxlade O, Schwartzman K, Benedetti A, Pai M, Heymann J, Menzies D. Developing a tuberculosis transmission model that accounts for changes in population health. Med Decis Mak 2011; 31: 53–68.

7 The World Bank. Death rate, crude (per 1,000 people). Washington, DC: The World Bank Group; 2016.

8 WHO. Global Tuberculosis Report 2013. Geneva: World Health Organization, 2013.

9 WHO. Anti-tuberculosis drug resistance in the world: fourth global report. Geneva: World Health Organization, 2008.

10 Sreeramareddy CT, Qin ZZ, Satyanarayana S, Subbaraman R, Pai M. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. Int J Tuberc Lung Dis 2014; 18: 255–66.

11 International Institute for Population Sciences (IIPS). Macro International National Family

Health Survey (NFHS-3), 2005–06. Volume I. Mumbai: IIPS, 2007.

12 Vijayan S, Khetarpal M, Datta M, et al. Chemists and less-than-fully-qualified providers dominate Mumbai's health provider universe (PD-647-30). Int J Tuberc Lung Dis 2014; 18: S146–47.

13 Suganthi P, Chadha VK, Ahmed J, et al. Health seeking and knowledge about tuberculosis among persons with pulmonary symptoms and tuberculosis cases in Bangalore slums. Int J Tuberc Lung Dis 2008; 12: 1268–73.

14 Selvam JM, Wares F, Perumal M, et al. Health-seeking behaviour of new smear-positive TB patients under a DOTS programme in Tamil Nadu, India, 2003. Int J Tuberc Lung Dis 2007; 11: 161–67.

15 Ananthakrishnan R, Jeyaraju AR, Palani G, Sathiyasekaran BWC. Care seeking behavior of the TB patients who were registered in an urban government tuberculosis control in Chennai, Tamilnadu, India. J Clin Diagn Res 2012; 6: 990–93.

16 Ramachandran G, Chandrasekaran V, Hemanth Kumar AK, Dewan P, Swaminathan S, Thomas A. Estimation of content of anti-TB drugs supplied at centres of the Revised National TB Control Programme in Tamil Nadu, India. Trop Med Int Health 2013: 18: 1141–44.

17 Achanta S, Jaju J, Kumar AM, et al. Tuberculosis management practices by private practitioners in Andhra Pradesh, India. PLoS One 2013; 8: e71119.

18 Datta K, Bhatnagar T, Murhekar M. Private practitioners' knowledge, attitude and practices about tuberculosis, Hooghly district, India. Indian J Tuberc 2010; 57: 199–206.

19 Vandan N, Ali M, Prasad R, Kuroiwa C. Assessment of doctors' knowledge regarding tuberculosis management in Lucknow, India: a public-private sector comparison. Public Health 2009; 123: 484–89.

20 Krishnan N, Ananthakrishnan R, Augustine S, et al. Impact of advocacy on the tuberculosis management practices of private practitioners in Chennai City, India. Int J Tuberc Lung Dis 2009; 13: 112–18.

21 Roy SK, Roy SK, Bagchi S, Bajpayee A, Pal R, Biswas R. Study of KAP of the private medical practitioners about national disease control programmes. Indian J Public Health 2005; 49: 256–57.

22 Uplekar MW, Juvekar SK, Parande SD, et al. Tuberculosis management in private practice and its implications. Indian J Tuberc 1996; 43: 19–22.

23 Baxi RK, Shah AR. Management of TB by the general practitioners of Vadodara city. Indian J Community Med 2006; 31: 10–12.

24 Anandhi CL, Nagaraj VK, Kumar R. Knowledge and practice pattern of non-allopathic indigenous medical practitioners regarding tuberculosis in a rural area of India. Indian J Tuberc 2002; 6: 553–55.

25 Satyanarayana S, Kwan A, Daniels B, et al. Use of standardised patients to assess antibiotic dispensing for tuberculosis by pharmacies in urban India: a cross-sectional study. Lancet Infect Dis 2016; 16: 1261–68.

26 Bate R, Jensen P, Hess K, Mooney L, Milligan J. Substandard and falsified anti-tuberculosis drugs: a preliminary field analysis. Int J Tuberc Lung Dis 2013; 17: 308–11.

27 Rajeswari R, Balasubramanian R, Bose MS, Sekar L, Rahman F. Private pharmacies in tuberculosis control—a neglected link. Int J Tuberc Lung Dis 2002; 6: 171–73.

28 Uplekar M, Juvekar S, Morankar S, Rangan S, Nunn P. Tuberculosis patients and practitioners in private clinics in India. Int J Tuberc Lung Dis 1998; 2: 324–29.

29 Central TB Division. TB India 2014: Revised National TB Control Programme Annual Status

Report. New Delhi: Directorate General of Health Services, Ministry of Health and Family Welfare, 2014.

30 Reed JB, McCausland R, Elwood JM. Default in the outpatient treatment of tuberculosis in two hospitals in Northern India. J Epidemiol Community Health 1990; 44: 20–23.

31 Tandon M, Gupta M, Tandon S, Gupta KB. Dots versus self-administered therapy (SAT) for patients of pulmonary tuberculosis: A randomised trial at a tertiary care hospital. Indian J Med Sci 2002; 56: 19–21.

32 Ambe G, Lonnroth K, Dholakia Y, et al. Every provider counts: effect of a comprehensive public-private mix approach for TB control in a large metropolitan area in India. Int J Tuberc Lung Dis 2005; 9: 562–68.

33 Gopi PG, Vasantha M, Muniyandi M, Chandrasekaran V, Balasubramanian R, Narayanan PR. Risk factors for non-adherence to directly observed treatment (DOT) in a rural tuberculosis unit, South India. Indian J Tuberc 2007; 54: 66–70.

34 Kulkarni P, Akarte S, Mankeshwar R, Bhawalkar J, Banerjee A, Kulkarni A. Non-adherence of new pulmonary tuberculosis patients to anti-tuberculosis treatment. Ann Med Health Sci Res 2013; 3: 67–74.

35 Zaman FA, Sheikh S, Das KC, Zaman GS, Pal R. An epidemiological study of newly diagnosed sputum positive tuberculosis patients in Dhubri district, Assam, India and the factors influencing their compliance to treatment. J Nat Sci Biol Med 2014; 5: 415–20.

36 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–88.

37 Denkinger CM, Pai M, Dowdy DW. Do we need to detect isoniazid resistance in addition to rifampicin resistance in diagnostic tests for tuberculosis? PLoS One 2014; 9: e84197.

38 Grandjean L, Gilman RH, Martin L, et al. Transmission of multidrug-resistant and drug-

susceptible tuberculosis within households: a prospective cohort study. PLoS Med 2015; 12: e1001843.

39 García-García ML, Ponce de León A, Jiménez-Corona ME, et al. Clinical consequences and transmissibility of drug-resistant tuberculosis in southern Mexico. Arch Intern Med 2000; 160: 630–36.

40 Van Soolingen D, Borgdorff MW, de Haas PE, et al. Molecular epidemiology of tuberculosis in the Netherlands: a nationwide study from 1993 through 1997. J Infect Dis 1999; 180: 726–36.

41 Burgos M, DeRiemer K, Small PM, Hopewell PC, Daley CL. Effect of drug resistance on the generation of secondary cases of tuberculosis. J Infect Dis 2003; 188: 1878–84.

42 Suen SC, Bendavid E, Goldhaber-Fiebert JD. Disease control implications of India's changing multi-drug resistant tuberculosis epidemic. PLoS One 2014; 9: e89822.

43 Sachdeva KS, Raizada N, Gupta RS, et al. The potential impact of up-front drug sensitivity testing on India's epidemic of multi-drug resistant tuberculosis. PLoS One 2015; 10: e0131438.

44 Mandal S and Arinaminpathy N. Transmission modeling and health systems: the case of TB in India. Int Health 2015; 7: 114–20.

45 Deshmukh RD, Dhande DJ, Sachdeva KS, et al. Patient and provider reported reasons for lost to follow up in MDRTB treatments: a qualitative study from a drug resistant TB centre in India. PLoS One 2015; 10: e0135802.

46 Jaiswal A, Singh V, Ogden JA, et al. Adherence to tuberculosis treatment: lessons from the urban setting of Delhi, India. Trop Med Int Health 2003; 8: 625–33.

47 Barnhoorn F, Adriannse H. In search of factors responsible for noncompliance among tuberculosis patients in Wardha district, India. Soc Sci Med 1992; 34: 291–306.

48 Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-

resistant tuberculosis with fi rst-line drugs: a systematic review and meta-analysis. Lancet Infect Dis 2016; published online Nov 16. http://dx.doi.org/10.1016/S1473- 3099(16)30407-8.

49 Lei X, Liu Q, Escobar E, et al. Public-private mix for tuberculosis care and control: a systematic review. Int J Infect Dis 2015; 34: 20–32.

50 Kundu D, Chopra K, Khanna A, Babbar N, Padmini TJ. Accelerating TB notification from the private health sector in Delhi, India. Indian J Tuberc 2016; 63: 8–12.

51 Liu Q, Abba K, Alejandria MM, Sinclair D, Balanag VM, Lansang MAD. Reminder systems to improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment. Cochrane Database Syst Rev 2014; 11: CD006594.

STUDY 2: "I REALLY NEEDED THEM TO TRUST ME, BUT THEY DIDN'T": HOW PATIENT-PROVIDER TRUST INFLUENCES TUBERCULOSIS TREATMENT OUTCOMES

In the previous study, the decision analytic model explored the complex TB patient treatment pathways in India, and identified the importance of strengthening care in the public sector. Unlike India, where there has been extensive research investigating treatment-seeking patterns among individuals with TB symptoms, there has been limited research of this topic conducted in South Africa. Furthermore, despite some research indicating that many South African TB patients seek care from private providers, and occasionally from traditional healers, there has been no exploration of the care that is currently provided by non-public providers for individuals with TB or TB symptoms.

This qualitative study explored treatment journeys of TB patients in Cape Town, South Africa, to understand care-seeking patterns, adherence, and retention-in-care among drug-susceptible and drug-resistant TB patients. Interviews conducted with private providers as part of this study revealed that providers who are familiar with TB symptoms will often screen for and diagnose TB, but will generally refer patients to public clinics once TB has been diagnosed, and do not prescribe TB treatment (appendix). However, it was common for patients who sought care initially from private providers to experience lengthy delays - often visiting multiple providers - before reaching the public clinics where they were finally diagnosed and initiated on treatment. More importantly, this qualitative research elucidated the important role of patient-provider trust in influencing both patient and provider behaviours that affect adherence, retention-in-care, as well as delays in accessing appropriate treatment and duration of treatment interruptions. This finding is explored and discussed in-depth in the following manuscript prepared for publication**. The details on care-seeking pathways and treatment delays can be found in the appendix, but are not discussed in the manuscript.**

Manuscript 2: Law S, Daftary A, Esmail A, Dheda K, Menzies D. "I really needed them to trust me, but they didn't": how the presence or absence of patient-provider trust influences tuberculosis treatment outcomes.

The following text is from a manuscript prepared for submission to Social Science & Medicine.

Abstract

Despite gradual improvements in treatment for tuberculosis (TB), patient losses to follow-up and poor retention-in-care are a growing concern amidst increasing rates of drug-resistance in Cape Town, South Africa. This study, guided by a constructivist grounded theory methodology, explores the role of patient-provider trust in TB treatment, and its relationship with often lengthy treatment journeys, and patient outcomes. Between Dec. 2015 and May 2017, in-depth and focus group interviews were conducted with 31 adult (drug-susceptible or drug-resistant) TB patients and 36 health care providers, including TB nurses and doctors, private doctors, and traditional healers.

Three main processes emerged that seem to influence patient-provider trust and patient outcomes. First, there was a marked absence of a baseline level of trust. Thus, an initial stage of building and establishing reciprocal trust was crucial, particularly during the first few patient-provider encounters. This involved patients adhering to provider recommendations and treatment protocols, and providers demonstrating empathy and compassion for patients' individual circumstances. Providers could achieve this through simple gestures such as positive greetings on patient arrival, and more concretely by actively listening, and addressing patients' questions and concerns in an honest, sincere fashion. Second, the manner by which patients and their providers dealt with emergent adherence barriers could quickly encourage or erode mutual trust. This was contingent on a baseline level of trust, without which patients were less forthcoming about their problems, and conversely, providers were less available to support patients in overcoming those problems. Third, the reconstruction of trust following its erosion due to any patient, or provider, error, proved to be difficult, especially after a patient lost the

trust of a provider, which could limit the patient's access to treatment options and social protection. Future strategies to improve patient retention-in-care and patient outcomes should focus on establishing trust early-on in treatment.

Introduction

Tuberculosis (TB) affects over 10 million people worldwide annually (World Health Organization [WHO], 2017). The global standard treatment for TB today consists of a six-month multi-drug regimen, optimized to prevent drug resistance, and achieve cure. Correct prescribing practices and adherence to medications is key to treatment success. Incorrect and insufficient treatment may allow TB bacteria that spontaneously mutate and become resistant to any given drug to multiply, leading to acquired drug resistance. Drug-resistance significantly complicates TB diagnosis and treatment with negative impacts on patient outcomes. Today, about 5% of all TB cases are multi-drug resistant (MDR), that is, resistant to isoniazid and rifampicin, the most potent TB drugs. Of these MDR-TB cases, up to 10% are extensively drug-resistant (XDR), with additional resistance to a second-line injectable and fluoroquinolone (WHO, 2017).

South Africa has a high burden of TB and MDR-TB, with over 400,000 and 20,000 new cases, respectively, in 2016 (WHO, 2017). While the high co-prevalence of HIV infection is understood to be a major driver of the TB epidemic, treatment success rates among new and relapse TB patients are similar among those with and without HIV infection, at 81 percent and 80 percent, respectively. On the other hand, treatment success rates are considerably lower at 54 percent among MDR-TB patients and 27 percent among patients with XDR-TB. Over the past decade, gradual improvements in MDR-TB treatment have not managed to diffuse the rate of patient loss to follow-up, defined as over 2 months of interruption to treatment (Department of Health [DoH], 2017). Treatment interruptions not only drive primary transmission of MDR-TB in the community, but also amplify the risk of developing XDR-TB in the patient.

A range of clinical, operational and social issues affect patient retention in TB treatment and care. A psychosocial aspect of patient care that has been poorly studied in TB but shown to affect

adherence and outcomes in chronic illnesses, such as HIV (Beach, Keruly & Moore, 2006) and diabetes (Lee & Lin, 2011), is the level of trust between a patient and his or her health provider. TB is typically not characterized as a chronic illness, but given its long treatment duration, can be viewed as such particularly in the case of MDR-TB (at least 9 months) and XDR-TB (upwards of 24 months). The concept of trust has been defined in different ways in different settings (Calnan & Rowe, 2007). This study follows Hall's definition of trust as "the optimistic acceptance of a vulnerable situation in which the trustor believes the trustee will care for the trustor's interests" (Hall, Dogan, Zheng & Mishra, 2001, p. 615). Research exploring trust in a wide variety of healthcare settings has found a number of provider behaviours to be associated with patient trust, such as: empathy and understanding of patient's individual experiences; reliability and dependability; clear, thorough evaluation and communication; provision of appropriate, effective treatment; and honesty and respectfulness towards patients (Rolfe, Cash-Gibson, Car, Sheikh & McKinstry, 2014; Thom & Campbell, 1997). There has however been limited research exploring the impact of provider trust on patient outcomes (Robinson, 2016). In South Africa, observations and studies of doctor-patient encounters suggest that trust may be a critical determinant of medical decision-making as well as patient outcomes (Kelly, 2017; Gilson, Palmer & Schneider, 2005; Ncama et al., 2008). Provider trust, for instance, may influence the ability of HIV-positive patients on antiretroviral treatment to access social disability grants, and this could affect treatment outcomes (Kelly, 2017).

As part of a broader qualitative study exploring TB treatment journeys – from symptom onset, to care-seeking, to treatment outcomes – this paper explores the role of trust in TB care, and the relationship between trust and TB treatment adherence and outcomes in Cape Town, South Africa. Potential strategies to foster patient-provider trust within TB treatment and care in resource-limited settings are also discussed.

Methodology

Study setting

This study was conducted in Cape Town, Western Cape province. Treatment for TB is provided

free of charge in the public sector, though patients are known to access health-related services from private doctors and traditional healers (Van Wyk, Enarson, Beyers, Lombard & Hesseling, 2011; Meintjes, Schoeman, Morroni, Wilson & Maartens, 2008). Patients with smear-negative MDR-TB, as well as stable non-XDR-TB, without extensive disease initiate ambulatory treatment at primary care facilities (City of Cape Town, 2016). Otherwise, treatment is initiated inpatient at a TB hospital. Treatment is standardized according to WHO guidelines: six months for new drug-susceptible (DS) TB (9 months if previously treated); and minimum 18 months for MDR-TB. Patients typically receive three treatment education and counselling sessions by a trained clinic staff in the first week of treatment, and a fourth session after two months. The sessions are guided by standardized graphic flipcharts, tailored to patients with MDR-TB and DS-TB. Patients with DS-TB must attend clinic daily for the first two weeks, where treatment intake is observed by a nurse – a global standard practice in TB known as directly observed therapy (DOT). Thereafter, a community health worker (CHW) performs a home assessment to help determine whether the patient is eligible to receive a monthly supply of treatment (Atkins, Biles, Lewin, Ringsberg & Thorson, 2010). If a patient is considered eligible to be placed out, the CHW visits the patient three times during the first week and once weekly thereafter to perform pill counts and monitor adherence. Non-eligible patients and patients with MDR-TB are required to attend clinic daily throughout their treatment (DoH, 2014).

Study population

Patient and provider participants were selected from four clinics and one TB hospital that cater to high volumes of TB patients. Clinics are located in historically segregated peri-urban areas outside the city centre, where residents are mostly Black (primarily isiXhosa-speaking Africans) or Coloured (of mixed race, primarily Afrikaans-speaking) South Africans. Black and Coloured populations are historically disproportionately affected by TB compared to other racial groups in South Africa (Packard, 1989).

Data collection & analysis

This study was guided by a constructivist grounded theory methodology (Charmaz, 2000), which

is rooted in the understanding that the researcher "is part of what is viewed rather than separate from it" (p. 524). Therefore data collection and subsequent analyses are influenced by the interactions between the researcher and the participants, as well as the social, cultural and structural contexts in which those interactions occur and are analyzed. Accordingly, the primary researcher (SL) spent 18 months (Dec. 2015 to May 2017) in the field, and maintained regular field notes, analytic memos and personal reflections to remain reflexive during data collection and analysis.

During this time, she recruited adult patients (18 years or older) with TB (including MDR-TB, pre-XDR-TB and XDR-TB) with the help of clinic staff and CHWs. Patients were purposively sampled to reflect a wide range of treatment experiences based on sex, race, age, history of previous TB treatment, HIV status, drug-resistance status, and adherence level as perceived by healthcare workers. The healthcare worker would first approach the patient to ask if they would speak with the researcher at routine clinic visits. If yes, then the researcher would meet the patient in a private room, describe the study and obtain signed informed consent. The researcher recruited CHWs, counsellors, sisters (South African term for nurses) and doctors from the same facilities. She also recruited a convenience sample of private doctors and traditional healers from clinic catchment areas by contacting them directly, in person or by phone. All patients, healthcare providers in the public sector and traditional healers who were approached agreed to participate in the study. Only 5 of 11 private practitioners contacted responded to phone calls or emails, of whom all agreed to be interviewed.

The researcher conducted in-depth interviews following a semi-structured, open-ended interview guide. Patients were asked to detail their TB-related experiences since the first time they experienced symptoms up until the time of interview. Interviews with providers focused on their work and personal experiences with TB, and their interactions with patients and other providers. All interviews were conducted in English, or in isiXhosa when preferred by the participant, digitally recorded, translated to English if necessary, transcribed, checked for accuracy, and de-identified.

Interview notes and transcripts were read and re-read, and initial open, line-by-line coding of transcripts was done manually (i.e. without the use of software) to examine, compare, conceptualize and categorize the data (Glaser, 1978; Charmaz, 2000). During initial open coding, the primary researcher stayed close to the data and kept the codes active (e.g. "Deciding to stop treatment"; "Balancing life and treatment priorities"), using participants' words to generate codes as often as possible, without imposing her own beliefs or extant theories on the data. These codes and a selection of transcripts were reviewed by and discussed with other authors (AD, DM) to enhance coding reliability. This was followed by focused coding, where the researcher used initial codes that reappeared frequently to organize and categorize the data, thereby identifying patterns and themes. Constant comparison between and within transcripts allowed continued refinement of themes and concepts, and an exploration of unexpected or contradictory findings (Charmaz, 2000). During this inductive analytic process, the concept of trust emerged as a major theme that was discussed frequently by participants throughout different stages of TB treatment. Thus the current paper examines participants' perceptions and experiences related to trust in TB care, and explores the relationship between trust and patients' TB treatment journeys. Initial findings were disseminated to clinic staff and relevant local stakeholders (including doctors and nurses within public clinics, managerial staff at the City of Cape Town's Department of Health, and representatives of a national TB-HIV non-governmental organization responsible for recruiting community health workers involved in TB and HIV care) for member-checking (Lincoln & Guba, 1985) and to obtain feedback. These discussions further informed the analysis.

Ethical statement

Ethics approval for the study was received from the Research Ethics Office (Institutional Review Board) at [removed institution name], the Human Research Ethics Committee (Faculty of Health Science) at the [removed institution name], and the City of Cape Town. All participants provided informed written consent and were reimbursed 50 South African rand (ZAR) for their time.

Findings

Overview of study participants

Sixty-nine consenting adult participants were interviewed: 33 adult TB or MDR-TB patients; 31 health care providers; and two group interviews with five health care providers. Two of the patients were former TB nurses and one was a traditional healer (see Table 1). Health care providers included: 11 CHWs; three TB counsellors; 12 TB nurses; five public TB doctors; five traditional healers; and five private practitioners (see Table 2). All interviews were conducted in English except two done in isiXhosa with traditional healers, for which an isiXhosa-speaking CHW not affiliated with the facilities aided in interpretation.

Fifteen patients had been lost to follow-up during a previous TB episode. They cited lack of stable access to food, work and money as major challenges to maintaining treatment. The obligation to serve as breadwinners (mostly, men) or caregivers (mostly, women) prevented them from prioritizing their own wellbeing over that of their family, particularly when family members were also unwell. Ensuing analyses of patient-provider trust must be understood in the context of these ongoing social and economic struggles.

Trust at the start of TB treatment journeys

Patient and provider participants did not assume they shared a baseline level of trust at public clinics. Rather, trust was something that had to be explicitly built and established during their initial interactions.

Many patients entered clinics laden with apprehension and mistrust after having faced lengthy diagnostic and treatment delays (up to 1 year), and negative experiences that they attributed to inefficiencies within the public system. Several patients expressed a preference for non-public providers, despite lacking the funds to support their services, and being aware of free testing and treatment in the public sector. Shorter waiting times and individualized attention were important drivers to seeking care from private practitioners and traditional healers.

> "Because of queuing, a lot of time there, you spending the whole day in there, that's why I didn't want to go to the clinic." (Female DS-TB Patient, age 38)

> "When you go to our clinics, you go for headache, you'll get the Panadol, you go for the stomach, you get the Panadol, is what we experience, that is why we decided go to the special [private] doctor." (Male MDR-TB Patient, age 42)

In rare cases, patients bore an underlying mistrust of the Western medical system, a sentiment that was voiced by some traditional healers who had dealt with patients who refused to visit a clinic in favour of traditional treatment.

> "[My brother] was glad about the traditional healers, he didn't believe about the clinics. But while he come to the clinic and find out that he got a TB, it was too late for him. Yes, he didn't make it." (Male MDR-TB Patient, age 33)

One of the first missed opportunities to build patient-provider trust in the clinic was when patients returned for their TB test results and began TB treatment. One patient described how his providers never took the time to educate him about his diagnosis and treatment:

> "You feel bad because they're not telling you the truth man. It's almost like here also he don't care, because I won't tell a person, 'if you don't take your tablets you're going to die.' No! I'll try to explain in a better way. Almost like he don't care if you die today or tomorrow." (Male MDR-TB Patient, age 38)

A few health care providers recognized the importance of building trust and rapport early in their encounters with new patients, as a way to encourage open discussions in the future:

> "You start a journey with the patients, and the patients become like, I won't say like friends, but you have that relationship with each person, it's different. Some of them they can be, they are very respectful of the nurses in this room and they will open up with you, share their problems with you, because you've known them for maybe three months now, or for four months, that they are on the treatment, so now they will share with you and I think

they, most of them, they feel open to speak with us." (Female TB Nurse)

However, a vast majority of interviews with patients and providers, as well as subsequent discussions of the study findings with local stakeholders, suggested that trust was not considered a priority, nor highlighted in provider education and training. A reliance on clinic protocols – such as daily DOT – seemed to disincline providers from investing in building patient trust, as suggested by the following TB nurse's view:

> "You don't actually need to trust the patient, but you need to have a follow-up on the patient…Once you have a working plan that considers a follow-up, that is much better than to trust and not doing anything about it." (Female TB Nurse)

A majority of providers in public clinics were more invested in educating patients; though they complained of having few opportunities partly because of a focus on reaching program targets in lieu of spending concentrated time with each patient. This TB counsellor, whose primary responsibility was to counsel and educate new patients at the start of treatment, laid this out clearly:

> "They [clinic managers] need stats…they don't care about these kinds of TB [counselling and education] sessions… So the managers, they want X amount of tests, but it's not working like that. We have to sit and explain to the client 15 to 20 minutes. It's not an easy job to be a counsellor." (Female TB Counsellor)

By contrast, traditional healers and private providers devoted a good amount of time and effort in comforting patients and setting the foundation for a trusting relationship. The way the following traditional healer described her initial encounters with patients was common to all interviewed healers:

> "First of all, I sit with them and talk, just to make them comfortable. You have to make them feel comfortable so that it will be easy to accept whatever you may tell them. So I make them laugh and also tell them about me so they feel free to talk to me." (Female

Traditional Healer)

From the provider's perspective, trust was something patients had to earn. Patients had to prove themselves to be trustworthy by following treatment guidelines, such as: adhering to treatment; returning for scheduled visits and tests; and following proper procedures if they were transferred to other clinics. When deciding whether a patient could be "placed out" to receive weekly, bi-weekly or monthly vs. daily supplies of medication, a TB nurse or doctor first decided whether the patient could be trusted.

> "We try to accommodate the patient…but like I said, you need to make sure that the patient is trustworthy." (Female TB Nurse)

Trust was also key to patient access to governmental disability assistance, which relied on providers completing a referral form to the South African Social Security Agency. The patient's trustworthiness, as perceived by providers, influenced the extent to which treating doctors completed this form or advocated for a disability grant.

> "We don't like to give the patients who's on drugs, we don't want to give him grant. I mean it's not fair on our tax money. And they're going to use their grant money to buy drugs. We not going to give him." (Female TB Doctor)

Trust during TB treatment

Several patients recollected specific incidents in their lives that limited or prohibited them from attending the clinic or continuing TB treatment. The capacity of patients to overcome these obstacles appeared to be heavily influenced by existing relationships they had with their providers, and the level of trust they perceived in such relationships. In the following example, a patient had been evicted from his squatter camp after other residents discovered he had TB. He had nearly given up treatment in order to prove he was TB-free:

> "I was cross, I was angry…I go to the clinic and tell the sister [nurse]…She said, 'No, you mustn't leave your medication, and don't satisfy the people. You are not some danger to

them because you are using your pills every day.'" (Male Pre-XDR TB Patient, age 42)

In the end, because he opened up to the TB nurse, the clinic was able to find a bed for him at the hospital where he could stay and continue treatment.

On the other hand, if this baseline level of trust was missing, patients were less open about their challenges during treatment. For example, a young female patient who had lost her parents when young reported struggling with adherence for over a year because she had no money, food, or support at home. The clinic had showed little empathy during this time. She thus avoided sharing her problems with any of her providers, assuming they would continue to deny her the necessary support:

> "(Laughing) Why are they gonna help me? They only tell me, 'if you are defaulting [interrupting treatment], you are defaulting.' That's all, they didn't even understand my situation that I told them." (Female DS-TB Patient, age 21)

Similarly, a young single mother with MDR-TB spoke about a period of time when she stopped taking her treatment because the side effects made it impossible for her to care for her son:

> "I couldn't handle my son, you see…I would go sleep, and then I would leave my son to play, and then the next thing he's sore here and he's sore there because I couldn't help." (Female MDR-TB Patient, age 20)

When asked whether she considered sharing her dilemma with the clinic staff to see if they could help, she said she was afraid the staff would judge her:

> "(Crying) I don't know, I think I felt like I was a bad mother, you know, because I couldn't go to my son…no, I'd rather keep it in and do it my way."

She stayed away from treatment for nearly four months and only returned when she became very ill again and had to restart treatment.

These examples demonstrate how patients' trust in their providers affected adherence. As suggested earlier, the converse was also true: providers' trust in their patients affected medical decisions around treatment options, and allowances for weekly or monthly medication refills. One young male patient felt the staff never trusted him. At the twenty-second month of his treatment, two months from completion, he was unable to continue attending the clinic due to territorial boundaries between his gang and that of the area surrounding the clinic. The clinic staff denied his requests for an extended supply of medication, and did not offer any alternatives to support him in continuing treatment:

> "Some of the staff they trust certain people, so for me, they didn't trust me that time, but I was faithful to my treatment, but I could see they were thinking that I'm not going to take my treatment… … I was trying to be honest, because I know how I really needed that treatment man, and how I needed for them to understand me because my situation with the gangsterism…And you know, yoh! I didn't feel nice man, because I really needed them to trust me, but they didn't…I look back into that times, and I tell myself, if those nurses could have trust me, then I wasn't here today, really." (Male XDR-TB Patient, age 25)

In his experience, no matter how hard he tried to show he could be trusted, the staff never did. He was unable to continue treatment, and eventually developed XDR-TB.

When it came to building and sustaining trust, every encounter mattered in a patient's treatment journey. At each visit, whether patients felt listened to and cared for by their providers seemed to affect their readiness to accept a providers' authority on medical decisions, and their adherence to recommended treatment. This was exemplified in the narrative of a young male patient, who had struggled with his treatment for five years due to difficult socioeconomic circumstances, but managed to finally finish his journey.

> "The sisters [nurses] here, they are nice to me, and they are glad I came every day to do my treatment. They always make me smile when I came here, they say, 'Hi, how are you!' So one time the sister [nurse] here, I told her, 'I'm sorry I was dropping [treatment] and

everything I did, I'm never doing that again, and this time I'm doing my treatment finish.' So she said, 'Okay, I want to see that this time.' So this is the time I'm going to show her I'm going to do it finish." (Male DS-TB Patient, age 25)

Four months after the interview, this patient was successfully cured. From his perspective, he only managed to accomplish this because of the positive attitude he perceived from his nurses – no matter how many times he interrupted treatment, they always greeted him cheerfully. The patient placed much value in this trust. It showed him that they cared for him and trusted him to fulfil his journey, all of which appear to have encouraged him to complete treatment and be cured.

Every provider involved in a patient's care – from the CHW, to the nurse, to the doctor – and every encounter within the health system – from diagnosis to treatment completion – played a role in the creation and maintenance of trust. An inadequate response from a single provider was sometimes enough to jeopardize it.

"As a patient, if I ask the doctor, I've got this and this and this and this, and then you don't tell me what is the cause of that thing…I won't trust you now…what makes me to come here, you see." (Male MDR-TB Patient, age 42)

Given the time and resource pressures on clinic staff (nurses, doctors and counsellors), CHWs described their attempts to fill the educational as well as emotional gap for patients. Many CHWs felt they were not adequately trained to deal with patients' medical and social issues.

"And if we have more training we can do much better. Because now if people ask me about do first aid, then I'll say, 'No, I don't know.' Then somewhere somehow it takes my value down to that person, because he or she trust on me was high, but now that there's something I don't know, it takes other percent, you see?" (Female CHW)

In feedback sessions, providers described feeling 'betrayed' by patients who interrupted treatment. This made it hard for them to remain optimistic when these patients returned to their

clinic to restart treatment. From their perspective, patients who interrupted treatment were breaking the trust the providers had for them. They felt they had to strike a fine balance between being harsh and kind, to ensure their patients understood the seriousness of treatment interruptions.

When the two patients who were formerly TB nurses reflected on this practice during their respective interviews, both expressed remorse for behaving in such restrictive and unsympathetic ways.

> "If I was still nursing, I have a better way to deal with the patient, I will approach him in a better manner, you understand, because I was also been there…If you approach your patient with a kind of way like, 'I care about you and I want you to get better', and that is the only way for [the patient] to take treatment and to participate in everything the hospital is giving you." (Pre-XDR patient and former TB nurse)

This nurse's comment reflected trust was not unidirectional; both providers and patients had to participate in the trust-building exercise throughout the treatment journey in order to sustain mutual trust and facilitate positive treatment experiences.

Trust after treatment interruptions

It appeared to be extremely difficult to reconstruct trust in this setting, once it had been broken. Several patients described it being impossible to regain the trust of their providers after bouts of treatment non-adherence. The same could be said about times when a provider had lost the trust of a patient. A female pre-XDR-TB patient (age 33) described how she lost trust in her providers very early on. She was first diagnosed with DS-TB. After attending the clinic every day for six months and completing treatment, she was then diagnosed with MDR-TB. Frustrated that her providers had not discovered her MDR-TB sooner, she did not return to the clinic right away. A month later, she returned and began MDR treatment, but she said her providers had lost trust in her by then.

After eight months of uninterrupted treatment, she asked clinic staff for a month's supply of treatment so she could travel to the Eastern Cape province to visit her son, who was staying with her aunt. They refused because they did not trust she would take the treatment. So she left without treatment. Five months later, she returned to the clinic to restart treatment. She was informed she must wait for a hospital bed to initiate treatment because the clinic did not trust her to adhere as an outpatient. After waiting six months, she was finally admitted. By this time, she was diagnosed with pre-XDR TB. When we interviewed her, she had just started treatment with bedaquiline – a new TB drug that requires an application to and approval from a national committee before a doctor can prescribe it – three months after her new diagnosis. But by then, her health had deteriorated rapidly, and on a return visit to the site, she had passed away as an inpatient, four months after she started bedaquiline treatment.

This patient's treatment journey serves as a cautionary tale of what could happen when the delicate trust between a patient and their providers is broken and fails to be reconstructed. Not only could this disruption affect a patient's behaviour and adherence to treatment, but additionally affect providers' attitudes and practices, and impede available treatment options.

When this patient's story was discussed as a hypothetical case in feedback sessions, most providers - particularly doctors - agreed with the medical decisions made along the way. From their perspective, providers had to find an optimal balance between treatment provision and prevention of drug resistance. The close monitoring of a patient known to be non-adherent, through hospitalization, was considered a justified decision to prevent the emergence of drug resistance. Doctors also supported rationing new and expensive treatments based on their opinions of whether patients could be trusted to adhere:

> "Oh a lot of time you can't actually say [who's responsible or not], but if they have a previous drug history usage, or you can actually see from the clinic notes if they were problematic in terms of running away or taking the medication, then you get an idea…Then you first want to monitor for say two weeks, three weeks and see if you can actually trust this patient to take the medication… I mean I don't want to start [every]

patient I get on bedaquiline because it's a new drug, it's expensive." (Female TB Doctor)

Discussion

Trust (or mistrust) between patient and provider is found to be crucial for treatment adherence in TB care in a limited number of studies investigating factors affecting TB adherence (Burtscher et al., 2016; Daftary & Padayatchi, 2016; Fried, Harris, Eyeles, & Moshabela, 2015). To our knowledge this is the first study exploring what constitutes patient-provider trust in the TB setting, how it is fostered and evolves through TB treatment journeys, and affects both patient and provider behaviours and health decisions.

TB treatment journeys span from six months to many years, particularly for patients who need to restart treatment due to interruptions, relapses, development of drug resistance, and re-infections. Given the complex social realities of patients in limited resource settings, many extraneous events could interfere with their treatment journey and trigger non-adherence and interruptions. At these important junctures, patient-provider trust can evolve through good communication and problem resolution, or it can erode through patient and provider behaviours that are perceived negatively by the other party. Thus, trust can shift over the long courses of TB treatment. In order to deal with the ebbs and flows of trust, and help facilitate positive experiences in care, patients and providers must acknowledge that TB treatment is a journey, rather than a series of repeated, disconnected clinical encounters. The ultimate objective of achieving a cure may be easiest fulfilled if investments are made into the pathway leading up to it.

In this study, many patients succeeded in finishing TB treatment despite their socioeconomic struggles. These successes appear to be closely tied to the establishment of reciprocal trust between patients and their providers. Patients who trusted their providers appeared to be more willing and open in sharing adherence problems as they arose, and ultimately more capable of working through those problems to achieve adherence. Providers who placed trust in their patients appeared to be more accommodating to those patient's needs, and ultimately more

supportive during their treatment journey.

Similar to other studies exploring trust in patient-provider relationships (Rolfe et al., 2014; Thom & Campbell, 1997), our exploration shows provider attitudes and behaviours, such as their empathy and understanding of patient's individual experiences, their ability to communicate clearly and respectfully, are important in building mutual trust in the TB setting. Our findings highlight the distinct building blocks of trust from the patient's as compared to provider's perspective. Patients came to trust their provider when they felt their questions were answered, and their medical and non-medical concerns were acknowledged and considered seriously. This falls in line with Hall's conceptual definition of trust as conditional on the trustor believing the trustee "will care for the trustor's interests" (Hall et al., 2001, p. 615). However, providers only trusted their patients when patients adhered to clinic appointments and abided by their recommendations. This falls in line with research done on adherence to ART in Zimbabwe (Campbell et al., 2015) and to TB treatment in Thailand (Sengupta et al., 2006), where providers often dichotomize patients as "good" (e.g. adherent, obedient, punctual) or "bad" (e.g. non-adherent, disobedient, tardy) and would vary their attitudes and behaviours accordingly.

Several obstacles to the establishment of patient-provider trust were identified. The realities of working in a resource-limited setting, where the health system is generally overburdened, understaffed, and under-trained, may restrict additional opportunities for providers to establish trust in their patients. Providers are often rushed, unable to provide the counselling and care their patients expect, and ill-resourced to address socioeconomic problems – as was seen in this study. Another hindrance to the establishment of trust is the global standardization of TB treatment. Unlike treatment for other chronic illnesses that allow for some flexibility and individualized case-management, many aspects of TB care are delivered under a regimented model. This includes the requirement of DOT– where each dose of TB medication is meant to be taken under the supervision of a trained health care worker, CHW, or treatment buddy (e.g. family, friend, co-worker) – as per the WHO's TB-DOTS strategy (WHO, 2017). This appears to limit providers' ability to modify treatment monitoring practices according to individual patient

characteristics, or to accommodate the plethora of non-medical challenges which underlie non-adherence. It also absolves providers from an obligation to spend time in evaluating a patient thoroughly unless it's a complicated or severe case, and from communicating treatment plans and involving patients in a process of shared decision-making. Managers as well as providers working at the frontline may refrain from defying standard procedures and expected targets, even if it would favour patient outcomes. Important components of trust, as identified in other studies (Rolfe et al., 2014; Thom & Campbell, 1997; Robinson, 2016) and discovered in this study, are essentially eliminated from TB care models by a rigid culture of standardization (Daftary, Calzavara & Padayatchi, 2015). Other research in similar TB care settings have found infection control practices specific to TB such as wearing masks, and keeping a 'safe' distance, may also create barriers to establishing trust (e.g. a smile cannot show through a mask) (Daftary & Padayatchi, 2016; Buregyeya et al., 2012).

The potential impact of providers' trust in patients on treatment outcomes has been poorly explored in TB research and health care practice. This study identified at least two potential impacts. First, provider's perceived trust in their patients influenced clinical decision making, which affected the options made available to patients such as access to new drugs and social assistance, and permission to attend the clinic less frequently or receive a 'pass-out' to visit family. Second, it influenced providers' day-to-day behaviours at the clinic, and willingness to accommodate their patients' extraneous needs. That providers' personal values and attitudes towards patient affect recommendations for disability grants, and reinforce doctors' role as "gatekeepers" of social grants, has been examined in the context of HIV care in South Africa (Kelly, 2017; de Paoli, Mills & Grønningsæter, 2012). Under the absence of clear eligibility guidelines, providers have been shown to decide which patients are deserving of a disability grants on an ad-hoc basis. Our study shows that public TB providers may also be making decisions – such as withholding or delaying treatment for patients with documented adherence problems – that are not based on any existing guidelines.

Our study also suggests that providers' trust (or mistrust) in their patients may encourage (or

erode) patients' trust towards the provider. A trusting provider may thus facilitate great trust among his or her patients and foster a positive relationship. However the converse may not necessarily be true. Whether or not patients trusted their provider did not appear to have an impact on the level of trust that providers returned to their patients. This non-reciprocity urges a consideration of the power differential in which patient-provider trust evolves, particularly within health care settings in places such as South Africa, where a history of medical paternalism and socioeconomic differences – including race differences – between patients and providers likely serves a critical role in the process of trust building and disruption (Packard, 1989; Coovadia, Jewkes, Barron, Sanders & McIntyre, 2009).

In this analysis of trust in TB care, three main processes emerged that seem to influence patient-provider trust and subsequently, patient outcomes (see Figure 1 for a schematic). First, in a setting where there is no baseline level of trust, the first few encounters between patients and their providers are crucial to the initial development and establishment of trust. Second, the active maintenance of reciprocal trust – throughout treatment - entails concerted efforts on the part of providers to avoid creating an environment of mistrust, and to deal with patients' concerns and barriers to treatment adherence in a timely and holistic manner. And third, reconstructing trust following its erosion due to a patient, or provider, (real or perceived) error is extremely challenging. Investing in an initial stage of trust establishment may help to avert this erosion.

Conclusion

Patient-provider trust can play an important role in retaining patients in TB care. Lack of real or perceived empathy from the providers, especially during times of hardships or struggle with TB treatment, often disrupts patient trust in their providers. In the absence of trust, patients are less likely to open up to providers and seek help, and risk interrupting or abandoning treatment. This in turn affects provider's trust in patients, which could limit available treatment options and access to financial support or social protection. When providers lose trust in their patients, due to non-adherence to treatment or providers' advice, it is nearly impossible to re-establish.

This study provides the impetus for the development and assessment of interventions that focus on fostering trust between TB patients and their providers. In particular, these strategies to build trust must be able to circumvent the rigidity of standardized TB treatment and management practices, which could be as simple as positively greeting patients when they arrive at the clinic, or showing a willingness to help patients work through their problems even when a clear solution is not in sight. Health care workers should be sensitized to engage with patients early-on in treatment to establish a baseline level of trust, thereby creating an environment of open communication. Global TB efforts should explore caregiving strategies used in managing chronic illnesses such as HIV that encourage trusting patient-provider relationships. As new diagnostic tests and effective TB drugs are slowly rolled out, there is an urgent need to concurrently address challenges to adherence to protect against a new wave of drug resistant TB. To do so, it is time to work on building trust in TB care.

References

Atkins, S., Biles, D., Lewin, S., Ringsberg K., & Thorson, A. (2010). Patients' experiences of an intervention to support tuberculosis treatment adherence in South Africa. Journal of Health Services Research & Policy, 15(3), 163-70.

Beach, M. C., Keruly, J., & Moore, R. D. (2006). Is the quality of the patient-provider relationship associated with better adherence and health outcomes for patients with HIV? Journal of General Internal Medicine, 21, 661–665.

Buregyeya, E., Mitchell, E.M.H, Rutebemberwa, E., Colebunders, R., Criel, B., Kiguli, J., & Nuwaha, F. (2012). Acceptability of masking and patient separation to control nosocomial Tuberculosis in Uganda: a qualitative study. Journal of Public Health, 20(6), 599-606.

Burtscher, D., Van den Bergh, R., Toktosunov, U., Angmo, N., Samieva, N., & Rocillo Arechaga, E. P. (2016). "My Favourite Day is Sunday": Community Perceptions of (Drug-Resistant) Tuberculosis and Ambulatory Tuberculosis Care in Kara Suu District, Osh Province, Kyrgyzstan. PLoS One, 11(3), e0152283.

Calnan, M., & Rowe, R. (2007). Trust and Health Care. Sociology Compass, 1/1 (2007), 283-308.

Campbell, C., Scott, K., Skovdal, M., Madanhire, C., Nyamukapa, C., & Gregson, S. (2015). A good patient? How notions of 'a good patient' affect patient-nurse relationships and ART adherence in Zimbabwe. BMC Infectious Diseases, 15, 404.

Charmaz, K. (2000). Grounded theory: Objectivist and constructivist methods. In N. K., Denzin, & Y. Lincoln (Eds.), The Handbook of Qualitative Research (pp. 509-535). Thousand Oaks, CA: Sage Publications, Inc.

City of Cape Town. (2016). State of Cape Town Report 2016. Cape Town: City of Cape Town.

Coovadia, H., Jewkes, R., Barron, P., Sanders, D., & McIntyre, D. (2009). The health and health system of South Africa: historical roots of current public health challenges. Lancet, 374, 817-34.

Daftary, A., Calzavara, L., & Padayatchi, N. (2015). The contrasting cultures of HIV and tuberculosis care. AIDS, 29(1), 1-4.

Daftary, A., & Padayatchi, N. (2016). Provider perspectives on drug-resistant tuberculosis and human immunodeficiency virus care in South Africa: a qualitative case study. International Journal of Tuberculosis and Lung Disease, 20(11), 1483-88.

de Paoli, M. M., Mills, E. A., & Grønningsæter, A. B. (2012). The ARV roll out and the disability grant: a South African dilemma? Journal of the International AIDS Society, 15, 6.

Department of Health. (2017). Towards Universal Health Coverage: Report of the Evaluation of South Africa Drug Resistant TB programme. Pretoria, South Africa: Department of Health, Republic of South Africa.

Department of Health. (2014). National Tuberculosis Management Guidelines 2014. Pretoria, South Africa: Department of Health, Republic of South Africa.

Fried, J., Harris, B., Eyeles, J., & Moshabela, M. (2015). Acceptable care? Illness constructions, healthworlds, and accessible chronic treatment in South Africa. Qualitative Health Research, 25, 622-35.

Gilson, L., Palmer, N., & Schneider, H. (2005). Trust and health worker performance: exploring a conceptual framework using South African evidence. Social Sciences and Medicine, 61(7), 1418-29.

Gilson, L. (2006). Trust in health care: theoretical perspectives and research needs. Journal of Health Organization and Management, 20(5), 359-75.

Glaser, B. G. (1978). Theoretical Sensitivity: Advances in the Methodology of Grounded Theory. California: The Sociology Press.

Hall, M., Dogan, E., Zheng, B., & Mishra A. (2001). Trust in Physicians and Medical Institutions. Does it Matter? The Milbank Quarterly, 79, 613–39.

Kelly, G. (2017). Patient agency and contested notions of disability in social assistance applications in South Africa. Social Science & Medicine, 175, 109-16.

Lee, Y. Y., & Lin, J. L. (2011). How much does trust really matter? A study of the longitudinal effects of trust and decision-making preferences on diabetic patient outcomes. Patient Education & Counseling, 85, 406–412.

Lincoln, Y.S., & Guba, E.G. (1985). Naturalistic inquiry. Newbury Park, CA: Sage.

Meintjes, G., Schoeman, H., Morroni, C., Wilson, D., & Maartens, G. (2008). Patient and provider delay in tuberculosis suspects from communities with a high HIV prevalence in South Africa: a cross-sectional study. BMC Infectious Diseases, 8, 72.

Ncama, B.P., McInerney, P.A., Bhengu, B.R., Corless, I. B., Wantland, D.J., Nicholas, P.K., McGibbon, C.A., & Davis, S.M. (2008). Social support and medication adherence in HIV disease in KwaZulu-Natal, South Africa. International Journal of Nursing Studies, 45(12), 1757-63.

Packard, R. M. (1989). White Plague, Black Labour - Tuberculosis and the Political Economy of Health and Disease in South Africa. Berkeley, CA: University of California Press.

Robinson, C. (2016). Trust, Health Care Relationships, and Chronic Illness: A Theoretical Coalescence. Global Qualitative Nursing Research, 3, 23333936664823.

Rolfe, A., Cash-Gibson, L., Car, J., Sheikh, A., McKinstry, B. (2014). Interventions for improving patients' trust in doctors and groups of doctors. Cochrane Database Systematic Reviews, 2014(3), CD004134.

Sengupta, S., Pungrassami, P., Balthip, Q., Strauss, R., Kasetjaroen, Y., Chongsuvivatwong, V., & Van Rie, A. (2004). Social impact of tuberculosis in southern Thailand: views from

patients, care providers and the community. International Journal of Tuberculosis and Lung Disease, 10(9), 1008-12.

Thom, D.H., & Campbell, B. (1997). Patient-physician trust: an exploratory study. Journal of Family Practice, 44(2), 169-76.

Van Wyk, S.S., Enarson, D.A., Beyers, N., Lombard, C., & Hesseling, A.C. (2011). Consulting private health care providers aggravates treatment delay in urban South African tuberculosis patients. International Journal of Tuberculosis and Lung Disease, 15(8), 1069-76.

World Health Organization. (2017). Global tuberculosis report 2017. Geneva: WHO.

Table 1. Characteristics of adult TB patients interviewed*

Patient Characteristic (N=33)	N (%) or median (IQR)
Age	37 (27-43)
Female	12 (36.4)
Race/ethnicity	
African (Black)	17 (51.5)
Coloured (Mixed race)	15 (45.5)
Other (e.g. Caucasian, Indian)	1 (3)
HIV-positive	12 (36.4)
On ARV treatment¶	11 (91.7)
Ever LTFU on ARV	4 (36.4)
Type of TB	
DS	11 (33.3)
MDR (excluding pre/XDR)	13 (39.4)
Pre-XDR	5 (15.2)
XDR	4 (12.1)
Previously treated	22 (66.7)
No. of previous treatment	2 (1-2)
Previously LTFU	15 (45.5)
Initial care-seeking action	
PHC	25 (75.8)
Public Hospital	6 (18.2)
Chemist	1 (3)
Private GP	1 (3)
Delay in diagnosis (weeks)	5 (2-21)
Months on treatment	4 (2-7)
Treatment outcome†	
Cured/Completed	11 (33.3)
LTFU	7 (21.2)
Failed	1 (3)
Death	3 (9.1)
Missing	2 (6.1)

*Patient demographics and TB treatment history and HIV status were extracted from patient records. Losses to follow-up (LTFU) on ARV treatment, delays in getting diagnosed and initial care-seeking action (of current TB episode) were self-reported by patients. Abbreviations: M = Male; F = Female; PHC = Primary Health Clinic; GP = General practitioner; Pre-XDR = form of MDR-TB that is additionally resistant to either a second-line injectable or a fluoroquinolone, but not both; ARV = antiretroviral therapy; LTFU = lost to follow-up.

¶ One HIV-positive patient reported he stopped taking ARVs (i.e. currently LTFU on ARV) but was continuing TB treatment.

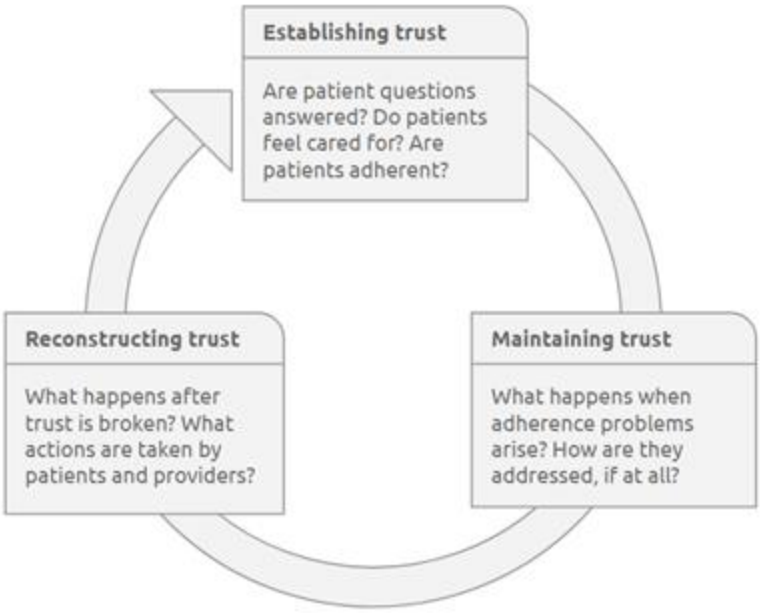
†Treatment outcomes recorded as of May 31, 2017.

Table 2. Characteristics of interviewed public and private providers

Provider Characteristic (N=36)	N (%) or median (IQR)
Age	
25-34	8 (22.2)
35-44	10 (27.8)
45+	18 (50)
Female	27 (75)
Race/ethnicity	
Black (African)	21 (58.3)
Coloured (Mixed race)	10 (27.8)
Other (e.g. Caucasian, Indian)	5 (13.9)
Years working with TB patients	5.5 (3-13.3)
Type of provider	
CHW	9 (25)
TB Nurse	10 (27.8)
TB Counsellor	2 (5.6)
TB Doctor	5 (13.9)
Private physician	5 (13.9)
Traditional healer	5 (13.9)

*Abbreviation: CHW = Community Health Worker

Figure 1. The different processes of patient-provider trust in TB care



STUDY 3: INTERVENTIONS TO IMPROVE RETENTION-IN-CARE AND TREATMENT ADHERENCE AMONG PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS: A SYSTEMATIC REVIEW

The first study of this thesis found that irregular adherence to treatment contributes greatly to the emergence of drug resistant-TB in India. Furthermore, the Indian MDR-TB epidemic is predicted to shift from one that is driven by acquired drug resistance to one driven by primary transmission. As such, it is imperative to improve adherence and retention-in-care, particularly among MDR-TB patients, in order to prevent transmission of the disease. The second study then found that patient-provider relationships, and mutual trust in particular, affect both patient and provider behaviours, and ultimately affect adherence, retention-in-care, as well as delays in accessing appropriate treatment, all of which may affect contagiousness and transmission. Although it was evident that building patient-provider relationships and rapport is important, many patients cited other issues that affected their adherence, including lack of psychosocial support as well as financial means to stay on treatment. There is a paucity of evidence comparing the effectiveness of support strategies that target different barriers to adherence in MDR-TB care. This study involves a systematic review to address this knowledge gap.

Manuscript 3: Law S, Daftary A,O'Donnell M, Padayatchi N, Calzavara L, Menzies D. Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review.

Citation:

Law S, Daftary A, O'Donnell M, Padayatchi N, Calzavara L, Menzies D. (2018.). Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review. Eur Respir J. 2018 Oct 11. pii: 1801030. doi: 10.1183/13993003.01030-2018. PMID: 30309972

Take home message:

To effectively improve retention rates in the treatment of drug-resistant tuberculosis, psychosocial support - provided through one-on-one counselling and home visits – should be provided throughout treatment, rather than only during the intensive phase.

Abstract

Background: The global loss to follow-up (LTFU) rate among drug-resistant TB (DR-TB) patients remains high at 15%. We conducted a systematic review to explore interventions to reduce LTFU during DR-TB treatment.

Methods: We searched for studies published between Jan. 2000 and Dec. 2017 that provided any form of psychosocial or material support for patients with DR-TB. We estimated point estimates and 95% confidence intervals (CI) of the proportion LTFU. We performed subgroup analyses and pooled estimates using an exact binomial likelihood approach.

Findings: We included 35 DR-TB cohorts from 25 studies. Cohorts that received any form of psychosocial or material support had lower LTFU rates than those that received standard care. Psychosocial support throughout treatment – via counselling sessions or home visits – was associated with lower LTFU rates compared to when support was provided through a limited number of visits or not at all, with pooled proportions LTFU of 8.4% (4.0-16.7%) and 20.5% (15.2 – 27.0%), respectively.

Conclusion: Our review suggests psychosocial support should be provided throughout DR-TB treatment in order to reduce treatment LTFU. Future studies should explore the potential of providing self-administered therapy complemented with psychosocial support during the continuation phase.

Introduction

Approximately 15% of 1.67 million annual global deaths due to tuberculosis (TB) are from rifampicin-resistant (RR) or multidrug-resistant tuberculosis (MDR-TB), a strain resistant to at least rifampicin and isoniazid, the two most effective first-line anti-TB drugs [1]. Treating RR/MDR-TB with second-line drugs is significantly costlier, longer, more toxic, and less effective than treating drug-susceptible TB. Rates of treatment non-completion and interruption rates in RR/MDR-TB are thus significantly higher. Approximately 15% of all RR/MDR-TB patients are lost to follow-up from treatment, defined as interrupting treatment for more than two months, and only half are successfully treated [1].

Treatment non-adherence and non-completion diminishes the quality-of-life of people living with RR/MDR-TB [2], and increases transmission of RR/MDR-TB. Developing effective interventions to improve adherence to treatment and retention in RR/MDR-TB care is thus crucial. An earlier systematic review [3] found MDR-TB treatment strategies that used a more comprehensive approach – including financial and nutritional support – tended to have lower loss to follow-up rates. However, the review, which included 75 studies, did not identify any non-observational, experimental trials for inclusion, and thus was subject to a high risk for confounding bias.

In light of increased global efforts to improve treatment and management for RR/MDR-TB, we have synthesized new evidence, including observational and quasi-experimental studies published since the earlier systematic review, on the effectiveness of interventions in RR/MDR-TB treatment that include various combinations of psychosocial or material support. We

describe and assess these interventions, their effectiveness in reducing losses to follow-up and improving adherence, and issues affecting their implementation.

Methods

This review is reported according to the PRISMA statement [4], registered on the PROSPERO database (#CRD42016052854), and analyzed according to MOOSE guidelines [5].

Search strategy

We searched MEDLINE (using PubMed), EMBASE and EMBASE Classic, and ISI-Web of Science, Scopus, PsychInfo, Global Health, Social Work abstracts, and Cochrane CENTRAL, for studies published between 2000 (the year the WHO first launched DOTS-Plus pilot projects for treatment and management of MDR-TB [6]) and Dec. 14, 2017. Our search strategy combined the following concepts: 1) tuberculosis; 2) adherence/compliance/default/drop-out; 3) concordance or contract; 4) linkage/referral/tracing; 4) reminder/monitor; 5) training/education/counselling; 6) motivational/behavioural/social support; 6) patient-centred care/retention; 7) health system or services intervention or program or strategy; 8) cash or reimbursement or refund or reward or incentives; 10) dietary or nutritional supplement or food; 11) directly observed therapy; and 15) evaluation (see **Supplement Table 1** for search details). No geographic or language restrictions were applied. We identified additional articles from reference lists of identified original articles, and four recent systematic reviews on: 1) strategies for reducing MDR-TB patient losses to follow-up [3]; 2) decentralized models of MDR-TB care [7]; 3) community-based MDR-TB treatment [8]; and 4) directly observed therapy (DOT) in MDR-TB treatment [9].

Study screening and eligibility criteria

We included primary studies that: 1) reported final treatment outcomes including losses to follow-up; and 2) examined a health services intervention targeting patients with RR/MDR-TB that included *at least* a psychosocial, educational, nutritional or economic component. We defined psychosocial to broadly include any support provided to patients to address their

psychological or social issues; educational support to include any education provided to patients pertaining to their TB treatment; nutritional support to include any food parcels or packages, as well as hot meals; and economic support to include any reimbursement for treatment-related expenses and lost wages. Studies that only examined surgical or drugs-related interventions, or different treatment delivery strategies without additional support, were not included. Studies were excluded if they: 1) reported fewer than 10 cases of RR/MDR-TB; 2) only included children (<18 years old) due to their likely dependence on adult caregivers for adherence; 3) provided only interim outcomes (defined as outcomes such as 6-month sputum conversion, that occurred before the planned end of treatment); 4) did not provide details on drug susceptibility testing for at least rifampicin; or 5) did not provide treatment with second-line drugs. One reviewer (SL) screened all titles and abstracts. Full reports of potentially relevant studies were screened by two independent reviewers (SL and AD), any discrepancies were resolved by discussion. We contacted authors of published abstracts and studies to obtain further information when necessary.

Types of outcome measures

Our primary outcome of interest was loss to follow-up, defined as treatment interruption for ≥2 months [1]. Secondary outcomes included any measures of treatment adherence.

Data extraction and analysis

One reviewer (SL) extracted relevant outcomes data, participant characteristics, details on the study intervention(s), and information necessary to assess study quality. We used the ROBINS-I tool [10] to assess the quality of cohort studies, and the Cochrane Risk of Bias Tool [11] for quasi-experimental trials. All extracted data were entered into Microsoft® Excel™.

We estimated unadjusted risk ratios and 95% confidence intervals to compare the proportions lost to follow-up in each arm or cohort in comparative studies. We conducted pooled analyses of all study cohorts to analyze the association between different types of psychosocial or materials support and losses to follow-up. We used the exact binomial likelihood approach, including a

random effect to account for between-study heterogeneity, to estimate pooled proportions lost to follow-up and 95% confidence intervals. This approach has been shown to produce less-biased estimates of the pooled effect and the between-study variability compared to normal approximation approaches [12]. We investigated heterogeneity using the I^2 statistic via subgroup analyses, and explored differences in geographic regions, XDR status, HIV prevalence, previous treatment, treatment delivery methods and types of adherence support. Cochran's Q test was done to test for subgroup differences. In our main analyses, we excluded patients who died or failed treatment (to exclude from the denominator patients who could not have experienced the outcome of lost to follow-up), and patients who were transferred out or not evaluated for final treatment outcomes. We conducted sensitivity analyses in which we considered patients who were transferred out or not evaluated as patients lost to follow-up. All statistical analyses were done in R (*R Foundation for Statistical Computing, Vienna, Austria*).

Results

Description of included studies

Our search strategy identified 5911 studies, of these we included 23 cohort studies and 2 quasi-experimental trials [13-37] in our analyses. These 25 studies included 35 different cohorts of RR/MDR-TB patients – distinguished on the basis of different types and levels of adherence support (see **Figure 1** for a flowchart of the study selection process). The types of treatment support provided to the included cohorts are summarized in **Table 1**. All but three studies [20, 22, 37] were conducted in high burden TB/MDR-TB countries [1].

Quality of Studies

We did not exclude any study based on our assessment of quality (see **Supplement Tables 4-5** for summaries and **Supplement Tables 9-10** for details). All included studies used routinely collected data within local TB systems to ascertain treatment outcomes. Reporting of intervention details varied across studies, and it was difficult to evaluate the fidelity of intervention implementation and delivery in three studies [19, 20, 25]. Some studies did not

provide important patient characteristics, such as: any previous TB treatment (n=2); previous treatment with second-line drugs (n=13); XDR-status (n=6); and HIV-status (n=6; these studies were conducted in settings where less than 10% of TB patients are infected with HIV) (see **Supplement Table 2**).

Five cohort studies included two or more separate cohort groups [14-17, 37], which allowed for comparison of outcomes. However, we did not include the control cohort in the study by Yu et al. [37] because we were not able to obtain adequate details on the care provided to that group, nor the proportions of patient lost to follow-up. Of the remaining four studies, two compared patient cohorts before and after implementation of an intervention [14, 17], and two analyzed concurrent cohort groups receiving different types of care [15-16]. None of the studies provided adjusted estimates for the effect of intervention on loss to follow-up rates to account for potential confounding. All four studies were considered to have serious risks of biases due to confounding, and two to have moderate risks of biases due to missing data (patients who were transferred out or not evaluated for final treatment outcomes) (**Supplement Table 4**).

There were two trials included in our analysis [13, 18]. Both were cluster randomized trials where health care facilities were randomized to provide routine care or the study interventions. The overall risk of performance bias was high for both studies because sites selected to implement the intervention were unblinded (**Supplement Table 5**). This may have affected overall performance beyond the intervention (i.e. spillover effect of the intervention into other standard elements of care), thereby possibly overestimating the benefit of the intervention. On the other hand, sites providing routine care could have also improved their care to compensate for the absence of an intervention, thereby underestimating the benefit. Furthermore, due to the small number of clusters randomized in each study, patient and site characteristics were not balanced between the intervention and control arms, which could lead to residual confounding. Baral et al. [13] adjusted for age and sex, but neither study accounted for clustering by site, nor adjusted for other important baseline confounders.

Results of Head-to-Head Comparisons

The results from the comparative cohort studies and trials are shown in **Fig. 2**. The non-intervention standard-of-care varied across the studies (see **Table 1** and **Supplement Table 8** for details). Given the variation in the control groups as well as the types of psychosocial or material support provided in the intervention groups, pooling of intervention effects was not possible. Patients who received some form of psychosocial or material support, in addition to the standard care were less likely to be lost to follow-up, with the exception of the study by Cox et al. [14]. In their pilot intervention study, Cox et al. [14] found no difference (risk ratio=1.04; 95%CI 0.83-1.32) between the control group, which received hospital-initiated MDR-TB treatment, and the intervention group, which received community-based, clinic-initiated treatment with routine counselling sessions and access to peer support group. The greatest reduction in the loss to follow-up rate was seen in two cohorts that received psychosocial support through daily home visits by community health workers, as well as home-based DOT, when compared to the standard-of-care [15-16]. In the cluster randomized trial by Baral et al. [13], the addition of individually tailored counselling sessions provided by nurses reduced the risk of lost to follow-up by 70% (risk ratio = 0.31; 95%CI 0.07-1.26), but adding a monthly income supplement did not improve the effect (risk ratio = 0.73; 95%CI 0.31-1.72).

Pooled Results Across Studies

Results from all study cohorts that received any form of psychosocial or material support – from both comparative and non-comparative studies – were pooled in the following analysis to investigate associations between different types of support and losses to follow-up (see **Supplement Table 2** for characteristics of included study cohorts). We excluded the standard-of-care or control groups in 2 studies that did not provide any psychosocial or material support [13, 16], as well as one comparative cohort study [14] because its intervention arm contained a subsample of a larger single-arm cohort study [31].

Final treatment outcomes were reported for a total of 6655 RR/MDR-TB patients in 31 study cohorts included in the analysis pooled across all cohorts (see treatment outcomes in

Supplement Table 3). After excluding patients who died, failed treatment, or were transferred out or not evaluated for final treatment outcomes, there remained a total of 5114 patients (median of 84 patients per study cohort). The pooled proportion lost to follow-up was 17% (95%CI 12-23%), as seen in the forest plot (**Fig. 3**). Study heterogeneity was high across all included study cohorts (I^2=96%), and remained high in subgroup analyses by WHO region (except in the Americas region where there was no statistical heterogeneity, likely because all three cohorts were largely based in Lima, Peru, within approximately the same period), HIV infection rate, proportions with XDR-TB, and previously TB treatment history (**Fig. 4**).

In subgroup analyses, study cohorts with more frequent contact with health workers throughout treatment – in the form of DOT visits, home visits or individual counselling sessions – tended to have fewer losses to follow-up (**Fig. 5**). Additionally, provision of financial support to reimburse rent or travel expenses, as well as to compensate lost wages during treatment, was also associated with fewer losses to follow-up. There was weak evidence of any association between providing food packages, group counselling, or counselling to family members, and losses to follow-up. In order to distinguish the effect of frequent DOT from that of adherence support, subgroup analyses according to types of adherence support provided were restricted to study cohorts that received either twice-daily or daily DOT throughout treatment (**Fig. 6**). Within study cohorts that received daily DOT, those that received individual counselling throughout treatment [15-16, 21, 23-26, 28-30, 32-33, 36-37] had fewer losses to follow-up than those that received a fixed [13, 17, 19, 20, 31], or unspecified [15, 27, 34] number of individual counselling sessions at the start of treatment. Similarly, those that received any home visits by health workers also had fewer losses to follow-up [15-16, 20, 23, 29-30, 32, 37]. Sensitivity analyses where patients who were transferred out were also considered as lost to follow-up (see **Supplement Figs. 19-21**), and when patients who died were considered lost to follow-up (see **Supplement Figs. 22-**24) yielded similar results. Furthermore, the findings remained consistent across strata of study cohorts stratified by prevalence of HIV co-infection (**Supplement Figs. 25-28**), and of previous TB treatment (**Supplement Figs. 29-32**).

Other adherence outcomes

Three studies reported the proportion of doses taken (or missed) by patients in addition to final treatment outcomes (**Supplement Table 6**), two of which did not include a comparison control group. In comparing treatment adherence before and after patients were enrolled into the study intervention, Gelmanova et al. [23] found an increase in proportion of doses taken from 52.2% (95%CI 47.5-56.9) to 81.4% (95%CI 76.8-86.0). These patients received increased staff time from nurses, as well as expanded access to psychosocial support, after they were enrolled into the study.

Feasibility of Implementation of Interventions

A summary of feasibility and implementation issues associated with study interventions is provided in **Supplement Table 7**. Issues with implementation of interventions varied among studies, but included: reluctance from health providers to follow new intervention-directed procedures, as opposed to standard procedures [16-17]; difficulties identifying and training support workers [29, 35]; and lack of clarity in intervention implementation [16]. Among studies that reported on cost-effectiveness, all found that the study intervention reduced losses to follow-up, and was more cost-effective than the standard treatment practices in their respective setting [23, 29, 34].

Discussion

Strategies to improve retention-in-care and treatment adherence among DR-TB patients are greatly needed to increase treatment success rates globally. This review found a broad range of adherence support interventions, all of which included some degree of educational and psychosocial counselling, as well as a variety of material support. However, very few studies reported on adherence outcomes in addition to patient losses to follow-up.

Our review found the provision of individual counselling support or home visits by health workers throughout treatment was associated with fewer losses to follow-up than when these interventions were provided only at the start of treatment, or not at all. This association

remained even after restricting the analyses to studies that provided daily DOT throughout treatment. Thus, although our study found lower lost to follow-up rates among studies that provided more frequent DOT, this could be conflated with the associated frequency of contact with providers as well as psychosocial support. This is supported by findings from Mohr et al. [17], which showed that self-administered therapy – supplemented with routine home visits by community health workers – during the continuation phase yielded a similar lost to follow-up rate compared to daily clinic-based DOT without home visits. Furthermore, Gelmanova et al. [23] showed significant improvements in treatment adherence rates among MDR-TB patients when staff time allocated to each patient was increased. These findings are consistent with those reported in a recent Cochrane systematic review (Karumbi 2015), which found that daily DOT did not improve TB cure rates compared to self-administered therapy when the frequency of contact with providers increased from monthly to every two weeks or more.

This review also provided evidence to support the effectiveness of financial compensation for rent or travel expenses, as well as lost wages, but not of group counselling, involvement of family in counselling sessions, or nutritional support, on improving retention-in-care. The lack of effectiveness of those strategies could be due to residual confounding. For example, Cox et al. [14] found no effect of a community-based pilot intervention (which provided routine counselling and access to a peer support group), and suggested this may be due to the higher numbers of patients who initiated treatment under intervention who otherwise would not have received treatment. Furthermore, very few studies reported on the ability to implement the study interventions or the fidelity of intervention delivery [16-17, 23, 28-29, 34-35]. Thus, the reported findings on intervention effectiveness may reflect issues with delivery such as: low engagement of patients and their families in support groups or counselling [38]; lack of buy-in from health workers [16-17, 32, 39]; or providers selectively providing adherence incentives, such as food packages, to patients deemed most worthy or needy [40]. Future research should explore issues with fidelity in the delivery and implementation of interventions through process evaluations [41].

One major limitation of this review was the inconsistent descriptions of interventions provided

by the included studies. We made extensive efforts to contact authors for more details, although we were not always successful. Among studies with sufficient details, we observed a wide variation in the educational and psychosocial support provided. Furthermore, although nearly all studies provided individual counselling to patients, the specifics of the counselling were not often described sufficiently. Thus, we considered individual counselling to broadly include any one-on-one time spent between patients and their health workers to address psychological, social, or treatment-related issues, and could provide both psychosocial and educational support. The observed benefit from these forms of support could be due to any on-going interactions between patients and their providers beyond directly observed therapy and routine medical check-ups. The benefit of counselling could be underestimated due to the lack of training or guidance provided to health workers in some studies compared to others.

Despite these limitations, the review provides a timely update on strategies to improve MDR-TB treatment retention-in-care, including results of two recent cluster randomized trials [13, 18]. Unlike the earlier review [3] which included all studies reporting treatment outcomes for RR/MDR-TB patients, we restricted our analysis to only those studies that explicitly provided patients with some form of psychosocial or material support, allowing a more nuanced analysis comparing the effectiveness of different types of support. Notably, no interventions utilized e-health tools to promote adherence to RR/MDR-TB treatment.

Our review provides the motivation for further examination of adherence interventions in RR/MDR-TB, preferably through RCTs, that compare the effectiveness of DOT to self-administered therapy, coupled with increased psychosocial and economic support throughout the treatment course. As evidenced by some recent cohort studies, and supported by expert commentaries [42-43], a shift to self-administered therapy has the potential to relieve health worker burden so that their time and resources may be utilized to build health literacy, empower patients, and deliver higher quality, patient-centered care.

Acknowledgement

We would like to thank McGill University librarian Genevieve Gore for her help in refining our search strategy. This work was supported by the Canadian Institutes of Health Research [FRN143999]. SL was supported by a Vanier Canada Graduate Scholarship.

Table 1. Description of treatment support provided in included study cohorts*

Study	N	Country, Study period	DOT Frequency (intensive/ continuation phase)	DOT location	Individual counselling	Home visits available	Financial support offered	Food packages provided	Group counselling	Counselling/ education offered to family
Studies with two or more patient cohorts										
Baral 2014 [13] (Control)**	33	Nepal, 2008	Daily/Daily	Clinic	No	No	No	No	No	N.S.
Baral 2014 [13] (Arm 1)	33	Nepal, 2008	Daily/Daily	Clinic	2 to 5 tailored sessions by trained nurse	No	No	No	Every 2-3 weeks	N.S.
Baral 2014 [13] (Arm 2)	42	Nepal, 2008	Daily/Daily	Clinic	2 to 5 tailored sessions by trained nurse	No	2000 Nepali Rupees per month	No	Every 2-3 weeks	N.S.
Cox 2014 [14] (Control)**	216	South Africa, 2005-2010	Daily/Daily	In-patient, hospital/Clinic	N.S.	No	No	No	No	No
Cox 2014 [14] (Intervention)**	571	South Africa, 2005-2010	Daily/Daily	Clinic	Routine counselling at start of treatment	No, but home assessment done by CHW at start of treatment	No	No	Weekly peer support groups	N.S.
Huerga 2017 [15] (Homa Bay)	28	Kenya, 2006-2012	Twice-Daily/Twice-Daily	Clinic/home	Weekly to monthly counselling sessions, and as needed	Daily home visits by CHW	Rent and travel	No	No	N.S.
Huerga 2017 [15] (Mathare)	70	Kenya, 2006-2012	Daily/Daily	Clinic	Weekly to monthly counselling sessions, and as needed	No	Rent and travel expenses	Daily hot meal & monthly food basket	No	N.S.

Huerga 2017 [15] (Nairobi)	71	Kenya, 2006-2012	Daily/Daily	Clinic	Counselling by nurses on request by doctors	No	Rent and travel expenses	No	No	N.S.
Loveday 2015 [16] (Hospital)**	813	South Africa, 2008-2010	Daily/None	In-patient, hospital	N.S.	No	No	No	No	N.S.
Loveday 2015 [16] (Site 1)	125	South Africa, 2008-2010	Daily/Daily	Clinic/home	Weekly educational sessions	Daily home visits by CHW	Travel expenses	No	No	Yes
Loveday 2015 [16] (Site 2 & 3)	350	South Africa, 2008-2010	Daily/None	Clinic/home	Unspecified frequency and duration	No	Travel expenses	No	No	Yes
Loveday 2015 [16] (Site 4)	261	South Africa, 2008-2010	Daily/None	Clinic	Unspecified frequency and duration	No	Travel expenses	No	No	Yes
Mohr 2017 [17] (SAT)	244	South Africa, 2010-2014	Daily/None	Clinic	4 standardized sessions during intensive phase, and 1 at start of continuation phase	Weekly visits by CHW at the start of continuation phase, monthly after	No	No	No	N.S.
Mohr 2017 [17] (SOC)	160	South Africa, 2010-2014	Daily/Daily	Clinic	4 standardized sessions during intensive phase	No	No	No	No	N.S.
Taneja 2017 [18] (Control)	50	India, 2014	Thrice-Weekly/None	Health facility (public/ private/NGO)	Thrice weekly during intensive phase, weekly thereafter	No	No	No	No	N.S.
Taneja 2017 [18] (Intervention)	50	India, 2014	Thrice-Weekly/None	Health facility (public/private /NGO)	Fortnightly at home & thrice weekly at clinic	Fortnightly visits from homecare	No	Daily provision of eggs	No	Yes

					during intensive phase, weekly at clinic & every 45 days at home thereafter	team during intensive phase, and every 45 days thereafter		and multi-grain biscuits		
Studies with a single patient cohort										
Alene 2017 [19]	481	China, 2011-2014	Daily/Daily	Clinic/home	Throughout initial hospitalization (1-2 months)	None specified	No	No	No	Yes
Bastard 2015 [20]	403	Armenia/ Georgia, 2002-2010	Daily/Daily	Clinic/home	Routine sessions	Daily by health personnel or CHW	Travel expenses	Yes, unspecified	Yes, unspecified	N.S.
Cox 2007 [21]	87	Uzbekistan, 2003-2005	Daily/Daily	Clinic	Daily counselling, or as needed	No	Travel expenses	Four meals daily during hospitalization; monthly food parcels after	No	N.S.
Escudero 2006 [22]	25	Spain, 1998-2000	Daily/None	In-patient, hospital	Repeatedly during hospitalization, monthly thereafter, by clinician/psychologist	No	No	No	No	N.S.
Gelmanova 2011 [23]	38	Russia, 2006-2008	Twice-Daily/Twice-Daily	Hospital/Home	Daily counselling, or as needed, by nurses and psychologist	Twice daily by a team of two nurses	Travel passes	Daily food parcels	No	Yes
Isaakidis 2011 [24]	35	India, 2007-2011	Twice-Daily/Twice-Daily	Health facility (public/ private/ NGO)	Monthly psychosocial follow-up	No	No	No	No	N.S.

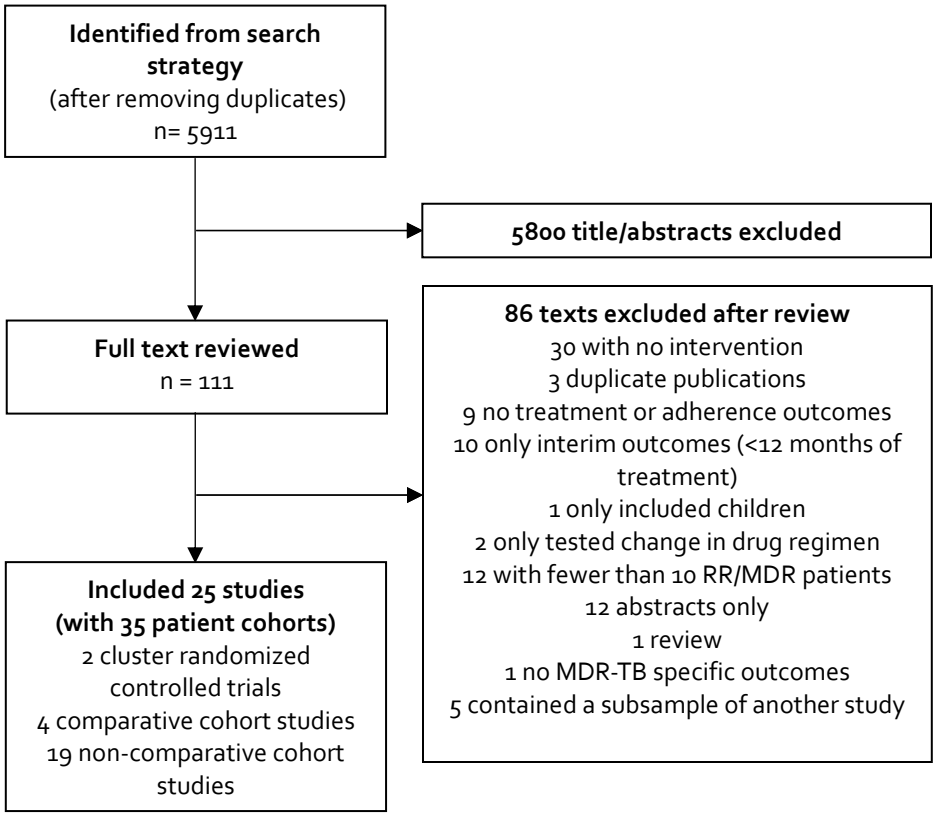
Joseph 2011 [25]	38	India, 2006-2007	Daily/Daily	Health facility (public/ private/NGO)	Initial education by medical officer and social worker, followed by daily adherence advice from trained DOT provider	No	No	No	No	Yes
Keshavjee 2008 [26]	608	Russia, 2000-2004	Daily/Daily	In-patient, hospital; Clinic/rural health outpost	Daily counselling, or as needed	No	No	Monthly food packages and meals for adherent patients	No	N.S.
Kliiman 2009 [27]	235	Estonia, 2003-2005	Daily/Daily	In-patient, hospital; Clinic	N.S.	No	Travel expenses	Yes, unspecified	No	N.S.
Meressa 2015 [28]	612	Ethiopia, 2009-2014	Daily/Daily	Clinic/home	Monthly counselling	Monthly visits by outpatient team	Rent and travel expenses	Monthly food baskets	No	Yes
Mitnick 2003 [29]	75	Peru, 1996-1999	Daily/Daily	Clinic/home	Daily counselling, or as needed	Daily by CHW	Travel expenses	Yes, unspecified	Weekly, bimonthly social support groups	Yes
Mitnick 2008 [30]	650	Peru, 1999-2002	Daily/Daily	Clinic/home	Daily counselling, or as needed	Daily by CHW	Travel expenses	Yes, unspecified	Weekly, bimonthly social support groups	Yes
Mohr 2015 [31]	853	South Africa, 2008-2012	Daily/Daily	Clinic	3 sessions in intensive phase and 1 in continuation phase	No	No	Yes, unspecified	Weekly peer support groups	Yes
Satti 2012 [32]	134	Lesotho, 2008-2009	Twice-Daily/Twice-Daily	Home	Daily counselling, or as needed	Twice daily by trained CHW	Travel expenses	Monthly food packages	No	Yes

Shin 2006 [33]	244	Russia, 1998-2000	Daily/Daily	Clinic/Rural health outpost	Daily counselling, or as needed	No	No	Monthly food packages/ meals for adherent patients	No	N.S.
Suarez 2002 [34]	298	Peru, 1997-1999	Daily/Daily	Clinic	N.S.	No	No	Weekly food parcels	N.S.	No
Thomas 2007 [35]	66	India, 1999-2003	Thrice-Weekly/ Thrice-Weekly	Health facility (public/ private/NGO)	Monthly sociological counselling	No	Monthly compensation for lost wages and travel expenses	No	No	N.S.
Vaghela 2015 [36]	101	India, 2009-2010	Daily/Daily	Health facility (public/ private/NGO)	Every 15 days during intensive phase, every 45 days thereafter	Visits by CHW every 15 days during intensive phase, every 45 days thereafter	None	Daily provision of eggs and multigrain biscuits	No	Yes
Yu 2015 [37]	126	Taiwan, 2007-2009	Twice-Daily/Twice-Daily	Clinic/home	Daily counselling, or as needed	Daily visits by medical team	Monthly income	No	No	Yes

*Studies with more than one arm/cohort – each arm shown separately. Abbreviations: CHW = community health worker; N.S.= none specified; DOT = directly observed therapy.

**Included in comparative analysis but excluded from pooled analysis (see text for details).

Figure 1. Flow diagram of literature search and study selection.



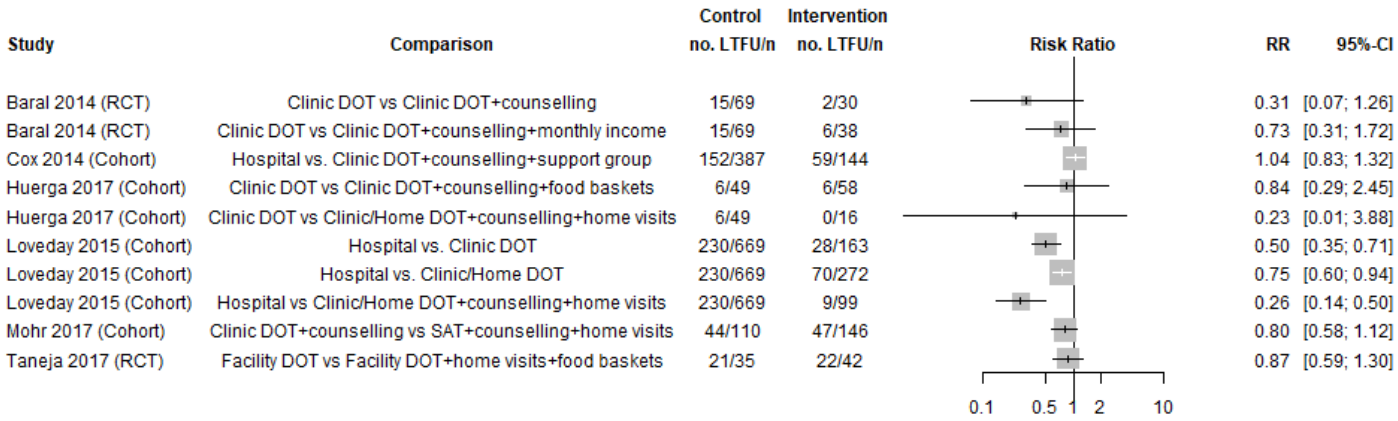


Figure 2. Forest plot of unadjusted risk ratios comparing proportions lost to follow-up (LTFU) between control and intervention arms in comparative studies (two or more patient cohorts). The size of the square is proportional to the size of the study sample. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded from the denominator. See Table 1 and Supplement Table 8 for details on treatment delivery and management for each study.

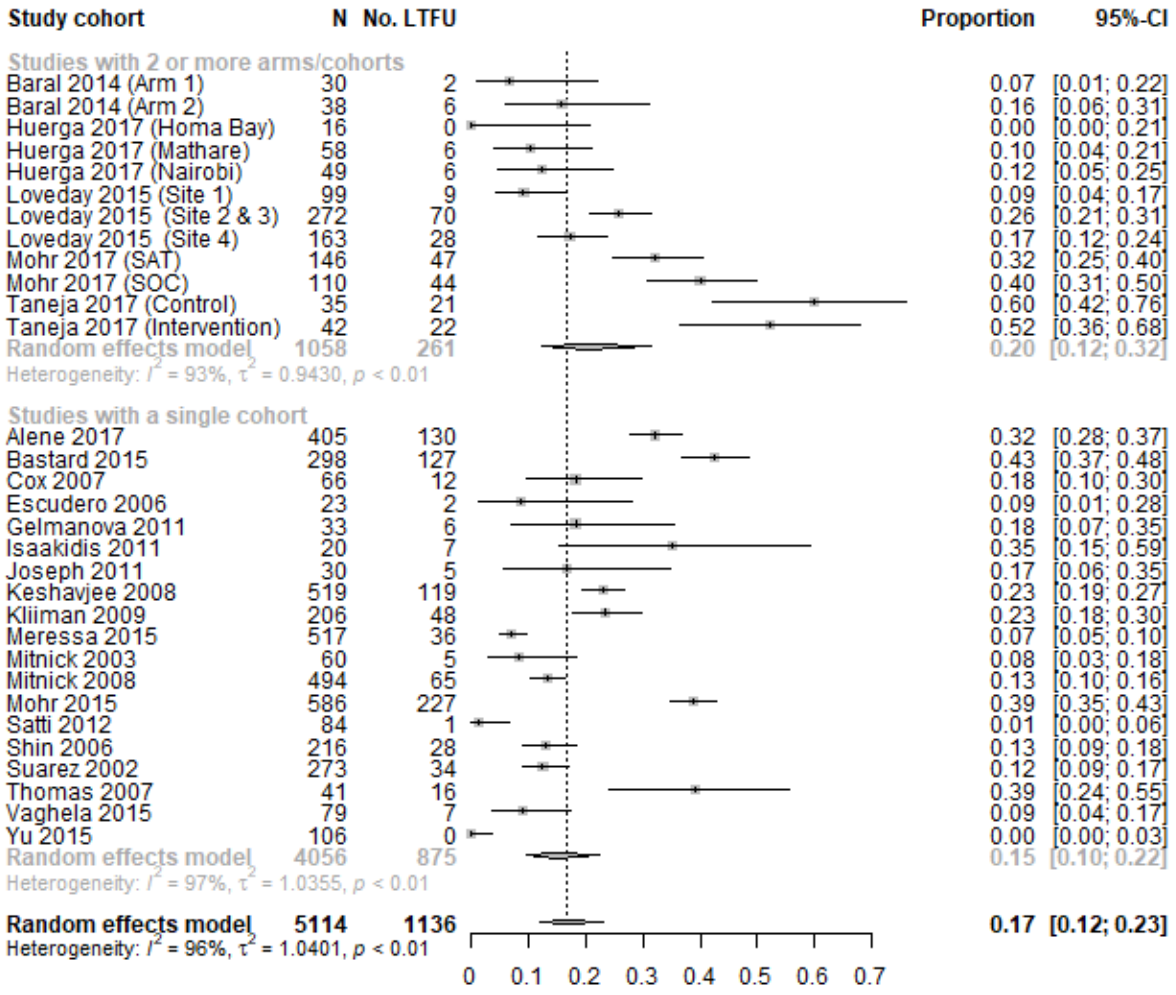


Figure 3. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts.
Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated were excluded. In studies with more than one cohort, each cohort is shown separately.

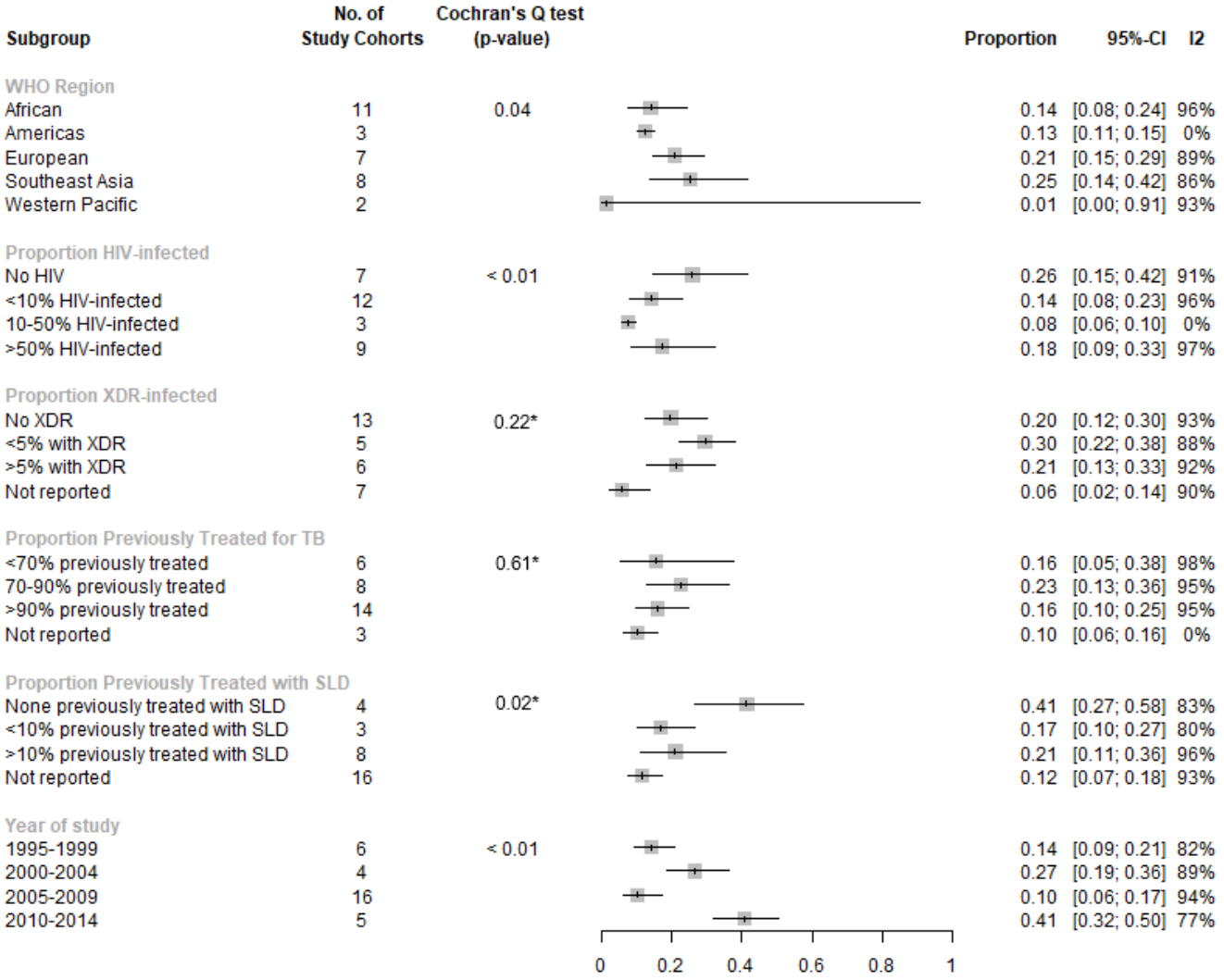


Figure 4. Forest plot of pooled proportions lost to follow-up (LTFU) stratified by study cohort characteristics.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated were excluded. WHO: World Health Organization; XDR: extensively drug-resistant; TB: tuberculosis. #: study cohorts that did not report a given characteristic were excluded from Cochran's Q-test for subgroup differences.

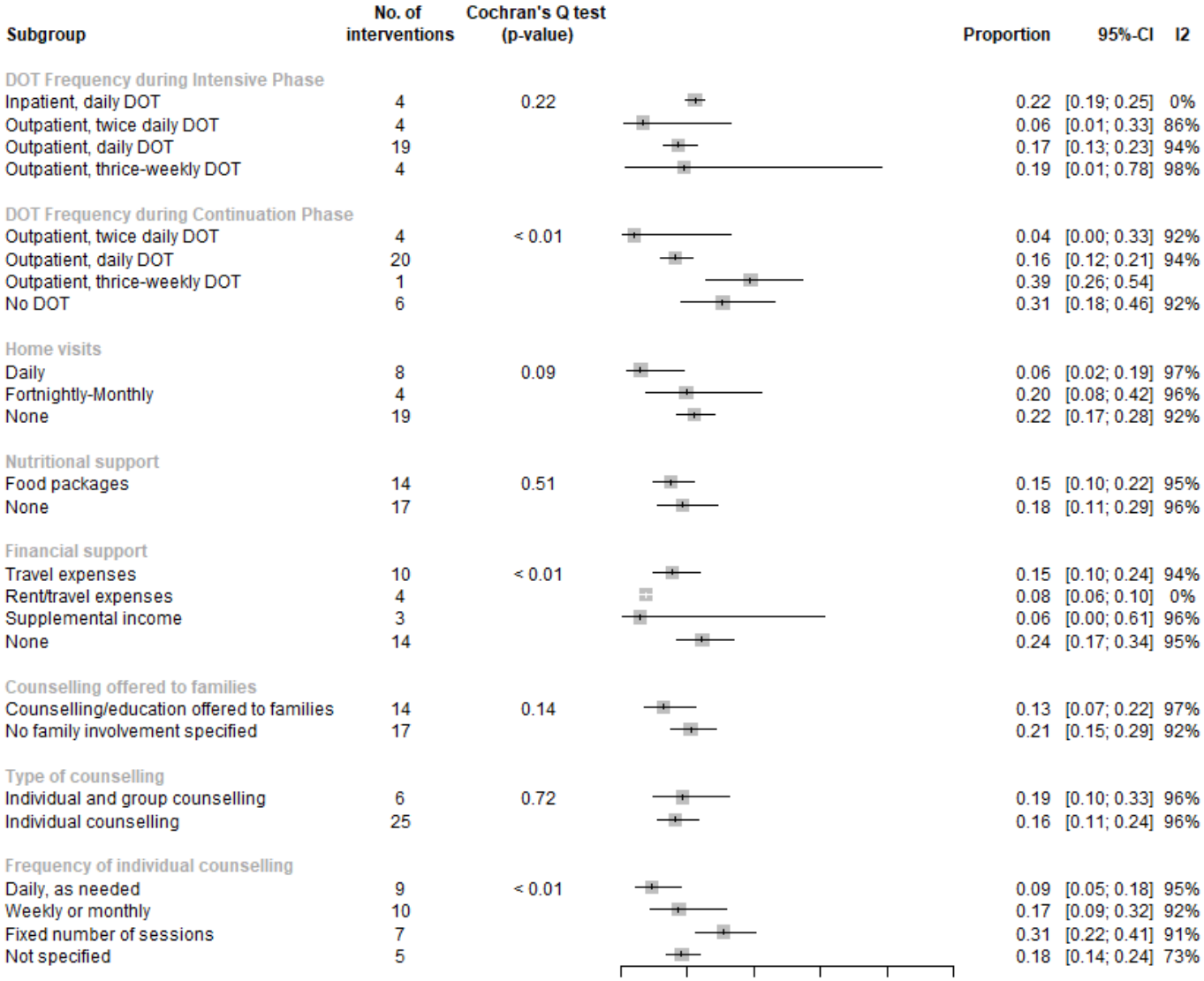


Figure 5. Forest plot of pooled proportions lost to follow-up (LTFU) stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated were excluded.

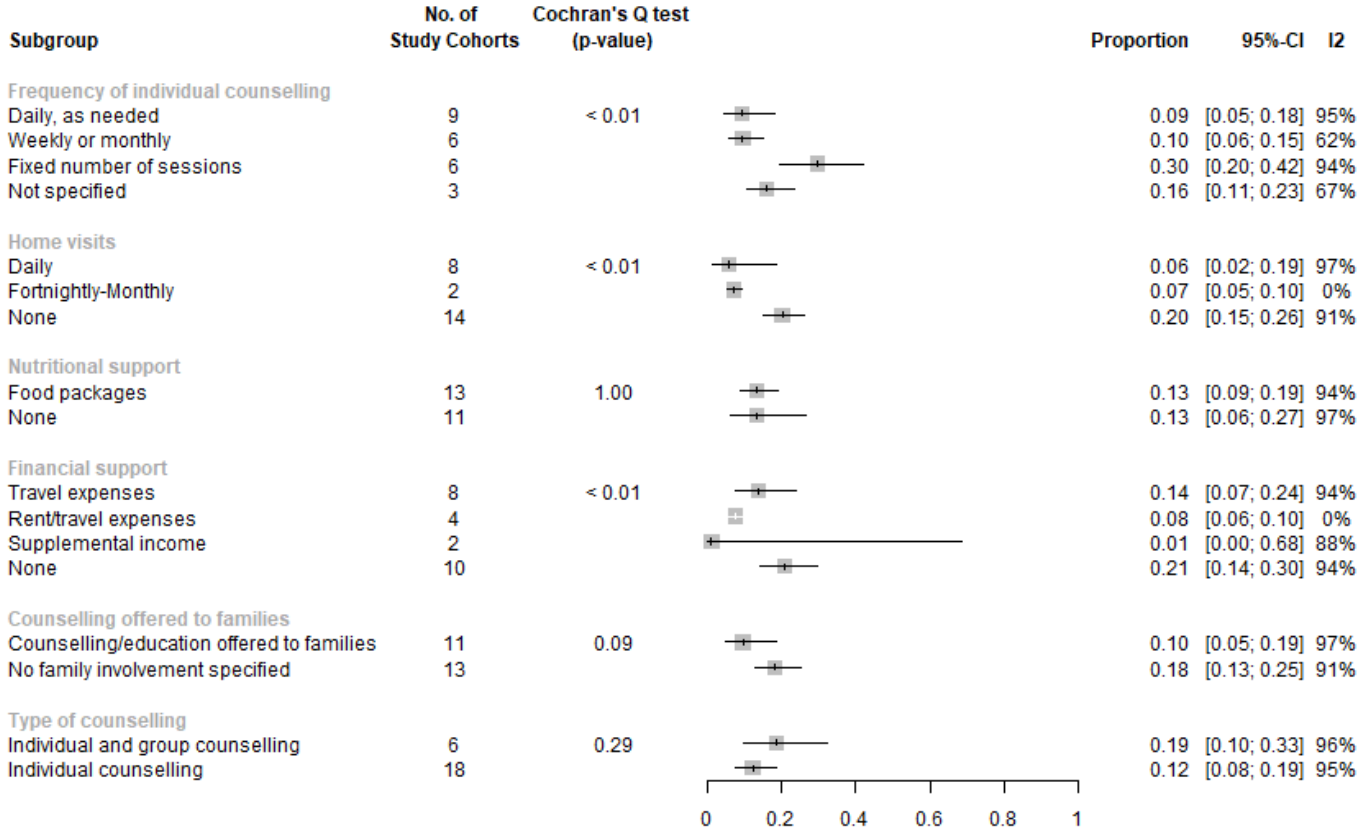


Figure 6. Forest plot of proportions lost to follow-up (LTFU) stratified by type of adherence support provided during treatment; this analysis compares cohorts across studies, but is restricted to cohorts that received twice-daily or daily directly observed therapy (DOT) throughout treatment.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated were excluded

References

1. World Health Organization [WHO]. Global Tuberculosis Report 2017. Geneva, WHO, 2017.
2. Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med 2007; 4(7): e238.
3. Toczek A, Cox H, du Cros P, Cooke G, Ford N. Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis. Int J Tuberc Lung Dis 2013; 17(3): 299-307.
4. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med 2008; 6: e1000097.
5. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GC, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting. JAMA 2000; 283(15): 2008-12.
6. WHO. Guidelines for establishing DOTS-Plus projects for the management of multidrug-resistant tuberculosis (MDR-TB). Geneva, WHO, 2000.
7. Ho J, Byrne AL, Linh NN, Jaramillo E, Fox GJ. Decentralized care for multidrug-resistant tuberculosis: a systematic review and meta-analysis. Bull World Health Organ 2017;95(8):584-593. doi:10.2471/BLT.17.193375.
8. Weiss P, Chen W, Cook VJ, Johnston JC. Treatment outcomes from community-based drug resistant tuberculosis treatment programs: a systematic review and meta-analysis. BMC Infect Dis 2014; 14:333.
9. Yin J, Yuan J, Hu Y, Wei X. Association between Directly Observed Therapy and Treatment Outcomes in Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis. PLoS One 2016; 11(3):e0150511.

10. Sterne J, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan A, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tuwgwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355:i4919.
11. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011.
12. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. J Clin Epidemiol 2008; 61(1):41-51.
13. Baral SC, Aryal Y, Bhattrai R, King R, Newell JN. The importance of providing counselling and financial support to patients receiving treatment for multi-drug resistant TB: mixed method qualitative and pilot intervention studies. BMC Public Health 2014;14:46.
14. Cox H, Hughes J, Daniels J, et al. Cox H, Hughes J, Daniels J, Azevedo V, McDermid C, Poolman M, Boulle A, Goemaere E, Cutsem Gv. Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. Int J Tuberc Lung Dis 2014;18:441-8.
15. Huerga H, Bastard M, Kamene M, Wanjala S, Arnold A, Oucho N, Chikwanha I, Varaine F. Outcomes from the first multidrug-resistant tuberculosis programme in Kenya. Int J Tuberc Lung Dis 2017;21:314-9.
16. Loveday M, Wallengren K, Brust J, Roberts J, Voce A, Margot B, Ngozo J, Master I, Cassell G, Padayatchi N. Community-based care vs. centralised hospitalisation for MDRTB patients, KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis 2015;19:163-71.
17. Mohr E, Daniels J, Beko B, Isaakidis JP, Cox V, Steele SJ, Muller O, Snyman L, De Azevedo V, Shroufi A, Trivino Duran L, Hughes J. DOT or SAT for Rifampicin-resistant tuberculosis? A non-randomized comparison in a high HIV-prevalence setting. PLoS ONE 2017;12:e0178054.

18. Taneja N, Chellaiyan VG, Daral S, Adhikary M, Das TK. Home Based Care as an Approach to Improve the Efficiency of treatment for MDR Tuberculosis: A Quasi-Experimental Pilot Study. J Clin Diagn Res 2017;11:LC05-LC8.
19. Alene KA, Yi HZ, Viney K, McBryde ES, Yang KY, Bai LQ, Gray DJ, Clements ACA, Xu ZH. Treatment outcomes of patients with multidrug-resistant and extensively drug resistant tuberculosis in Hunan Province, China. BMC Infect Dis 2017;17.
20. Bastard M, Sanchez-Padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, Bonnet M. Effects of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia. J Infect Dis 2015;211:1607-15.
21. Cox HS, Kalon S, Allamuratova S, Sizaire V, Tigay ZN, Rusch-Gerdes S, Karimovich HA, Kebede Y, Mills C. Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan: treatment complexity and XDR-TB among treatment failures. PLos One 2007;14.
22. Escudero E, Pena JM, Alvarez-Sala R, Vazquez JJ, Ortega A. Multidrug-resistant tuberculosis without HIV infection: Success with individualised therapy. Int J Tuberc Lung Dis 2006;10:409-14.
23. Gelmanova IY, Taran DV, Mishustin SP, Golubkov AA, Solovyova AV, Keshavjee S. 'Sputnik': A programmatic approach to improve tuberculosis treatment adherence and outcome among defaulters. Int J Tuberc Lung Dis 2011;15:1373-9.
24. Isaakidis P, Cox HS, Bhanumati V, Chiara M, Silva Ed, Homa M, Ladomirska J, Sotgiu G, Migliori GB, Pontali E, Saranchuk P, Rodrigues C, Reid T. Ambulatory multi-drug resistant tuberculosis treatment outcomes in a cohort of HIV-infected patients in a slum setting in Mumbai, India. PLoS ONE 2011;36.
25. Joseph P, Desai VB, Mohan NS, Fredrick JS, Ramachandran R, Raman B, Wares F, Ramachandran R, Thomas A. Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India. Indian J Med Res 2011;133:529-34.

26. Keshavjee S, Gelmanova IY, Farmer PE, Mishustin SP, Strelis AK, Andreev YG, Pasechnikov AD, Atwood S, Mukherjee JS, Rich ML, Furin JJ, Nardell EA, Kim JY, Shin SS. Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet 2008;372:1403-9.
27. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. Eur Respir J 2009;33:1085-94.
28. Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, Prasad P, Prasad R, Fekade B, Tedla Y, Yusuf H, Tadesse M, Tefera D, Ashenafi A, Desta G, Aderaye G, Olson K, Thim S, Goldfeld AE. Achieving high treatment success for multidrug-resistant TB in Africa: Initiation and scale-up of MDR TB care in Ethiopia - An observational cohort study. Thorax 2015;70:1181-8.
29. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcantara F, Sanchez E, Sarria M, Becerra M, Fawzi MC, Kapiga S, Neuberg D, Maguire JH, Kim JY, Farmer P. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. New Eng J Med 2003;348:119-28.
30. Mitnick CD, Shin SS, Seung KJ, Rich MS, Atwood SS, Furin JJ, Fitzmaurice GM, Alcantara Viru F, Appleton SC, Bayona JN, Bonilla CA, Chalco K, Choi S, Franke MF, Fraser HS, Guerra D, Hurtado R, Jazayeri D, Joseph K, Llaro K, Mestanza L, Mukherjee JS, Munoz M, Palacios E, Sanchez E, Sloutsky A. Comprehensive treatment of extensively drug-resistant tuberculosis. New Eng J Med 2008;359:563-74.
31. Mohr E, Cox V, Wilkinson L, Moyo S, Hughes J, Daniels J, Muller O, Cox H. Programmatic treatment outcomes in HIV-infected and uninfected drug-resistant TB patients in Khayelitsha, South Africa. Trans R Soc Trop Med Hyg 2015;109:425-32.
32. Satti H, McLaughlin MM, Hedt-Gauthier B, Atwood SS, Omotayo DB, Ntlamelle L, Seung KJ. Outcomes of Multidrug-Resistant Tuberculosis Treatment with Early Initiation of Antiretroviral Therapy for HIV Co-Infected Patients in Lesotho. PLoS ONE 2012;7.

33. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Andreev YG, Golubchikova VT, Tonkel TP, Yanova GV, Nikiforov M, Yedilbayev A, Mukherjee JS, Furin JJ, Barry DJ, Farmer PE, Rich ML, Keshavjee S. Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia. Int J Tuberc Lung Dis 2006;10:402-8.
34. Suárez PG, Floyd K, Portocarrero J, Alarcón E, Rapiti E, Ramos G, Bonilla C, Sabogal I, Aranda I, Dye C, Raviglione M, Espinal MA. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: A national cohort study in Peru. Lancet 2002;359:1980-9.
35. Thomas A, Ramachandran R, Rehaman F, Jaggarajamma K, Santha T, Selvakumar N, Krishnan N, Mohan NS, Sundaram V, Wares F, Narayanan PR. Management of multi drug resistance tuberculosis in the field: Tuberculosis Research Centre experience. Indian J Tuberc 2007;54:117-24.
36. Vaghela JF, Kapoor SK, Aditi K, Dass RT, Ashwani K, Bhatnagar AK. Home based care to multi-drug resistant tuberculosis patients: a pilot study. Indian J Tuberc 2015;62:91-6.
37. Yu MC, Chen HY, Chien SH, Jou R. An integrated MDR-TB management programme results in favourable outcomes in northern Taiwan. Eur Respir J 2015;45:272-5.
38. Acha J, Sweetland A, Guerra D, Chalco K, Castillo H, Palacios E. Psychosocial support groups for patients with multidrug-resistant tuberculosis: Five years of experience. Glob Public Health 2007;2:404-17.
39. Brust JC, Shah NS, Scott M, Chaiyachati K, Lygizos M, van der Merwe TL, Bamber S, Radebe Z, Loveday M, Moll AP, Margot B, Lalloo UG, Friedland GH, Gandhi NR. Integrated, home-based treatment for MDR-TB and HIV in rural South Africa: an alternate model of care. Int J Tuberc Lung Dis 2012;16:998-1004.
40. Lutge E, Lewin S, Volmink J, Friedman I, Lombard C. Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. Trials 2013; 14:154.

41. Munro A, Bloor M. Process evaluation: the new miracle ingredient in public health research? Qualitative Research 2010; 10(6): 699-713.
42. Metcalfe JZ, O'Donnell MR, Bangsberg DR. Moving beyond directly observed therapy for tuberculosis. PLoS Med 2015l 12(9):e1001877.
43. Benbaba S, Isaakidis P, Das M, Jadhav S, Reid T, Furin J. Direct Observation (DO) for Drug-Resistant Tuberculosis: Do we really DO? PLoS One 2015;10:e0144936.

STUDY 4: STRENGTHENING THE TUBERCULOSIS CASCADE OF CARE TO REDUCE TUBERCULOSIS MORTALITY AND DRUG RESISTANCE: A DYNAMIC MODELLING STUDY

In this final study, the model from the first study was modified to investigate the emergence of drug resistance in South Africa. The first modelling study found strengthening TB care in the public system, particularly by improving adherence to treatment, would have the greatest effect on reducing the emergence of MDR-TB. The comparison scenarios in that study focused on improving care in the different health sectors in India, which included the care provided by public, private or informal providers and private chemists, and examining how those improvements would affect the future epidemic. However, the situation in South Africa represents a different challenge. Unlike India, the non-public sectors in South Africa, as found in the qualitative study (Study 2), provide TB treatment to few patients, and nearly all TB patients are treated in the public sector. Furthermore, South Africa's TB epidemic is fueled by the HIV co-epidemic, where more than half of all TB cases are co-infected with HIV. Thus, exploring the epidemic in South Africa may provide different insights on how to best control the MDR-TB epidemic globally.

The modifications made in this study to the Markov-based decision analytic model were informed by findings discussed in the second and third studies. The second study provided an in-depth exploration of the TB cascade of care in South Africa, and the particular care-seeking experiences of TB and MDR-TB patients in an urban setting. It revealed the importance of the patient-provider relationships throughout a patient's treatment journey, at different stages of the care cascade. Building trust at the start of care can have importance consequences on retention-in-care, particularly for MDR-TB patients who often experience long and difficult treatment journeys. Their experiences point to many aspects of the TB care cascade that could be improved to support patients through diagnosis and treatment. The third study focused on support strategies to reduce losses to follow-up during MDR-TB treatment. This study found – consistent with the findings in Study 2 – that providing psychosocial support in the form of individual counselling, or home visits, throughout treatment was associated with greater retention-in-care. It showed that any time spent between patients and providers that focused

on the patient as a person, and not just on the drugs and clinical monitoring, could greatly reduce losses to follow-up.

This study used decision analytic modelling to compare the potential effects of strategies targeting different points of the TB care cascade on reducing TB mortality, and on the emergence of drug resistance. The specific differences compared to the model based in India from Study 1 are as follows:

- Based on the findings from the qualitative research in the second study, we assumed a negligible proportion of non-public providers would prescribe TB drugs. Therefore, TB patients were only treated in the public sector in the South African model, even if they sought care initially from a non-public provider. Seeking care from a non-public provider only increased the delay experienced before starting treatment, and affected no other TB-related parameter.
- HIV affected the pathogenesis of TB in the following ways (see manuscript for references and estimates):
    - Increased the risk of progressing to active TB disease after infection, including reactivation from latent TB disease.
    - Increased the case fatality rate during TB treatment
    - Antiretroviral therapy (ART) reduced the impact of HIV on TB disease progression and mortality
    - Isoniazid preventative therapy (IPT) reduced the risk of disease progression in people living with HIV
- Initial losses to follow-up, that is patients who are diagnosed with TB but do not return to care for treatment initiation, was specifically modelled, based on the findings from the qualitative study in Study 3.
- Rapid testing via Xpert, which tests for TB and resistance to rifampicin simultaneously, is widely available in South Africa and thus was added to the model.

- A recently published systematic review by Gegia et al. (2017) provided updated estimates of the risk of acquired drug resistance after a poor treatment outcome among drug-susceptible and INH-resistant patients.
- New regimens for the treatment of RR/MDR-TB have recently been introduced nationally in South Africa, including the WHO-recommended "Short MDR regimen" (9 to 12 months), and a bedaquiline-based MDR-TB that eliminates the use of second-line injectable agents.
    - The potential impact of these new regimens was explored in this model, and was supported by recent meta-analyses on treatment outcomes using the shortened MDR regimen (Ahmad Khan, 2017), and a bedaquiline-based regimen (Borisov, 2016).

Manuscript 4: Law S, Oxlade O, Menzies D. Strengthening the tuberculosis cascade of care to reduce tuberculosis mortality and drug resistance: A dynamic modelling study.

The following text is a manuscript prepared for submission to ERJ.

Abstract

Background

Rifampicin-resistant and multidrug-resistant tuberculosis (RR/MDR-TB) contributes to high TB mortality in South Africa. We conducted a modelling study to compare the effectiveness of strategies, targeting different stages of the TB cascade of care, in reducing TB mortality and RR/MDR-TB incidence.

Methods

We constructed a Markov-based, dynamic decision analytic model to represent the TB epidemic in South Africa. This included a probabilistic framework reflecting the TB cascade of care and the impact of HIV on TB disease progression and reactivation rates. South Africa-specific HIV/TB management practices and epidemiological data were obtained from published literature. We

compared the impact of strategies targeting different stages along the TB cascade of care on projected TB outcomes for years 2017 to 2035. Modeled strategies included: reducing progression and reactivation of TB disease among people living with HIV; reducing diagnostic errors and treatment delays; reducing initial and treatment losses to follow-up; and improving RR/MDR-TB treatment outcomes via newly recommended second-line regimens. Model outcomes, which included TB mortality and incidence, were stratified by underlying drug resistance.

Findings

Among strategies that targeted a single stage of the cascade, those targeting the earliest stage by reducing TB disease in people living with HIV, would lead to the greatest reductions in mortality and RR/MDR-TB incidence (by up to 27% and 21% compared to the *status quo* scenario, respectively). Among strategies targeting various stages along the cascade, strengthening care to reduce treatment delays, and initial and treatment losses to follow-up, would lead to the largest reductions in TB mortality and RR/MDR-TB incidence (by approximately 41% and 30% compared to the *status quo* scenario, respectively). These reductions were greater than those found with strategies involving new second-line regimens for RR/MDR-TB treatment, such as the WHO-recommended shorter MDR regimen of 9 to 12 months, or a bedaquiline-based, injection-free regimen.

Interpretation

Evidence-based strategies to improve retention-in-care among all TB patients are urgently needed to prevent the continued emergence of RR/MDR-TB and associated mortality.

Funding

The Canadian Institutes for Health Research.

Introduction

Drug resistance against rifampicin, the most potent first-line tuberculosis (TB) drug, has

emerged rapidly worldwide over the past few decades. The rate of emergence of drug resistance has not yet decreased, in spite of increased efforts to diagnose and treat drug resistant TB, including the global scale-up of Xpert MTB/RIF testing for resistance to rifampicin in all TB cases.[1] Treatment outcomes among rifampicin-resistant (RR-TB) patients, particularly among those with additional resistance to isoniazid (INH), known as multidrug-resistant TB (MDR-TB), remain poor globally, where only half are successfully treated.[1]

RR/MDR-TB is a significant contributor to TB mortality. Mortality among RR/MDR-TB patients is approximately 16%, four times that of new or relapsed patients without resistance to rifampicin, which is roughly 4%.[1] To curb the spread of RR/MDR-TB, the national TB programs must strengthen services provided along the continuum of TB care (also known as the TB cascade of care) for both drug-susceptible TB (DS-TB) and RR/MDR-TB patients. Currently, of over 10 million people who develop active TB disease each year, up to 40% never initiate treatment, and of those who do start treatment, approximately 20% have poor outcomes and are at elevated risk of developing drug resistance.[1] The situation is much worse among RR/MDR-TB cases, where less than half of 400,000 individuals who develop active TB disease are notified and treated, of whom half have poor outcomes and are at risk of infecting others.[1]

The World Health Organization (WHO) recently recommended new RR/MDR treatment regimens, including a shortened regimen of 9 to 12 months,[2] and a bedaquiline-based oral treatment,[3] which have shown promising results to improve RR/MDR treatment outcomes.[4,5] These new regimens are among many strategies adopted globally to target different stages of the TB care cascade. There is uncertainty around which stages of the DS-TB or RR/MDR-TB care cascades should be targeted to have the greatest impact on TB mortality and drug resistance. This study uses a dynamic, Markov-based, decision analytic model to project the TB and RR/MDR-TB epidemics in South Africa. We chose South Africa as a case study because of its high burden of drug-resistant TB,[1,6] and because of reliable RR/MDR-TB data made available from a national survey of drug resistance among TB patients, conducted between 2012 and 2014.[7] The South African TB epidemic is also exacerbated by the HIV co-epidemic, insomuch that

HIV increases the TB progression and reactivation rate, as well as TB-related morbidity and mortality.[8] Thus, although RR/MDR-TB is a global phenomenon, exploring the epidemic in South Africa could provide insights on how to curb the epidemic not only in settings with a high burden of RR/MDR-TB, but also in settings with a high prevalence of HIV. Our primary objective is to compare the potential impact on TB mortality and the emergence of drug resistance of interventions targeted at four different stages of the cascade: 1) before the onset of TB symptoms; 2) between onset of TB symptoms and getting tested for TB; 3) between testing for TB and initiating treatment; and 4) after initiating TB treatment. Our secondary objective is to explore the impact of strategies that target multiple stages of the cascade simultaneously.

Methods

Model design

We constructed a dynamic Markov model using decision analysis software (TreeAge Professional, 2017) to represent South Africa's epidemic. The model, as described in detail elsewhere[9,10] and in the appendix, included a probabilistic framework reflecting the TB care cascade for patients with drug-susceptible or drug-resistant TB, and the impact of HIV on TB disease progression (see Fig. 1). Model variables related to the natural history of tuberculosis were derived from published systematic reviews and meta-analyses when possible. If not available then we pooled estimates from primary studies, using a random effects method to account for between-study heterogeneity (appendix). South African TB/HIV epidemiological data, and TB/HIV management practices, were also obtained from published literature (table 1).

We calibrated the model to predict a TB epidemic that matched the WHO-estimated TB incidence, as well as the prevalence of INH and RR/MDR resistance, between 2007 and 2016.[11] This period was chosen because the national TB incidence peaked in 2007, and consistent data is publicly available. During model calibration, we adjusted several key TB pathogenetic variables, including the relative transmissibility of RR/MDR-TB (appendix).

HIV was assumed to increase TB disease progression and reactivation rates, as well as case

fatality rate during TB treatment (appendix).[6] Both ART and isoniazid preventative therapy (IPT) reduced the effect of HIV on TB progression and reactivation, and ART alone reduced the impact of HIV on mortality during TB treatment. Different ART coverage rates applied for people living with HIV, with or without active TB disease.

Table 1. South African health system parameters used in model (base-case)

	Value	Range	Source
ART coverage, %			
HIV/TB co-infected	84.7	n/a	UNAIDS, 2018[12]
All people living with HIV	55.4	n/a	WHO, 2018[11]
ART 3-year retention rate, %			
All people living with HIV	72.3	67.4-76.9	Fox, 2011[13]
IPT coverage, %			
All people living with HIV	51	n/a	UNAIDS, 2018[12]
IPT completion rate, %			
All people living with HIV treated with IPT	59	53.6-64.0	Golub, 2011 [14]
First healthcare provider visited, %			
Non-public	30.4	n/a	Hirschowitz, 2001 [15]
Public	69.6	n/a	*Ibid.*
Private provider refers to public provider, %	8	8-28	Van Wyk, 2011 [16]
Patient delay (symptoms to first action), days	47.3	11.5-194.2	Pronyk, 2001 [17]; Mentijes, 2008 [18]*
Health system delay (first action to starting treatment), days			
Non-Public, all patients	55.9	36.8 - 84.8	Pronyk 2001[7]; Meintjes 2008[8]; Barker 2006[19]*
Public, all patients without DST	44.8	32.6 - 61.6	*Ibid.*
Public, if received culture DST	78.1	73.4 - 83.0	Hanrahan, 2012[20]; Cox, 2015[21]; Jacobson, 2013[22]; Iruedo 2017[23]*
Public, if received LPA DST testing	44	20-69	Cox, 2017[24]
Public, if received Xpert testing	22	2-43	*Ibid*.
% of total TB patients correctly diagnosed (with or without DST)			
All patients	82	77.5-87.3	Naidoo, 2017[25]
% of total TB patients tested via Xpert			
All patients	73.2	n/a	WHO, 2018[11]
% initial LTFU			
Initial/retreatment	*25*	22-28	Claassens,2013[26]
MDR regimen, did not fail treatment	45	43-47	Cox, 2017[26]
MDR regimen, failed treatment	37	33-41	Naidoo, 2017[15]**
Death rate for patients initially LTFU			
Die, any TB	30.5	27.3-33.9	Botha, 2008[27]; Evans, 2017[28]; Ebonwu, 2013[29]***
% treatment LTFU			
Initial treatment	6.6	n/a	WHO, 2018[11]
Retreatment	22.6	n/a	*Ibid.*

MDR treatment	27.6	n/a	*Ibid.*
Duration between treatment LTFU and reinitiating treatment, months	7.7	4.2-22.7	Personal communication from Marx, 2012[30]

Abbreviations: LTFU = lost to follow-up

*****Pooled estimate from random effects model via maximum likelihood estimation, inverse variance weighting, and log-transformed means. Means and standard deviation were estimated from median, IQR and ranges using appropriate formulas provided by Wan et al, 2014.[31]

**We assumed as the reported proportion of patients who received their diagnosis but did not initiate treatment.

***Pooled estimate from random effects model using an exact binomial likelihood approach.[32]

TB treatment pathways in the model

Our model assumed that all people with active tuberculosis would seek care for TB symptoms, either from public or non-public providers. Information regarding how individuals initially access the health system was obtained from a representative national survey conducted in 1999.[17] All patients were assigned a patient delay of 47.3 days (95%CI 11.5-194.2)[17,18] between onset of symptoms and seeking care (table 1). Due to the negligible proportion of TB patients who paid out-of-pocket for TB treatment in one study,[25] we assumed all patients in our model were diagnosed and treated in the public sector, even if they sought care first from a non-public provider. Those who were diagnosed with TB, without additional drug susceptibility testing, and started on non-MDR treatment were assigned a health system delay of 44.8 days (95%CI 32.6-61.6)[17-19] if they first sought care from a public provider, and of 55.9 days (95%CI 36.8-84.8)[17-19] if from a non-public provider (table 1). RR/MDR-TB patients who received culture-based drug susceptibility testing were assigned a health system delay of 78.1 days (95%CI 73.4-83.0).[20-23] Patients who sought care from a private provider, and were referred directly to a public provider, were assigned the same delay as those who sought care first from a public provider. Not all individuals were diagnosed or received treatment with tuberculosis drugs when they sought care (table 1). If they received no tuberculosis drugs, they could die of TB, or be spontaneously cured, but could not acquire drug resistance (appendix).

If a patient did not respond to treatment, relapsed, or did not complete their first treatment, they would return for retreatment, but with different durations of patient delay. Those who did not respond to treatment (i.e. failed) would return to treatment without delay; those who were

lost to follow-up would return after 7.7 months (IQR 4.2-22.7);[30] and those who relapsed after cure would return after the same delay as during their first treatment seeking action (table 1). All RR/MDR patients who received drug susceptibility testing were started on a second-line MDR regimen. If they were not cured or did not complete treatment, they would receive no further treatment, and experience mortality at the same rate as initially untreated.[33] TB patients could be lost from the care cascade at any of the following stages: before diagnosis; after diagnosis but before initiating treatment (i.e. initial loss to follow-up); and after initiating treatment (i.e. treatment loss to follow-up).

All individuals with active TB disease could transmit their disease to other uninfected individuals, and those with drug-resistant strains could transmit it to anybody who is uninfected or who has a less resistant strain. Individuals became non-infectious after initiating correct treatment, but could become infectious again if they fail, relapse or are lost to follow-up from treatment (appendix).

Outcomes

The base case analysis began in 2017 and assumed no further changes in provider or patient behaviours, nor in TB/HIV treatment or management. Recent changes to TB/HIV management practices included: line probe assay (LPA) testing which was introduced in late 2009, and reduced the DST delay to 44 days (IQR 20-69 days) by 2011[24]; Xpert MTB/RIF which was introduced in 2011 and further shortened the delay to 22 days (IQR 2-43 days);[24] revised guidelines that all TB cases - new or previously treated - received DST for resistance to rifampicin via Xpert; and ART and IPT coverage was increased among people living with HIV.[12]

Epidemiological outcomes were projected for South Africa in 2035. We assumed the annual HIV incidence rate continued to decrease at the same average rate seen between 2001 and 2016,[18] of approximately 5.5% per year. Model projected outcomes were stratified by underlying drug resistance and HIV status, and included annual risk of infection, incidence of new disease, and tuberculosis-related mortality.

Table 2. Scenarios for comparison in model projections

Strategy group	Target patients	Strategy	Description of change achieved by 2020	Reference for proposed change
Single target strategies				
1	TB/HIV	ART coverage, TB	Increase proportion of TB patients with HIV on ART to 84.7% to 90%	90-90-90 by 2020 national targets (Health Systems Trust, 2016)[34]
	HIV	ART coverage	Increase proportion of all HIV patients, with or without TB, on ART from 55.4% to 90%	*Ibid.*
	TB/HIV	ART retention, TB	Increase ART retention rate among TB patients with HIV from 72.3% to 90%	*Ibid.*
	HIV	ART retention	Increase ART retention rate among all HIV patients from 72.3% to 90%	*Ibid.*
	HIV	IPT coverage	Increase proportion of HIV patients started on IPT from 51% to 90%	*Ibid.*
	HIV	IPT completion	Increase proportion of HIV patients who complete IPT from 59% to 90%	*Ibid.*
2	TB	Public delay	Reduce public provider delay from 44.8 days to 5 days (with or without Xpert)	National strategic plan target (South African National AIDS Council, 2011)[35]
	TB	Private referral	Increase private provide referral rate from 8% to 100%	Hypothetical strategy
	TB	Misdiagnoses	Increase proportion of TB patients correctly diagnosed from 82% to 90% (excluding DST)	90-90-90 by 2020 national targets [34]
	TB/MDR	Xpert access	Increase Xpert coverage from 73.2% to 100% of all TB patients	National strategic plan target [35]
	TB/MDR	Xpert delay	Decrease public provider delay from 22 days to 5 days among Xpert-tested	*Ibid.*
3	DS/INHR	Initial LTFU, DS/INHR	Decrease initial LTFU among DS/INHR-TB patients from 25 to 10%	90-90-90 by 2020 national targets [34]
	RR/MDR	Initial LTFU, RR/MDR	Decrease initial LTFU among RR/MDR-TB patients from 37-45% to 10%	*Ibid.*
4	DS/INHR	Treatment LTFU, DS/INHR	Decrease treatment LTFU among DS/INHR-TB patients by 0.53 times by increasing psychosocial support, i.e. from 6.6% to 3.5% among new patients and from 22.6% to 12.0% among retreatment patients.	Effect of increase psychosocial support for new and retreated, non-MDR, patients (van Hoorn, 2016)[36]
	RR/MDR	Treatment LTFU, RR/MDR	Decrease treatment LTFU among RR/MDR-TB patients by 0.2 times by increasing psychosocial support, i.e. from 28% to 6%.	Effect of increase psychosocial support for RR/MDR

				patients (Law, 2018)[37]
	MDR	Short MDR	Expand access to shortened MDR regimen for all eligible RR/MDR-TB patients from 0% to 70% of RR/MDR-TB patients.*	WHO 2016 updated recommendation[7]
	MDR	Bedaquiline	Expand access to bedaquiline-based, oral MDR-TB treatment from 0% to 100% of RR/MDR-TB patients.**	National department of health 2018 updated recommendation[8]
Combination strategies			***Included strategies defined above***	
1	TB/HIV	Optimize ART, TB	ART coverage + ART retention, TB	
	HIV	Optimize ART	ART coverage + ART retention	
	HIV	Optimize IPT	IPT coverage + IPT completion	
	HIV	ART/IPT adherence	ART retention + IPT completion	
2	TB/MDR	Optimize Xpert	Xpert access + Xpert delay	
	TB	Diagnostic delay	Misdiagnoses + Xpert access + Xpert delay	
	TB	Health system delay	Misdiagnoses + Xpert access + public delay + private referral	
3	TB	Initial LTFU	Initial LTFU, DS/INHR + Initial LTFU, RR/MDR	
4	TB	Treatment LTFU	Treatment LTFU, DS/INHR + Treatment LTFU, RR/MDR	
	RR/MDR	MDR treatment	Increase access to shortened MDR regimen to 70% and bedaquiline-based regimen to 30% of all RR/MDR-TB patients.	
3 & 4	DS/INHR	All LTFU, DS/INHR	Initial LTFU, DS/INHR + Treatment LTFU, DS/INHR	
	RR/MDR	All LTFU, RR/MD	Initial LTFU, RR/MDR + Treatment LTFU, RR/MDR	
	TB	All LTFU, all TB	Initial LTFU, DS/INHR + Treatment LTFU, DS/INHR + Initial LTFU, RR/MDR + Treatment LTFU, RR/MDR	
1, 3-4	TB/HIV	HIV/TB adherence	Initial LTFU, DS/INHR + Treatment LTFU, DS/INHR + Initial LTFU, RR/MDR + Treatment LTFU, RR/MDR + ART retention, TB	
2 & 4	TB/MDR	Diagnostics & treatment	Xpert access + Xpert delay+ bedaquiline	
2-4	DS/INHR	Strengthen care, DS/INHR	Misdiagnoses + public delay + Initial LTFU, DS/INHR + Treatment LTFU, DS/INHR	
2-4	RR/MDR	Strengthen care, RR/MDR	Misdiagnoses + DST delay + Initial LTFU, RR/MDR + Treatment LTFU, RR/MDR	
2-4	TB	Strengthen care, all TB	Misdiagnoses + public delay + Initial LTFU, DS/INHR + Treatment LTFU, DS/INHR + Initial LTFU, RR/MDR + Treatment LTFU, RR/MDR	

*Probabilities of poor MDR treatment outcomes under a shortened regimen were as follows (Khan, 2017[5]): death 6.4%; LTFU among surviving = 7.2%; and failure among retained = 2.5%.

** Probabilities of poor MDR treatment outcomes under a bedaquiline-based regimen were as follows (Borisov, 2017[4]): death = 13.4%; LTFU among surviving = 8.4%; failure among retained = 9.7%.

Projecting impact of different TB/HIV management strategies

We considered scenarios where a single improvement to TB/HIV management practice or

treatment was introduced within the model, while keeping all other variables constants. The improvements targeted different stages of the cascade of care, and were grouped together based on the cascade stage and type of TB patients they targeted (Fig. 1 and Table 2). These strategies reflected: recent and upcoming changes to TB/HIV practices; proposed national targets for HIV and TB outcomes by 2020; and hypothetical improvements to existing TB/HIV care, including those that would reduce initial and treatment losses to follow-up, as well as health system errors and delays (table 2). We then combined different scenarios that either all targeted the same stages of the cascade, or targeted different stages of the cascade, to assess the potential impact of different broader strategies (table 2). To be consistent with global goals set for year 2020,[38] our model assumed all planned program improvements were made by 2020, with no further changes for the remaining 15 years up to 2035.

Sensitivity analyses

To quantify the combined statistical uncertainty of model parameters, a probabilistic sensitivity analysis was done that reported 95% uncertainty ranges (UR), generated from 5000 Monte Carlo simulation trials. All parameters reporting ranges in table 1 and the appendix, that were not adjusted during model calibration, were defined as distributions with means, and confidence intervals (CI) from the published literature. Probability variables (such as the probability of seeking care from a public provider, or the probabilities of different treatment outcomes) were defined by beta distributions. Non-probability variables (such as patient and health system delays) were defined by log-normal distributions.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, and data interpretation, or writing of the report. All authors had full access to the data and the corresponding author had final responsibility for the decision to submit for publication.

Findings

In the base-case (status quo) scenario where no further changes were made to the South African

health care system with respect to TB treatment and management, but the annual HIV incidence continued to decrease steadily, our model projected the total TB incidence would decrease by approximately half, from 583.1 per 100,000 population in 2016 to 297.8 per 100,000 population (95%UR 185.4 – 4.48 per 100,000 population) in 2035. The RR/MDR-TB incidence would decrease by about a third, from 46.3 per 100,000 population in 2016 to 30.8 per 100,000 population (95% UR 16.9 – 184.0 per 100,000 population) in 2035. The total TB mortality would decrease by over half, from 161.0 per 100,000 population in 2016 to 68.6 per 100,000 population (95% UR 40.2 – 149.5 per 100,000 population).

In terms of single-target strategies, those in group 1 targeting people living with HIV, with or without active TB disease, had the greatest effect on reducing both TB mortality and incidence of RR/MDR-TB projected for 2035 (figure 2), compared to the base-case scenario. Among people living with HIV, increasing the proportion treated with ART from 55.4% to 90% by 2020, would lead to the greatest reductions in TB mortality and RR/MDR-TB incidence, by 27% and 21% respectively. This strategy was followed closely by increasing the proportion of people living with HIV who received IPT from 51% to 90% by 2020, which would lead to reductions in TB mortality and RR/MDR-TB incidence of 19% and 18%, respectively.

Strategies in group 2, which aimed to reduce diagnostic errors or treatment delays, were found to have relatively low impact on incidence and mortality rates, compared to the base-case scenario. The projected effects on overall TB mortality and RR/MDR-TB incidence ranged from zero to 13%. The greatest reductions in TB mortality and RR/MDR-TB incidence were projected when the proportion of TB patients diagnosed increased from 82% in 2017 (table 2) to 90% in 2020, and when the proportion of TB patients diagnosed via Xpert increased from 73% in 2017 to 100% in 2020, respectively.

Strategies in group 3 and 4 that targeted only RR/MDR-TB patients and aimed to reduce initial/treatment losses to follow-up or improve treatment outcomes, would lead to reductions in RR/MDR-TB incidence by 10% to 19%, but would reduce TB mortality by only 2% to 7%. Strategies in group 3 and 4 that only target DS/INHR-TB patients would lead to 3% to 16%

reduction in TB mortality, but would increase RR/MDR-TB incidence slightly - by 1% to 2%.

Of the different combinations of strategies, strengthening existing care for both DS/INHR-TB and RR/MDR-TB patients would have the greatest impact on TB mortality and RR/MDR-TB incidence (figure 3). This strategy, which combined strategies from groups 2 to 4, did not introduce new procedures or treatment regimens, but focused on improving existing care (table 2). This combined strategy was projected to result in reductions in TB mortality and RR/MDR-TB incidence of 41% and 30% compared to the base-case scenario, respectively. In contrast, combining three strategies, which have all been newly introduced in South Africa - Xpert testing of all TB cases, decrease Xpert testing delays to 5 days, and expanding access to bedaquiline to all RR/MDR-TB patients, were projected to reduce TB mortality and RR/MDR-TB incidence by 13% and 28%, compared to the base-case scenario, respectively.

Table 3. Model projected TB mortality and incidence in 2035: base-case and hypothetical scenarios

Strategy group	Target patients	Strategy	TB mortality (per 100,000 population)		TB incidence (per 100,000 population)	
			RR/MDR	Total	RR/MDR	Total
Status quo - base case			**14.5**	**68.6**	**30.8**	**297.8**
Single target strategies						
1	TB/HIV	**ART coverage, TB**	14.1	67.1	30.4	294.5
	HIV	**ART coverage**	10.6	50.4	24.3	247.1
	TB/HIV	**ART retention, TB**	13.5	64.2	29.8	290.1
	HIV	**ART retention**	12.3	58.5	27.8	274.5
	HIV	**IPT coverage**	11.4	55.5	25.2	256.4
	HIV	**IPT completion**	12.1	58.9	26.4	267.1
2	TB	**Public delay**	14.4	67.4	30.6	292.3
	TB	**Private referral**	14.4	68.3	30.7	296.4
	TB	**Misdiagnoses**	14.1	59.9	30.4	286.2
	TB/MDR	**Xpert access**	12.3	66.0	27.2	292.3
	TB/MDR	**Xpert delay**	14.3	67.2	30.3	291.9
3	DS/INHR	**Initial LTFU, DS/INHR**	14.7	57.4	31.5	285.1
	RR/MDR	**Initial LTFU, RR/MDR**	10.1	64.5	24.8	293.3
4	DS/INHR	**Treatment LTFU, DS/INHR**	14.7	66.3	31.2	291.5
	RR/MDR	**Treatment LTFU, RR/MDR**	12.8	67.1	27.7	295.4
	MDR	**Short MDR**	9.3	63.6	24.9	293.3
	MDR	**Bedaquiline**	9.5	63.9	26.3	294.4
Combination strategies						

1	TB/HIV	**Optimize ART, TB**	13.4	63.6	29.9	290.1
	HIV	**Optimize ART**	9.4	44.5	22.9	235.7
	HIV	**Optimize IPT**	11.5	56.1	25.3	258.1
	HIV	**ART/IPT adherence**	10.3	49.8	23.9	244.7
2	TB/MDR	**Optimize Xpert**	12.1	64.3	26.7	284.6
	TB	**Diagnostic delay**	11.2	46.4	25.7	259.3
	TB	**Health system delay**	11.7	55.3	26.3	270.2
3	TB	**Initial LTFU**	10.3	53.2	25.4	280.5
4	TB	**Treatment LTFU**	13.0	64.8	28.1	289.1
	RR/MDR	**MDR treatment**	9.3	63.6	24.9	293.3
3 & 4	DS/INHR	**All LTFU, DS/INHR**	14.9	55.4	31.9	278.9
	RR/MDR	**All LTFU, RR/MDR**	8.7	63.2	21.8	291.0
	TB	**All LTFU, all TB**	8.9	49.7	22.5	271.7
1, 3-4	TB/HIV	**HIV/TB adherence**	8.4	46.8	22.0	265.8
2 & 4	TB/MDR	**Diagnostics & treatment**	6.9	59.4	22.1	281.1
2-4	DS/INHR	**Strengthen care, DS/INHR**	14.7	47.3	31.8	268.0
2-4	RR/MDR	**Strengthen care, RR/MDR**	8.0	53.2	20.7	273.3
2-4	TB	**Strengthen care, all TB**	8.3	40.5	21.7	254.8

Discussion

This study compared the impact of strategies which targeted different stages of the DS-TB and RR/MDR-TB cascades of care, on projected TB mortality and RR/MDR-TB incidence in South Africa between 2017 and 2035. Our model estimated that single target strategies targeting the prevention of TB disease among people living with HIV through increased ART or IPT coverage, would lead to the greatest reductions in TB mortality and RR/MDR-TB incidence. Our model predicted that compared to continued use of the standard injectable-based MDR-TB regimen of 18 to 24 months, expanding access to bedaquiline-based, injection-free, MDR regimens, or using a shortened regimen, would reduce TB mortality and RR/MDR-TB incidence in 2035 by 7% and 19%, respectively. However, strengthening care provided to RR/MDR-TB patients, to reduce initial and treatment losses to follow-up, would lead to greater reductions in TB mortality and RR/MDR-TB incidence of 8% and 29%, respectively. This shows that providing higher quality of care to patients could have equal or greater benefits than introducing better MDR-TB regimens.

Our study had several limitations. First, our model was calibrated according to publicly available epidemiological data on TB and HIV in South Africa,[11,12] which are estimated from country-level notification data (prone to missingness and misclassification errors). These estimates of TB/HIV incidence, prevalence and mortality are associated to several potential sources of uncertainty (e.g. imputation techniques for missing data, or estimation models used).[39] Thus, our model projections could be biased if these TB and HIV estimates are inaccurate. However, the main objective of the study was not to make projections on the TB epidemic, but rather to compare the potential effectiveness of different strategies. Thus, any biases in model projections should have little impact on the relative differences in TB mortality and incidence when comparing different scenarios. Second, we made several assumptions to limit the complexity of the model, but based them on published evidence as best as possible. For example, one main assumption was that drug-resistance patterns and HIV co-infection did not affect initial and treatment losses to follow-up. This is supported by several recent cohort studies.[40,41] We also assumed that the introduction of Xpert testing did not affect the proportion of patients correctly diagnosed (i.e. did not change the sensitivity or specificity of TB diagnostics). South African TB diagnostic guidelines recommends aspirates (or cough sputum) as the main sample type for testing, for which Xpert has a sensitivity of 83.1% (95% CI 71.4–90.7%) and specificity of over 98.7%, compared to traditional culture methods.[42] Thus, under our model assumption, it is possible that the proportion of active TB cases diagnosed via Xpert could be overestimated. However, our base-case scenario was based on the TB diagnostic rate reported in 2016, by which time nearly 73.2% of all notified TB cases were diagnosed via Xpert.[11] Thus, the impact of Xpert's lower sensitivity on our model projections is likely minimal.

Finally, we did not incorporate cost estimates in our model, and thus we were not able to compare cost-effectiveness of different strategies. This would be particularly interesting to explore for strategies that may incur greater costs than others, such as expanding access to bedaquiline-based MDR regimens or Xpert for diagnosis. Future studies should compare the cost-effectiveness of different strategies, and also explore the potential for less costly ways to improve existing care and increase retention-in-care for all TB patients. For example, recent

cohort studies[43,44] suggest substituting directly observed therapy with self-administered therapy has the potential to relieve health worker burden and public resources, while enhancing the quality of patient-centred care.

Despite these limitations, our study had many strengths. We maximized the validity of our model by obtaining parameter estimates from systematic reviews, and by pooling estimates from published studies using appropriate statistical methods, when possible. Furthermore, our study incorporated recently published estimates on the effectiveness of newly recommended second-line regimen (i.e. the shorter MDR regimen and a bedaquiline-based, injection-free regimen).[38-39] Thus, we were able to estimate the potential impact of expanding access to new MDR treatment in a high-burden setting. We also compared a wide variety of strategies and framed them according to the cascades of TB care, which allow for a nuanced exploration of how targeting different stages along the cascade could affect TB mortality and incidence.

Previous modeling studies have explored some similar strategies, such as a recent study by Houben et al.,[45] which included models from six different modelling groups, and had also projected the impact of improving post-diagnosis care (such as increasing access to psychosocial support and providing adherence counselling). Houben et al. projected TB incidence and mortality between 2015 and 2026, and found "improvements in linkage to care and treatment success" among TB patients would reduce TB incidence by an additional 8% (0-25%) compared to the base-case scenario. Similarly, our study found that by reducing initial losses to follow-up (by improving linkage to care) and treatment losses to follow-up (thereby increasing treatment success) among all TB patients, the overall TB incidence would be reduced by approximately 9% more than in the base-case scenario, and more specifically, would further reduce RR/MDR-TB incidence by a further 27%.

One important finding from our study is that although improving HIV care could greatly reduce TB mortality and incidence, focusing on improving TB care – on its own – could provide equal if not greater benefits. Thus, national health agencies should strive to provide high quality, patient-centred, care to all TB patients, not only to HIV-TB coinfected persons. Furthermore, our

model findings are generalizable to other high RR/MDR-TB burden settings, even in the absence of an HIV co-epidemic. Importantly, improving existing TB care and infrastructure would likely have greater long-term benefits than introducing new, potentially costly, MDR regimens. Additionally, national TB programs should be cautious of focusing on improving care among DS/INHR-TB patients or new patients alone – without simultaneously improving care for RR/MDR-TB patients – as this could actually result in an increase in RR/MDR-TB incidence, with marginal impact on TB mortality.

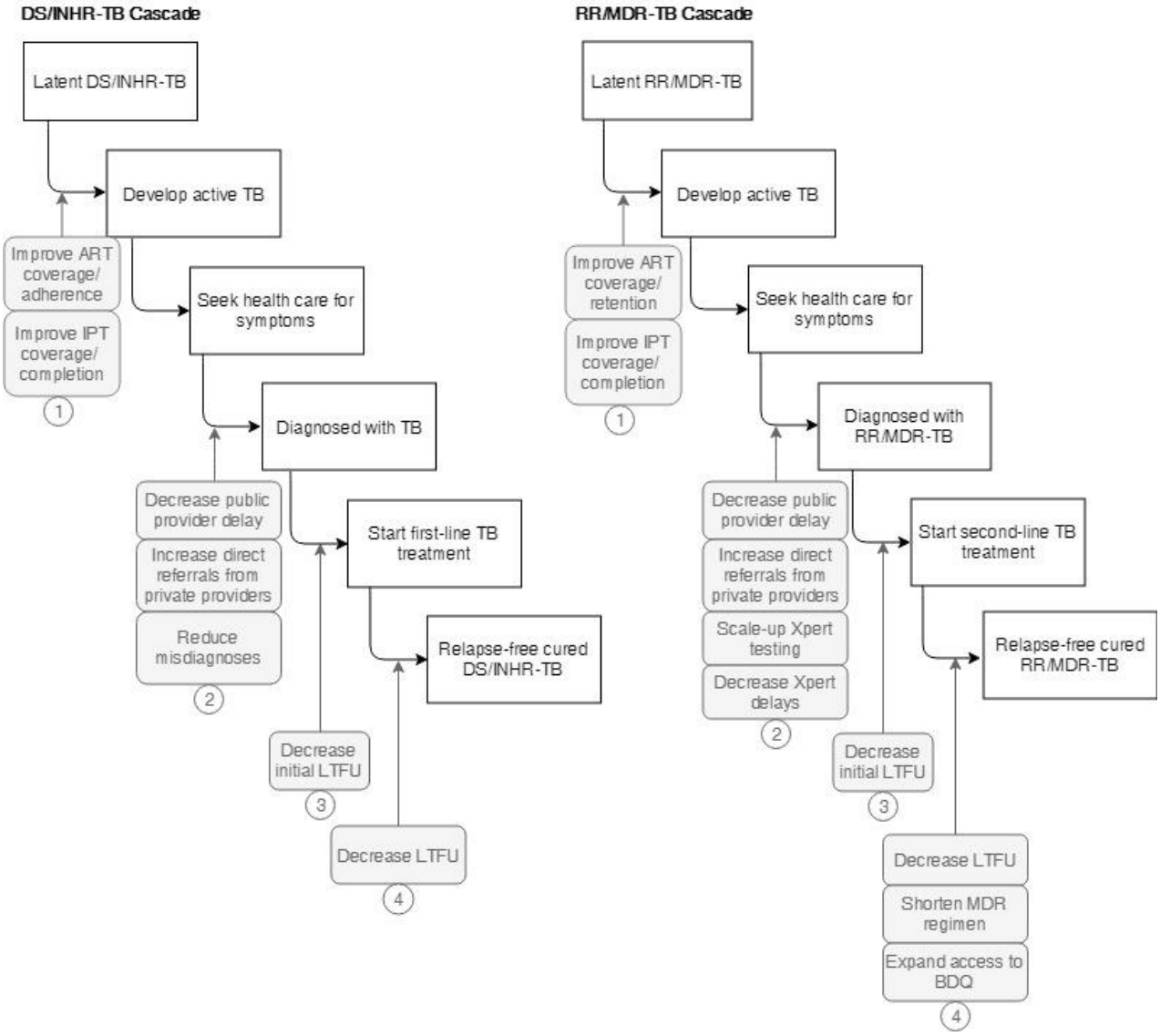
Conclusion

Our model projects that increasing ART and IPT coverage among people living with HIV would have the greatest impact on TB mortality and RR/MDR-TB incidence. However, when comparing strategies that target multiple stages along the care cascade, the most effective combination involved strengthening existing care to reduce treatment delays, as well as losses to follow-up, among all TB patients. This strategy was more effective than introducing new shortened, or injection-free, MDR regimens.

Acknowledgements

SL was supported by a Vanier Canada Graduate Scholarship.

Fig. 1 – Cascades of care for DS/INHR-TB and RR/MDR-TB



*The square boxes represent the different disease and treatment stages along the cascades of care; the shaded boxes represent potential corrective strategies targeting different stages; and the numbers reflect groups of strategies that target the same stage of the cascade.

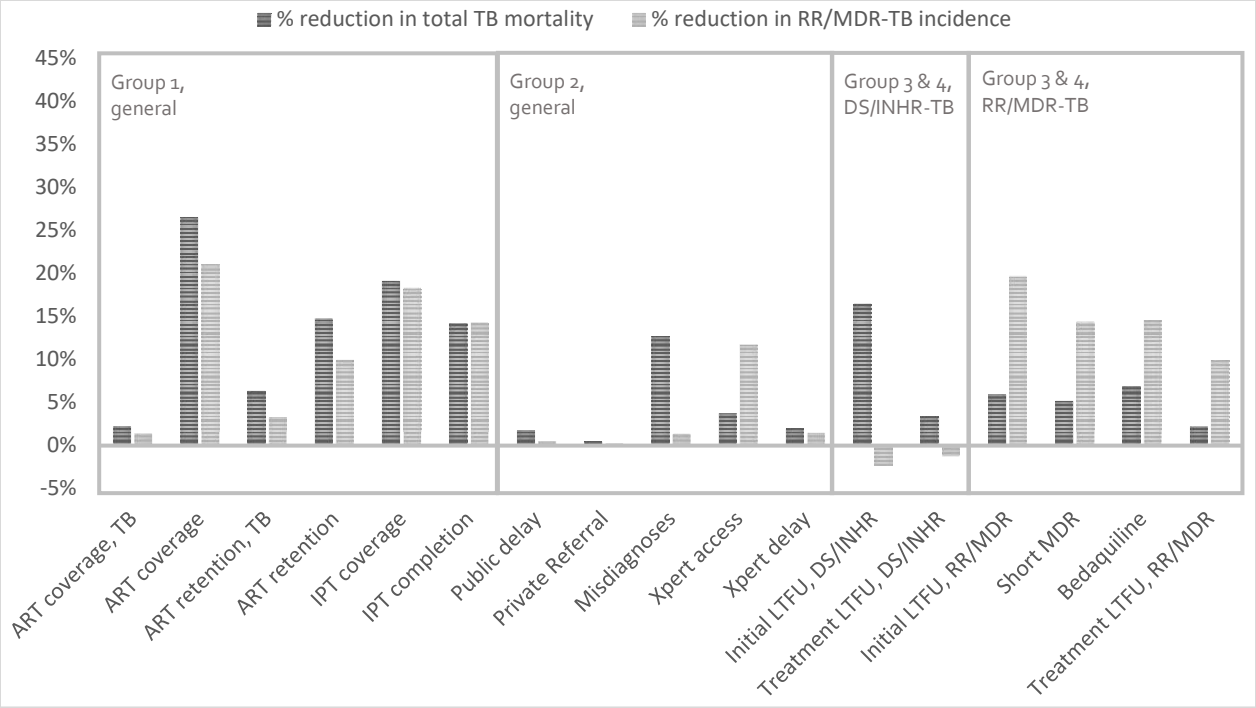


Figure 2. Effect of single target strategies on reducing TB mortality and RR/MDR-TB incidence. Each group of strategies targets a different stage in either or both cascades of care for DS/INHR-TB and RR/MDR-TB. Group 1, general, strategies target people living with HIV with or without active TB disease, and aim to reduce HIV-related TB incidence and mortality by increasing ART or IPT coverage and retention/completion. Group 2, general, strategies target all TB patients by reducing diagnostic errors and delays. Group 3 & 4 strategies target either DS/INHR-TB or RR/MDR-TB patients by reducing initial and treatment losses to follow-up (LTFU), and by expanding access to newer second-line regimens to improve RR/MDR-TB treatment outcomes. See Table 2 for description of each strategy and Table 3 for detailed results.

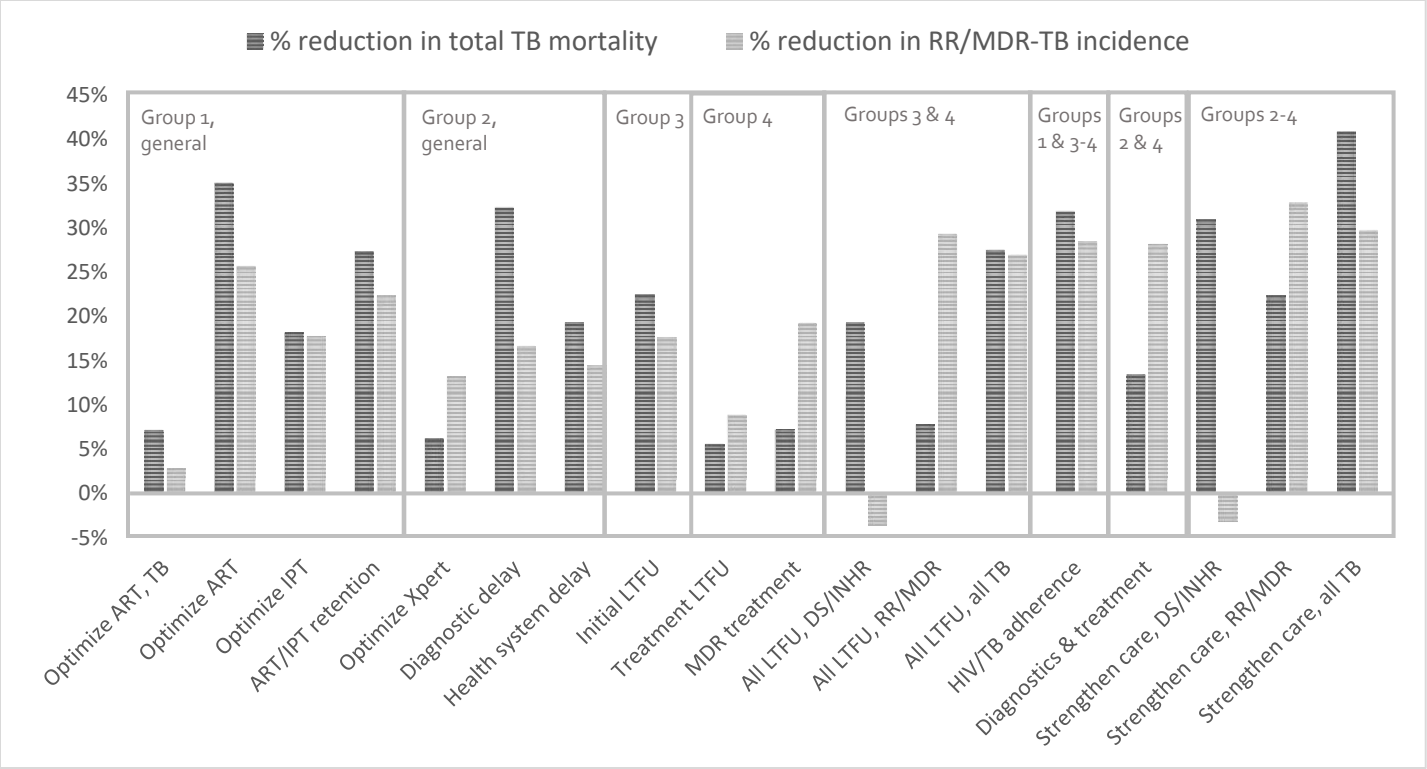


Figure 3. Effect of combined strategies on reducing TB mortality and RR/MDR-TB incidence. Each group of strategies targets a different stage in either or both cascades of care for DS/INHR-TB and RR/MDR-TB. Group 1 strategies target people living with HIV with or without active TB disease, and aim to reduce HIV-related TB incidence and mortality by increasing ART or IPT coverage and retention/completion. Group 2 strategies target all TB patients by reducing diagnostic errors and delays. Group 3 strategies aim to reduce initial LTFU. Group 4 strategies aim to improve treatment outcomes. See Table 2 for description of each strategy and Table 3 for detailed results.

References

1. World Health Organization [WHO]. Global Tuberculosis Report 2017. Geneva, Switzerland: World Health Organization, 2017.
2. WHO, WHO treatment guidelines for drug-resistant tuberculosis: 2016 Update - October 2016 revision. Geneva, Switzerland: World Health Organization, 2016.
3. National Department of Health. Media Statement: New Bedaquiline data shows reduction in TB mortality cases. Pretoria, South Africa: National Department of Health; 2018.

4. Borisov SE, Dheda K, Enwerem M, Romero Levet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J, 2017; 49(5): pii: 1700387.
5. Ahmad Khan F, Salim MAH, du Cros P, Casas EC, Khamraev A, Sikhondze W, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. Eur Respir J, 2017;50(1) : pii: 1700061.
6. Vassall A, Siapka M, Foster N, Cunnama L, Ra L, Fielding K, McCarthy K, Churchyard G, Grant A, Sinanovic E. Cost-effectiveness of Xpert MTB/RIF for tuberculosis diagnosis in South Africa: a real-world cost analysis and economic evaluation. Lancet, 2017; 5(7): e710-19.
7. National Institute for Communicable Diseases. South African Tuberculosis Drug Resistance Survey 2012-14. Johannesburg, South Africa: National Institute for Communicable Diseases, Division of the National Health Laboratory Service, 2016.
8. Abdool Karim SS, Churchyard GJ, Abdool Karim Q, Lawn SD. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. Lancet, 2009; 374(9693): 921-33.
9. Oxlade O, Schwartzman K, Benedetti A, Pai M, Heymann J, Menzies D. Developing a tuberculosis transmission model that accounts for changes in population health. Med Decis Mak, 2011; 31: 53–68.
10. Law S, Piatek AS, Vincent C, Oxlade O, Menzies D. Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study. Lancet Public Health, 2017;2(1):e47-e55.
11. WHO. WHO TB burden estimates. Geneva, Switzerland: WHO; 2018. Downloaded from http://www.who.int/tb/country/data/download/en/ on February 2, 2018.
12. UNAIDS. UNAIDS 2018 estimates. Geneva, Switzerland: UNAIDS; 2018. Downloaded from http://aidsinfo.unaids.org/ on February 2, 2018.

13. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Trop Med Int Health, 2011; 15(s1):1-15.

14. Golub JE, Pronyk P, Mohapi L, Thsabangu N, Moshabela M, Struthers H. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS, 2009; 23(5): 631-6.

15. Hirschowitz R, Sekwati WM, Budlender D. South Africa in transition: Selected findings from the October household survey of 1999 and changes that have occurred between 1995 and 1999. Pretoria, South Africa: Statistics South Africa; 2001.

16. Van Wyk SS, Enarson DA, Beyers N, Lombard C, Hesseling AC. Consulting private health care providers aggravates treatment delay in urban South African tuberculosis patients. Int J Tuberc Lung, 2011; 15(8):1069-76.

17. Pronyk PM, Makhubele MB, Hargreaves JR, Tollman SM, Hausler HP. Assessing health seeking behaviour among tuberculosis patients in rural South Africa. Int J Tuberc Lung, 2001; 5(7): 619-27.

18. Meintjes G, Schoeman H, Morroni C, Wilson D, Maartens G. Patient and provider delay in tuberculosis suspects from communities with a high HIV prevalence in South Africa: A cross-sectional study. BMC Infectious Diseases, 2008; 8:72.

19. Barker RD, Millard FJC, Malatsi J, Mkoana L, Ngoatwana T, Agarawal S, de Valliere S. Traditional healers, treatment delay, performance status and death from TB in rural South Africa. Int J Tuberc Lung, 2006; 10(6):670–675.

20. Hanrahan CF, Dorman SE, Erasmus L, Koornhof H, Coetzee G, et al. The Impact of Expanded Testing for Multidrug Resistant Tuberculosis Using Genotype MTBDRplus in South Africa: An Observational Cohort Study. PLoS ONE, 2012; 7(11): e49898.

21. Cox HS, Daniels JF, Muller O, Nicol MP, Cox V, van Cutsem G, et al. Impact of Decentralized Care and the Xpert MTB/RIF Test on Rifampicin-Resistant Tuberculosis Treatment Initiation in Khayelitsha, South Africa. Open Forum Infectious Diseases, 2015; 2(1): ofv014.

22. Jacobson KR, Theron D, Kendall EA, Franke MF, Barnard M, van Helden PD, et al. Implementation of GenoType MTBDR*plus* Reduces Time to Multidrug-Resistant Tuberculosis Therapy Initiation in South Africa . Clin Infect Dis, 2013; 56(4): 503–508.
23. Iruedo J, O'Mahony D, Mabunda S, Wright G, Cawe B. The effect of the Xpert MTB/RIF test on the time to MDR-TB treatment initiation in a rural setting: a cohort study in South Africa's Eastern Cape Province. BMC Infect Dis, 2017; 17: 91.
24. Cox H, Dickson-Hall L, Ndjeka N, van't Hoog A, Grant A, Cobelens F, et al. Delays and loss to follow-up before treatment of drug-resistant tuberculosis following implementation of Xpert MTB/RIF in South Africa: A retrospective cohort study. PLoS Med, 2017; 14(2): e1002238.
25. Naidoo P, Theron G, Rangaka MX, Chihota VN, Vaughan L, Brey ZO, et al. The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. J Infect Dis, 2017;216(S7): S702–13.
26. Claassens MM, du Toit E, Dunbar R, Lombard C, Enarson DA, Beyers MW, et al. Tuberculosis patients in primary care do not start treatment. What role do health system delays play? Int J Tuberc Lung Dis, 2013; 17(5):603–607.
27. Botha E, Den Boon S, Verver S, Dunbar R, Lawrence KA, Bosman M, et al. Initial default from tuberculosis treatment: how often does it happen and what are the reasons? Int J Tuberc Lung Dis, 2008; 12(7):820–823.
28. Evans D, Schnippel K, Govathson C, Sineke T, Black A, Long L, et al. Treatment initiation among persons diagnosed with drug resistant tuberculosis in Johannesburg, South Africa. PLoS ONE, 2017: 12(7): e0181238.
29. Ebonwu JI, Tint KS, Ihekweazu C. Low treatment initiation among multi-drug resistant tuberculosis patients in Gauteng, South Africa, 2011. Int J Tuberc Lung Dis, 2013; 17(8):1043-8.
30. Marx FM, Dunbar R, Enarson DA, Beyers N. The Rate of Sputum Smear-Positive Tuberculosis after Treatment Default in a High-Burden Setting: A Retrospective Cohort Study. PLoS ONE, 2012; 7(9): e45724.

31. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol, 2014;14:135.
32. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. J Clin Epidemiol 2008; 61(1):41-51.
33. Moyo S, Cox HS, Hughes J, Daniels J, Synman L, De Azevedo V, et al. (2015) Loss from Treatment for Drug Resistant Tuberculosis: Risk Factors and Patient Outcomes in a CommunityBased Program in Khayelitsha, South Africa. PLoS ONE 10(3): e0118919.
34. Health Systems Trust. The 90-90-90 Compendium: An introduction to 90-90-90 in South Africa. Volume 1. Durban, South Africa: Health Systems Trust; 2016.
35. South African National AIDS Council. National Strategic Plan on HIV, STIs and TB 2012–2016. Pretoria: South African National AIDS Council; 2011.
36. van Hoorn R, Jaramillo E, Collins D, Gebhard A, van den Hof S. The Effects of Psycho-Emotional and Socio-Economic Support for Tuberculosis Patients on Treatment Adherence and Treatment Outcomes - A Systematic Review and Meta-Analysis. PLoS One, 2016; 11(4):e0154095.
37. Law S, Daftary A, O'Donnell M, Padayatchi N, Calzavara L, Menzies D. Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review. Eur Resp J, 2018; (in press).
38. WHO. The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva, Switzerland: World Health Organization, 2018.
39. Glaziou P, Sismanidis C, Pretorius C, Floyd K. (2016) Methods used by WHO to estimate the Global burden of TB disease. arXiv:1603.00278 [q-bio.QM].
40. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, Weyer K, Lancaster J, van der Walt M. Outcomes of Multi-Drug Resistant Tuberculosis (MDR-TB) among a Cohort of South African Patients with High HIV Prevalence. PLoS ONE, 2011; 6(7): e20436.

41. Kigozi G, Heunis C, Chikobvu P, Botha S, van Rensburg D. Factors influencing treatment default among tuberculosis patients in a high burden province of South Africa. International Journal of Infectious Diseases, 2017; 54:95-102.
42. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. (2014). Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. ERJ 44: 435-46.
43. Metcalfe JZ, O'Donnell MR, Bangsberg DR. Moving beyond directly observed therapy for tuberculosis. PLoS Med 2015l 12(9):e1001877.
44. Benbaba S, Isaakidis P, Das M, Jadhav S, Reid T, Furin J. Direct Observation (DO) for Drug-Resistant Tuberculosis: Do we really DO? PLoS One 2015;10:e0144936.
45. Houben RMGJ, Menzies NA, Sumner T, Huynh GH, Arinaminpathy N, Goldhaber-Fiebert JD, et al. Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. Lancet Glob Health, 2016;4(11):e806-e815.

CONCLUSION

This thesis used several different quantitative and qualitative methods to explore TB patient treatment journeys and their relationship to the emergence of drug resistance in India and South Africa. Modeling methods were used to estimate the effects of potential interventions targeted at increasing access and reducing delays to appropriate treatment, and improving patient retention-in-care. This work met the stated research objectives as follows:

1) In India, to estimate the impact of seeking and receiving TB care from different health sectors (public, private and informal), as well as the potential impact of improving different elements of TB care in the different sectors, on MDR-TB incidence, prevalence and mortality.

The published manuscript from the first study examined the complex health system-related issues across all health sectors in India, and how these issues—including lengthy delays in care-seeking—affected the emergence of drug resistance in India. Between 2012 and 2032, the decision analytic model projected a modest increase in isoniazid-resistant tuberculosis and a nearly two-fold increase in rifampicin-resistant tuberculosis or multidrug-resistant tuberculosis, and a substantial shift from a treatment-generated (i.e. acquired) multidrug-resistant tuberculosis epidemic to one that is transmission-generated (i.e. primary). Despite the large proportions of TB patients who seek and receive care from non-public sectors, the public sector was projected to be the largest contributor to drug-resistant tuberculosis. This was due to two main reasons. First, the larger number of patients treated in the public sector – who all received rifampicin as part of standard therapy – compared to other sectors. Second, the high rate of poor treatment adherence among publicly treated patients increased the risk of acquiring drug resistance. Evidence-based strategies to improve provider practices and patient adherence, particularly in the public sector, are urgently needed to prevent this.

2) In South Africa, to explore TB treatment journeys, as well as issues affecting adherence and retention-in-care, among patients with drug-susceptible and drug-resistant TB.

The second study explored TB patient treatment journeys in Cape Town, South Africa. This

qualitative study revealed that patient-provider trust played an important role in retaining patients in TB care and in their adherence to treatment. Patients who felt they were not trusted by their providers, and as a result had lesser trust in their care, had more difficulties discussing adherence barriers and problems with their providers. Thus, in the absence of trust – which was commonplace in the patient-provider relationships explored – patients were more likely to have poor adherence and be lost to follow-up, leading to a higher risk of acquiring drug resistance. On the other hand, lack of provider trust towards patients could limit available treatment options and access to financial support or social protection. This was particularly detrimental for MDR-TB patients who faced longer treatment journeys. The research highlights the need for strategies to build patient-provider trust, particularly in a way that circumvents the rigidity of current standardized TB treatment and management practices, including directly observed therapy.

3) To systematically review the effectiveness of psychosocial, educational and material support interventions in improving treatment adherence and retention-in-care among MDR-TB patients.

This systematic review identified 25 studies that described a broad range of adherence support interventions, all of which included some degree of educational and psychosocial counselling, as well as a variety of material support. Most importantly, the review found the provision of individual counselling support, or home visits by health workers, throughout treatment was associated with fewer losses to follow-up than when these interventions were provided only at the start of treatment, or not at all. Economic support through reimbursement for travel and rent expenses, as well as compensation for lost wages, was also effective in reducing losses to follow-up. This review provides the motivation for increased psychosocial and economic support throughout treatment for MDR-TB patients. The review also suggested the need for trials that directly compared psychosocial support with standard patient support including directly observed therapy.

4) In South Africa, to estimate the impact of strategies targeting different stages of the cascade of TB care to reduce the incidence and mortality due to drug-susceptible and drug-resistant TB in South Africa.

This modelling study compared TB/HIV management and treatment strategies that target single, or a combination of, stages of the cascade of TB care in South Africa. Among single-target strategies, increasing antiretroviral or isoniazid prophylactic treatment coverage among people living with HIV would lead to the greatest reductions in TB mortality and MDR-TB incidence by the year 2035. On the other hand, strategies that reduced initial or treatment losses to follow-up among non-MDR TB patients, would lead to relatively large reductions in mortality, but increase MDR-TB incidence, compared to a status quo scenario. However, when strategies were combined to strengthen existing care for among *all* TB patients (including DS-TB and MDR-TB patients), the model projected the largest reductions in MDR-TB incidence and TB mortality by the year 2035. These findings suggest that national TB programs should focus on improving existing TB care – that is, reducing treatment delays and improving retention-in-care – in order to prevent further emergence of MDR-TB, and decrease TB mortality. This is particularly important in the context of new TB drugs and diagnostic tests being introduced globally, which not only might take away from efforts to strengthen existing care, but also potentially introduce further, or amplify, drug resistance without addressing the root causes of the emergence of drug resistance.

Implications of the research

This thesis emphasizes the need for more intensive and concerted efforts to improve adherence and retention-in-care within public sectors, where the great majority of TB patients are treated. The two modelling studies conducted in India and South Africa found that poor treatment adherence, as well as losses to follow-up before and during treatment, were the greatest contributors to TB mortality and the emergence of MDR-TB. These studies also showed that strategies which improve care for drug-sensitive patients without improving care for MDR-TB patients could lead to greater increases in MDR-TB incidence.

The findings from the modelling studies were reinforced by the qualitative study and the systematic review. The qualitative study demonstrated the importance of trust between TB patients and their providers, as this was a key determinant of treatment adherence and losses to follow-up. Patients who lacked trust towards their providers, or who were not trusted by their providers, had more difficulties staying adherent to treatment. Thus, a strategy to strengthen existing TB care should emphasize early trust-building between providers and patients. This finding was supported by the systematic review, which showed that providing psychosocial support throughout treatment, via counselling or home visits, greatly reduced losses to follow-up. By providing psychosocial support to TB patients, national TB program could create opportunities for patients to share treatment-related problems with providers, and enhance patient-provider trust.

There has been growing interest among TB researchers to explore lengthy treatment journeys, particularly in settings such as India where there is a large non-public sector. However, there remains a paucity of qualitative research exploring treatment journeys in detail, as well as research to explore the impact of important junctures along the journeys on the emergence of drug resistance. This thesis research adds to this literature by exploring TB treatment journeys using different methods, as well as in different settings. By considering patient experiences with TB care as long journeys, this research draws attention to stages along treatment journeys where care could be improved in order to increase treatment success rates, and prevent amplification of drug resistance. This is a different approach from most other research which focuses only on one stage along the cascade of care, and does not consider what happens before and after starting TB treatment, as well as what happens during treatment interruptions and after previous courses of treatment.

Most notably, by exploring patient journeys from beginning to end, the qualitative study revealed that during TB treatment, it is not only important for patients to trust their providers, but it is equally important for providers to trust their patients. The trust that providers have in their patients could affect their behaviours – including treatment and care-related decisions – as

well as the behaviours of their patients. This finding is unlikely to be unique to this particular study setting nor disease, yet it is not discussed in other published literature on patient-provider trust (Calnan 2007; Thom 1997; Hall 2991). This finding also challenges the commonly cited definition of trust, which assumes that trust is a one-way phenomenon where the trustor is powerless or vulnerable, and the trustee has all the power and knowledge (Hall 2001). This research showed that both patients and providers – regardless of the power and knowledge imbalance – need to trust each other during TB treatment in order to improve the chances of treatment success.

The development and implementation of strategies to improve retention-in-care during TB treatment should be evidence-based. This thesis demonstrated the considerable impact that improving existing care to TB patients could have on the emergence of drug-resistant TB, as well as on TB mortality. Furthermore, it showed that providing psychosocial support and building reciprocal trust between patients and providers could greatly improve retention-in-care. There is a great need now for conducting quality, adequately powered, experimental trials to compare the effectiveness (and cost-effectiveness) of different interventions to improve adherence and retention-in-care, particularly during MDR-TB treatment. As new drugs such as bedaquiline, clofazimine and linezolid are rolled out globally, it is more important than ever to provide patient-centred care that builds trust, promotes better adherence, and improves retention-in-care. If these strategies are not implemented soon, then emergence of a new epidemic of resistance to these new drugs seems inevitable.

BIBLIOGRAPHY

Abdool Karim SS, Churchyard GJ, Abdool Karim Q, Lawn SD. (2009). HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. Lancet; 374(9693): 921-33.

Acha J, Sweetland A, Guerra D, Chalco K, Castillo H, Palacios E. (2007). Psychosocial support groups for patients with multidrug-resistant tuberculosis: Five years of experience. Glob Public Health;2:404-17.

Achanta S, Jaju J, Kumar AM, et al. (2013). Tuberculosis management practices by private practitioners in Andhra Pradesh, India. PLoS One; 8: e71119.

Ahmad Khan F, Salim MAH, du Cros P, Casas EC, Khamraev A, Sikhondze W, et al. (2017). Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. Eur Respir J;50(1) : pii: 1700061.

Alene KA, Yi HZ, Viney K, McBryde ES, Yang KY, Bai LQ, Gray DJ, Clements ACA, Xu ZH. (2017). Treatment outcomes of patients with multidrug-resistant and extensively drug resistant tuberculosis in Hunan Province, China. BMC Infect Dis;17.

Ambe G, Lonnroth K, Dholakia Y, et al. (2005). Every provider counts: effect of a comprehensive public-private mix approach for TB control in a large metropolitan area in India. Int J Tuberc Lung Dis; 9: 562–68.

Anandhi CL, Nagaraj VK, Kumar R. (2002). Knowledge and practice pattern of non-allopathic indigenous medical practitioners regarding tuberculosis in a rural area of India. Indian J Tuberc; 6: 553–55.

Ananthakrishnan R, Jeyaraju AR, Palani G, Sathiyasekaran BWC. (2012). Care seeking behavior

of the TB patients who were registered in an urban government tuberculosis control in Chennai, Tamilnadu, India. J Clin Diagn Res; 6: 990–93.

Atkins S, Biles D, Lewin S, Ringsberg K, & Thorson A. (2010). Patients' experiences of an intervention to support tuberculosis treatment adherence in South Africa. Journal of Health Services Research & Policy, 15(3), 163-70.

Azadi M, Bishai DM, Dowdy DW, Moulton LH, Cavalcante S, Saraceni V, et al. (2014). Cost-effectiveness of tuberculosis screening and isoniazid treatment in the TB/HIV in Rio (THRio) Study. Int J Tuberc Lung Dis, 18(12), 1443-1448.

Aziz MA. (2004). Anti-tuberculosis drug resistance in the world: third global report: the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance, 1999–2002. Geneva, Switzerland: World Health Organization.

Baral SC, Aryal Y, Bhattrai R, King R, Newell JN. (2014). The importance of providing counselling and financial support to patients receiving treatment for multi-drug resistant TB: mixed method qualitative and pilot intervention studies. BMC Public Health ;14:46.

Barker RD, Millard FJC, Malatsi J, Mkoana L, Ngoatwana T, Agarawal S, de Valliere S (2006). Traditional healers, treatment delay, performance status and death from TB in rural South Africa. Int J Tuberc Lung, 2006; 10(6):670–675.

Barnhoorn F, Adriannse H. (1992). In search of factors responsible for noncompliance among tuberculosis patients in Wardha district, India. Soc Sci Med; 34: 291–306.

Bastard M, Sanchez-Padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, Bonnet M. (2015). Effects of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia. J Infect Dis;211:1607-15.

Bate R, Jensen P, Hess K, Mooney L, Milligan J. (2013). Substandard and falsified anti-tuberculosis drugs: a preliminary field analysis. Int J Tuberc Lung Dis; 17: 308–11.

Baxi RK, Shah AR. (2006). Management of TB by the general practitioners of Vadodara city. Indian J Community Med; 31: 10–12.

Beach, M. C., Keruly, J., Moore, R. D. (2006). Is the quality of the patient-provider relationship associated with better adherence and health outcomes for patients with HIV? Journal of General Internal Medicine; 21: 661–665.

Benbaba S, Isaakidis P, Das M, Jadhav S, Reid T, Furin J. (2015). Direct Observation (DO) for Drug-Resistant Tuberculosis: Do we really DO? PLoS One;10:e0144936.

Borisov SE, Dheda K, Enwerem M, Romero Levet R, D'Ambrosio L, Centis R, et al. (2017). Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J; 49(5): pii: 1700387.

Botha E, Den Boon S, Verver S, Dunbar R, Lawrence KA, Bosman M, et al. (2008). Initial default from tuberculosis treatment: how often does it happen and what are the reasons? Int J Tuberc Lung Dis; 12(7):820–823.

Briggs AH, Weinstein MC, Fenwick EA., Karnon J, Sculpher M., Paltie D, on behalf of the ISPOR-SMDR Modeling Good Research Practices Task Force. (2013). Model Parameter Estimation and Uncertainty Analysis: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group - 6. Med Dec Mak; 32: 722-732.

Brust JC, Shah NS, Scott M, Chaiyachati K, Lygizos M, van der Merwe TL, et al. (2012). Integrated, home-based treatment for MDR-TB and HIV in rural South Africa: an alternate model of care. Int J Tuberc Lung Dis;16:998-1004.

Buregyeya, E., Mitchell, E.M.H, Rutebemberwa, E., Colebunders, R., Criel, B., Kiguli, J., & Nuwaha, F. (2012). Acceptability of masking and patient separation to control nosocomial Tuberculosis in Uganda: a qualitative study. Journal of Public Health; 20(6): 599-606.

Burgos M, DeRiemer K, Small PM, Hopewell PC, Daley CL. (2003). Effect of drug resistance on the generation of secondary cases of tuberculosis. J Infect Dis; 188: 1878–84.

Burtscher, D., Van den Bergh, R., Toktosunov, U., Angmo, N., Samieva, N., & Rocillo Arechaga, E. P.(2016). "My Favourite Day is Sunday": Community Perceptions of (Drug-Resistant) Tuberculosis and Ambulatory Tuberculosis Care in Kara Suu District, Osh Province, Kyrgyzstan. PLoS One; 11(3): e0152283.

Calnan, M., & Rowe, R. Trust and Health Care. (2007). Sociology Compass; 1/1 (2007):283-308.

Campbell, C., Scott, K., Skovdal, M., Madanhire, C., Nyamukapa, C., & Gregson, S. (2015). A good patient? How notions of 'a good patient' affect patient-nurse relationships and ART adherence in Zimbabwe. BMC Infect Dis; 15: 404.

Canetti, G. (1969). Advances in techniques of testing mycobacterial drug sensitivity, and the use of sensitivity tests in tuberculosis control programmes. Bull World Health Organ;41: 21-43.

Canetti, G. (1965). Present aspects of bacterial resistance in tuberculosis. Am Rev Respir Dis; 92(5): 687-703.

Carspecken PF. (1996). Critical ethnography in educational research: A theoretical and practical guide. New York: Routledge.

Caws M, Duy PM, Tho DQ, Lan NTN, Farrar J. (2006). Mutations prevalent among rifampin-and isoniazid-resistant Mycobacterium tuberculosis isolates from a hospital in Vietnam. Journal of clinical microbiology; 44: 2333–2337.

Central TB Division. (2014). TB India 2014: Revised National TB Control Programme Annual Status Report. New Delhi: Directorate General of Health Services, Ministry of Health and Family Welfare.

Channing, L., & Sinanovic, Edina. (2014). Modelling the cost-effectiveness of a new infant vaccine to prevent tuberculosis disease in children in South Africa. Cost Eff Resour Alloc; 12:20.

Charles, N., Thomas, B., Watson, B., Raja Sakthivel, M., Chandrasekeran, V., & Wares, F. (2010). Care seeking behavior of chest symptomatics: a community based study done in South India after the implementation of the RNTCP. PLoS One; 5(9): 0012379.

Charmaz, K. Grounded theory. (1995).In Smith, J., Harré, R., Langenhove, L. (Eds.), Rethinking methods in psychology (pp. 27–65). London: Sage.

Charmaz, K. (2000). Grounded theory: Objectivist and constructivist methods. In Denzin, N., Lincoln, Y. (Eds.), Handbook of qualitative research (2nd ed., pp. 509–535). Thousand Oaks, CA: Sage.

City of Cape Town. (2016). State of Cape Town Report 2016. Cape Town: City of Cape Town.

Claassens MM, du Toit E, Dunbar R, Lombard C, Enarson DA, Beyers MW, et al. (2013). Tuberculosis patients in primary care do not start treatment. What role do health system delays play? Int J Tuberc Lung Dis; 17(5):603–607.

Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. (2005). Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Economics; 14: 339-347.

Coovadia, H., Jewkes, R., Barron, P., Sanders, D., & McIntyre, D. (2009). The health and health system of South Africa: historical roots of current public health challenges. Lancet; 374: 817-34.

Cox H, Dickson-Hall L, Ndjeka N, van't Hoog A, Grant A, Cobelens F, et al. (2017). Delays and loss to follow-up before treatment of drug-resistant tuberculosis following implementation of Xpert MTB/RIF in South Africa: A retrospective cohort study. PLoS Med; 14(2): e1002238.

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

Cox HS, Daniels JF, Muller O, Nicol MP, Cox V, van Cutsem G, et al. (2015). Impact of Decentralized Care and the Xpert MTB/RIF Test on Rifampicin-Resistant Tuberculosis Treatment Initiation in Khayelitsha, South Africa. Open Forum Infectious Diseases; 2(1): ofv014.

Cox HS, Kalon S, Allamuratova S, Sizaire V, Tigay ZN, Rusch-Gerdes S, Karimovich HA, Kebede Y, Mills C. (2007). Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan: treatment complexity and XDR-TB among treatment failures. PLos One;14.

Creswell J, Sahu S, Sachdeva SK, Ditiu L, Barreira D, Mariandyshev A, et al. (2014). Tuberculosis in BRICS: challenges and opportunities for leadership within the post-2015 agenda. Bull World Health Org; 92: 459-460.

Crofton J, Mitchison DA. (1948). Streptomycin resistance in pulmonary tuberculosis. BMJ;2: 1009-1015.

Daftary A & Padayatchi N. (2016). Provider perspectives on drug-resistant tuberculosis and human immunodeficiency virus care in South Africa: a qualitative case study. Int J Tuberc Lung Dis; 20(11): 1483-88.

Daftary A, Calzavara L & Padayatchi N. (2015). The contrasting cultures of HIV and tuberculosis care. AIDS;29(1): 1-4.

Daftary A & Padayatchi N. (2012). Social constraints to TB/HIV healthcare: Accounts from co-infected patients in South Africa. AIDS Care; 24(12):1480-1486.

Dandona R, Dandona L, Mishra A, Dhingra S, Venkatagopalakrishna K & Chauhan LS. (2004). Utilization of and barriers to public sector tuberculosis services in India. Natl Med J India; 17(6): 292-299.

Datta K, Bhatnagar T, Murhekar M. (2010). Private practitioners' knowledge, attitude and practices about tuberculosis, Hooghly district, India. Indian J Tuberc; 57: 199–206.

de Paoli, MM., Mills, EA., & Grønningsæter, AB. (2012). The ARV roll out and the disability grant: a South African dilemma? JAIDS; 15: 6.

Denkinger CM, Pai M, Dowdy DW. (2014). Do we need to detect isoniazid resistance in addition to rifampicin resistance in diagnostic tests for tuberculosis? PLoS One; 9: e84197.

Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. (2014). Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Resp J; 44: 435-46.

Denzin NK & Lincoln Y. (2005). Handbook of Qualitative Research (3rd ed.). Thousand Oaks, CA: Sage.

Department of Health. (2007). South Africa Demographic and Health Survey 2003. Pretoria: Department of Health, Medical Research Council.

Department of Health. (2014). National Tuberculosis Management Guidelines 2014. Pretoria, South Africa: Department of Health, Republic of South Africa.

Department of Health. (2017).Towards Universal Health Coverage: Report of the Evaluation of South Africa Drug Resistant TB programme. Pretoria, South Africa: Department of Health, Republic of South Africa.

Department of Health (2004). National Antiretroviral Treatment Guidelines. Pretoria, South Africa: National Department of Health, South Africa.

Department of Health (2010). The South African Antiretroviral Treatment Guidelines 2010. Pretoria, South Africa: Department of Health, Republic of South Africa.

Department of Health (2004). The South African National Tuberculosis Control Programme Practical Guidelines 2004. Pretoria, South Africa: Department of Health, Republic of South Africa.

Department of Health (2013). The South African Antiretroviral Treatment Guidelines 2013. Pretoria, South Africa: Department of Health, Republic of South Africa.

DerSimonian R, Laird N. (1986).Meta-analysis in clinical trials. Control Clin Trials; 7: 177–88.

Deshmukh RD, Dhande DJ, Sachdeva KS, et al. (2015). Patient and provider reported reasons for lost to follow up in MDRTB treatments: a qualitative study from a drug resistant TB centre in India. PLoS One; 10: e0135802.

Ditkowsky JB, & Schwartzman K. (2014). Potential cost-effectiveness of a new infant tuberculosis vaccine in South Africa--implications for clinical trials: a decision analysis. PLoS One; 9(1): e83526.

Ebonwu JI, Tint KS, Ihekweazu C. (2013). Low treatment initiation among multi-drug resistant tuberculosis patients in Gauteng, South Africa, 2011. Int J Tuberc Lung Dis; 17(8):1043-8.

Edginton ME, Sekatane CS, Goldstein, SJ. (2002). Patient's beliefs: do they affect tuberculosis control? A study in a rural district of South Africa. Int J Tuberc Lung Dis; 6(12): 1075-1082.

Enarson, DA. (1995). The International Union Against Tuberculosis and Lung Disease model National Tuberculosis Programmes. Bull Int J Tuberc LUn Dis; 76(2): p. 95-99

Escudero E, Pena JM, Alvarez-Sala R, Vazquez JJ, Ortega A. (2006). Multidrug-resistant tuberculosis without HIV infection: Success with individualised therapy. Int J Tuberc Lung Dis;10:409-14.

Espinal, M.A. (2003). Time to abandon the standard retreatment regimen with first-line drugs for failures of standard treatment Editorial. Int J Tuberc Lung Dis; 7: 607-8.

Evans D, Schnippel K, Govathson C, Sineke T, Black A, Long L, et al.(2017). Treatment initiation among persons diagnosed with drug resistant tuberculosis in Johannesburg, South Africa. PLoS ONE: 12(7): e0181238.

Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, Weyer K, Lancaster J, van der Walt M. (2011). Outcomes of Multi-Drug Resistant Tuberculosis (MDR-TB) among a Cohort of South African Patients with High HIV Prevalence. PLoS ONE; 6(7): e20436.

Finlay A, Lancaster J, Holtz TH, Weyer K, Miranda A, van der Walt M. (2002). Patient- and provider-level risk factors associated with default from tuberculosis treatment, South Africa, 2002: a case-control study. BMC Public Health; 12: 56. doi: 10.1186/1471-2458-12-56

Foster N, Vassall A, Cleary S, Cunnama L, Churchyard G, Sinanovic E. (2015). The economic burden of TB diagnosis and treatment in South Africa. Soc Sci Med; 130: 42-50.

Fox MP, Rosen S. (2011). Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Trop Med Int Health; 15(s1):1-15.

Fried J, Harris B, Eyeles J, Moshabela M. (2015). Acceptable care? Illness constructions, health-worlds, and accessible chronic treatment in South Africa. Qual Health Res; 25: 622-35.

Gandy M, Zumla A. (2002). The resurgence of disease: social and historical perspectives on the 'new' tuberculosis. Soc Sci Med; 55(3): 385-96.

García-García ML, Ponce de León A, Jiménez-Corona ME, et al. (2000). Clinical consequences and transmissibility of drug-resistant tuberculosis in southern Mexico. Arch Intern Med; 160: 630–36.

Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D (2017). Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. Lancet Infect Dis, 2017 Feb;17(2):223-234.

Gelmanova IY, Taran DV, Mishustin SP, Golubkov AA, Solovyova AV, Keshavjee S. (2011). 'Sputnik': A programmatic approach to improve tuberculosis treatment adherence and outcome among defaulters. Int J Tuberc Lung Dis;15:1373-9.

Gilson L. (2006). Trust in health care: theoretical perspectives and research needs. J Health Org Manage; 20(5): 359-75.

Gilson L, Palmer N, Schneider H. (2005). Trust and health worker performance: exploring a conceptual framework using South African evidence. Soc Sci Med; 61(7): 1418-29.

Glaser BG (1978). Theoretical Sensitivity: Advances in the Methodology of Grounded Theory. California: The Sociology Press.

Glaziou P, Sismanidis C, Pretorius C, Floyd K. (2016). Methods used by WHO to estimate the Global burden of TB disease. arXiv:1603.00278 [q-bio.QM].

Golub JE, Pronyk P, Mohapi L, Thsabangu N, Moshabela M, Struthers H. (2009). Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS; 23(5): 631-6.

Gopi PG, Vasantha M, Muniyandi M, Chandrasekaran V, Balasubramanian R, Narayanan PR. (2007). Risk factors for non-adherence to directly observed treatment (DOT) in a rural tuberculosis unit, South India. Indian J Tuberc; 54: 66–70.

Grandjean L, Gilman RH, Martin L, et al.(2015). Transmission of multidrug-resistant and drug-susceptible tuberculosis within households: a prospective cohort study. PLoS Med; 12: e1001843.

Guba EG & Lincoln YS. (1994). Competing paradigms in qualitative research. In N. K. Denzin & Y. S. Lincoln (Eds.), Handbook of qualitative research (pp. 105-117). Thousand Oaks, CA: Sage.

Guba E & Lincoln Y. (1985). Naturalistic Inquiry. Beverley Hills, CA: Sage.

Hall M, Dogan E, Zheng B & Mishra A. (2001). Trust in Physicians and Medical Institutions. Does it Matter? The Milbank Quarterly: 79; 613–39.

Hamza TH, van Houwelingen HC, Stijnen T. (2008). The binomial distribution of meta-analysis was preferred to model within-study variability. J Clin Epidemiol; 61(1):41-51.

Han LL., et al. (2005). Acquisition of drug resistance in multidrug-resistant Mycobacterium tuberculosis during directly observed empiric retreatment with standardized regimens. Int J Tuberc Lung Dis. 9(7): p. 818-21.

Hanrahan CF, Dorman SE, Erasmus L, Koornhof H, Coetzee G, et al. (2012). The Impact of Expanded Testing for Multidrug Resistant Tuberculosis Using Genotype MTBDRplus in South Africa: An Observational Cohort Study. PLoS ONE; 7(11): e49898.

Health Systems Trust. (2016). The 90-90-90 Compendium: An introduction to 90-90-90 in South Africa. Volume 1. Durban, South Africa: Health Systems Trust.

Higgins JPT, Green S (editors). (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration.

Hirschowitz R, Sekwati WM, Budlender D. (2001). South Africa in transition: Selected findings from the October household survey of 1999 and changes that have occurred between 1995 and 1999. Pretoria, South Africa: Statistics South Africa.

Ho J, Byrne AL, Linh NN, Jaramillo E, Fox GJ. (2017). Decentralized care for multidrug-resistant tuberculosis: a systematic review and meta-analysis. Bull World Health Organ;95(8):584-593. doi:10.2471/BLT.17.193375.

Houben RMGJ, Menzies NA, Sumner T, Huynh GH, Arinaminpathy N, Goldhaber-Fiebert JD, et al. (2016). Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. Lancet Glob Health;4(11):e806-e815.

Huerga H, Bastard M, Kamene M, Wanjala S, Arnold A, Oucho N, Chikwanha I, Varaine F. (2017). Outcomes from the first multidrug-resistant tuberculosis programme in Kenya. Int J Tuberc Lung Dis;21:314-9.

International Institute for Population Sciences (IIPS). (2007). Macro International National Family Health Survey (NFHS-3), 2005–06. Volume I. Mumbai: IIPS.

Iruedo J, O'Mahony D, Mabunda S, Wright G, Cawe B. (2017). The effect of the Xpert MTB/RIF test on the time to MDR-TB treatment initiation in a rural setting: a cohort study in South Africa's Eastern Cape Province. BMC Infect Dis; 17: 91.

Isaakidis P, Cox HS, Bhanumati V, Chiara M, Silva Ed, Homa M, et al. (2011). Ambulatory multi-drug resistant tuberculosis treatment outcomes in a cohort of HIV-infected patients in a slum setting in Mumbai, India. PLoS ONE;36.

Iseman, M.D. (1993). Treatment of Multidrug-Resistant Tuberculosis. N Engl J Med; 329(11):784-791.

Jacobson KR, Theron D, Kendall EA, Franke MF, Barnard M, van Helden PD, et al.(2013). Implementation of GenoType MTBDR*plus* Reduces Time to Multidrug-Resistant Tuberculosis Therapy Initiation in South Africa . Clin Infect Dis; 56(4): 503–508.

Jaggarajamma, K., Balambal, R., Muniyandi, M., Vasantha, M., Thomas, B., Nirupa, C, et al. (2009). Perceptions of tuberculosis patients about private providers before and after implementation of Revised National Tuberculosis Control Programme. Indian J Tuberc; 56(4): 185-190.

Jaggarajamma, K., Sudha, G., Chandrasekaran, V., Nirupa, C., Thomas, A., Santha, T., et al. (2007). Reasons for non-compliance among patients treated under Revised National Tuberculosis Control Programme (RNTCP), Tiruvallur district, south India. Indian J Tuberc, 54(3), 130-135.

Jaiswal A, Singh V, Ogden JA, et al.(2003). Adherence to tuberculosis treatment: lessons from the urban setting of Delhi, India. Trop Med Int Health; 8: 625–33.

Johnson R, et al., (2006). Drug resistance in Mycobacterium tuberculosis. Current Issues in Molecular Biology; 8(2): 97-111.

Joseph P, Desai VB, Mohan NS, Fredrick JS, Ramachandran R, Raman B, et al. (2011). Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India. Indian J Med Res;133:529-34.

Kapoor, S. K., Raman, A. V., Sachdeva, K. S., & Satyanarayana, S. (2012). How did the TB patients reach DOTS services in Delhi? A study of patient treatment seeking behavior. PLoS One; 7(8): e42458. doi: 10.1371/journal.pone.0042458

Kelly G. (2017). Patient agency and contested notions of disability in social assistance applications in South Africa. Soc Sci Med; 175: 109-16.

Keshavjee S, Gelmanova IY, Farmer PE, Mishustin SP, Strelis AK, Andreev YG, et al. (2008). Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet;372:1403-9.

Kigozi G, Heunis C, Chikobvu P, Botha S, van Rensburg D. (2017). Factors influencing treatment default among tuberculosis patients in a high burden province of South Africa. International Journal of Infectious Diseases; 54:95-102.

Kim JY, Shakow A, Mate K, Vanderwarker C, Gupta R, Farmer P. (2005). Limited good and limited vision: multidrug-resistant tuberculosis and global health policy. Soc Sci Med; 61(4): 847-59.

Kim SJ. (2005). Drug-susceptibility testing in tuberculosis: methods and reliability of results. European Respiratory Journal; 25(3): 564-9.

Kliiman K, Altraja A. (2009). Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. Eur Respir J;33:1085-94.

Krishnan N, Ananthakrishnan R, Augustine S, et al. (2009). Impact of advocacy on the tuberculosis management practices of private practitioners in Chennai City, India. Int J Tuberc Lung Dis; 13: 112–18.

Kulkarni P, Akarte S, Mankeshwar R, Bhawalkar J, Banerjee A, Kulkarni A. (2013). Non-adherence of new pulmonary tuberculosis patients to anti-tuberculosis treatment. Ann Med Health Sci Res; 3: 67–74.

Kundu D, Chopra K, Khanna A, Babbar N, Padmini TJ. (2016). Accelerating TB notification from the private health sector in Delhi, India. Indian J Tuberc; 63: 8–12.

Law S, Daftary A, O'Donnell M, Padayatchi N, Calzavara L, Menzies D. (in press). Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review. Eur Resp J.

Law S, Piatek AS, Vincent C, Oxlade O, Menzies D. (2017). Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study. Lancet Public Health;2(1):e47-e55.

Lee YY & Lin JL. (2011). How much does trust really matter? A study of the longitudinal effects of trust and decision-making preferences on diabetic patient outcomes. Patient Education & Counseling; 85: 406–412.

Lei X, Liu Q, Escobar E, et al. (2015). Public-private mix for tuberculosis care and control: a systematic review. Int J Infect Dis; 34: 20–32.

Lincoln, Y.S., & Guba, E.G. (1985). Naturalistic inquiry. Newbury Park, CA: Sage.

Liu Q, Abba K, Alejandria MM, Sinclair D, Balanag VM, Lansang MAD. (2014). Reminder systems to improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment. Cochrane Database Syst Rev; 11: CD006594.

Loveday M, Padayatchi N, Brust J, Voce A, Wallengren K. (2013). The treatment journey of a patient with multidrug-resistant tuberculosis in South Africa: is it patient-centred? Int J Tuberc Lung Dis; 17: 56-59.

Loveday M, Wallengren K, Brust J, Roberts J, Voce A, Margot B, Ngozo J, Master I, Cassell G, Padayatchi N. (2015). Community-based care vs. centralised hospitalisation for MDRTB patients, KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis;19:163-71.

Lutge E, Lewin S, Volmink J, Friedman I, Lombard C. (2013). Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. Trials; 14:154.

Lutge EE, Wiysonge CS, Knight SE, Volmink J. (2012). Material incentives and enablers in the management of tuberculosis. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD007952.

M'Imunya JM, KredoT, Volmink J. (2012). Patient education and counselling for promoting adherence to treatment for tuberculosis. Cochrane Database of Systematic Reviews, Issue 5. Art. No.: CD006591.

Mandal S and Arinaminpathy N. (2015). Transmission modeling and health systems: the case of TB in India. Int Health; 7: 114–20.

Marx FM, Dunbar R, Enarson DA, Beyers N. (2012). The Rate of Sputum Smear-Positive Tuberculosis after Treatment Default in a High-Burden Setting: A Retrospective Cohort Study. PLoS ONE; 7(9): e45724.

Marx FM, Dunbar R, Hesseling AC, Enarson DA, Fielding K, Beyers N (2012). Increased risk of default among previously treated tuberculosis cases in the Western Cape Province, South Africa. International Journal of Tuberculosis and Lung Disease, 16(8): 1059-65.

Medical Research Council [MRC]. (1952). Prevention of streptomycin resistance by combined chemotherapy. BMJ; 1: 1157-1162

Meintjes G, Schoeman H, Morroni C, Wilson D, Maartens G (2008). Patient and provider delay in tuberculosis suspects from communities with a high HIV prevalence in South Africa: a cross-sectional study. BMC Infectious Diseases; 8: 72.

Meintjes G, Schoeman H, Morroni C, Wilson D, Maartens G (2008). Patient and provider delay in tuberculosis suspects from communities with a high HIV prevalence in South Africa: A cross-sectional study. BMC Infectious Disease 8: 72.

Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, et al. (2015). Achieving high treatment success for multidrug-resistant TB in Africa: Initiation and scale-up of MDR TB care in Ethiopia - An observational cohort study. Thorax;70:1181-8.

Metcalfe JZ, O'Donnell MR, Bangsberg DR. (2015). Moving beyond directly observed therapy for tuberculosis. PLoS Med; 12(9):e1001877.

Mishra G, Mulani J. (2013). Tuberculosis prescription practices in private and public sector in India. Natl J Integr Res Med; 4: 71–78.

Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcantara F, et al. (2003). Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. New Eng J Med;348:119-28.

Mitnick CD, Shin SS, Seung KJ, Rich MS, Atwood SS, Furin JJ, et al. (2008). Comprehensive treatment of extensively drug-resistant tuberculosis. New Eng J Med;359:563-74.

Mitnick C, S.C. Appleton, Shin SS. (2008). Epidemiology and treatment of multidrug resistant tuberculosis. Seminars in Respiratory & Critical Care Medicine; 29(5): 499-524.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. (2008). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med; 6: e1000097.

Mohr E, Cox V, Wilkinson L, Moyo S, Hughes J, Daniels J, Muller O, Cox H. (2015). Programmatic treatment outcomes in HIV-infected and uninfected drug-resistant TB patients in Khayelitsha, South Africa. Trans R Soc Trop Med Hyg ;109:425-32.

Mohr E, Daniels J, Beko B, Isaakidis JP, Cox V, Steele SJ, et al. (2017). DOT or SAT for Rifampicin-resistant tuberculosis? A non-randomized comparison in a high HIV-prevalence setting. PLoS ONE;12:e0178054.

Møller V, Ersta I. (2012). Stigma associated with tuberculosis in a time of HIV/ AIDS: Narratives from the Eastern Cape, South Africa. South African Review of Sociology; 38(2), 103-119.

Moyo S, Cox HS, Hughes J, Daniels J, Synman L, De Azevedo V, et al. (2015) Loss from Treatment for Drug Resistant Tuberculosis: Risk Factors and Patient Outcomes in a CommunityBased Program in Khayelitsha, South Africa. PLoS ONE; 10(3): e0118919.

Mukherjee JS, et al. (2004). Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet; 363(9407): 474-81.

Munro A, Bloor M. (2010). Process evaluation: the new miracle ingredient in public health research? Qualitative Research; 10(6): 699-713.

Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J (2007). Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Medicine, 24; 4(7): e238.

Naidoo P, Theron G, Rangaka M, Chihota V, Vaughan L, Brey Z, Pillay Y (2017). The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. Journal of Infectious Diseases, 216(S7): S702-13.

Naidoo P, Dick J, Cooper D. (2009). Exploring Tuberculosis Patients' Adherence to Treatment Regimens and Prevention Programs at a Public Health Site. Qualitative Health Research, 19: 55-70.

National Department of Health. (2018). Media Statement: New Bedaquiline data shows reduction in TB mortality cases. Pretoria, South Africa: National Department of Health.

National Department of Health. (2017). The 2015 National Antenatal Sentinel HIV & Syphilis Survey. Pretoria, South Africa: National Department of Health.

National Institute for Communicable Diseases. (2016). South African Tuberculosis Drug Resistance Survey 2012-14. Johannesburg, South Africa: National Institute for Communicable Diseases, Division of the National Health Laboratory Service.

Ncama BP, McInerney PA, Bhengu BR, Corless IB, Wantland DJ, Nicholas PK, et al. (2008). Social support and medication adherence in HIV disease in KwaZulu-Natal, South Africa. International Journal of Nursing Studies, 45(12): 1757-63.

Ogden J, Walt G, Lush L. (2003). The politics of 'branding' in policy transfer: the case of DOTS for tuberculosis control. Social Science & Medicine, 57(1): 179-88.

Oxlade O, Schwartzman K, Benedetti A, Pai M, Heymann J, Menzies D. (2011). Developing a tuberculosis transmission model that accounts for changes in population health. Med Decis Mak; 31: 53–68.

Oxlade O, Piatek A, Vincent C, Menzies, D. (2015). Modeling the impact of tuberculosis interventions on epidemiologic outcomes and health system costs. BMC Public Health, 15: 141.

Packard RM. (1989). White Plague, Black Labour - Tuberculosis and the Political Economy of Health and Disease in South Africa. Berkeley, CA: University of California Press.

Patton MQ. (1990). Qualitative evaluation and research methods (2nd ed.). Newbury Park, CA: Sage Publications.

Pronyk RM, Makhubele MB, Hargreaves JR, Tollman SM, Hausler HP (2001). Health seeking behaviour among tuberculosis patients in rural South Africa. International Journal of Tuberculosis and Lung Disease, 5(7): 619-27.

Rabiee R, Agardh E, Coates MM, Allebeck P, Danielsson A-K (2017). Journal of Global Health, 7(1): 010404.

Raiffa H, Schlaifer R. (1959). Probability and statistics for business decisions. New York: McGraw-Hill.

Rajeswari R, Balasubramanian R, Bose MS, Sekar L, Rahman F. (2002). Private pharmacies in tuberculosis control—a neglected link. Int J Tuberc Lung Dis; 6: 171–73.

Ramachandran G, Chandrasekaran V, Hemanth Kumar AK, Dewan P, Swaminathan S, Thomas A. (2013). Estimation of content of anti-TB drugs supplied at centres of the Revised National TB Control Programme in Tamil Nadu, India. Trop Med Int Health: 18: 1141–44.

Ramaswamy S, Musser J. (1998). Molecular genetic basis of antimicrobial agent resistance in *Mycobacterium tuberculosis*: 1998 update. Tubercle and Lung Disease; 79: 3–29.

Raviglione, M.C. and A. Pio. (2002). Evolution of WHO policies for tuberculosis control, 1948-2001. Lancet. 359(9308): p. 775-80.

Reed JB, McCausland R, Elwood JM. (1990). Default in the outpatient treatment of tuberculosis in two hospitals in Northern India. J Epidemiol Community Health; 44: 20–23.

Rieder H, Av D, Kam K, Kim S, Chonde T. (2007). Priorities for tuberculosis bacteriology services in low-income countries. Paris, France: International Union Against Tuberculosis and Lung Disease

Rintiswati N, Mahendradhata Y, Suharna, et al. (2009). Journeys to tuberculosis treatment: a qualitative study of patients, families and communities in Jogjakarta, Indonesia. BMC Public Health;9:158. doi:10.1186/1471-2458-9-158

Robinson C. (2016). Trust, Health Care Relationships, and Chronic Illness: A Theoretical Coalescence. Global Qualitative Nursing Research; 3: 233339366648 23.

Rolfe A, Cash-Gibson L, Car J, Sheikh A, McKinstry B. (2014). Interventions for improving patients' trust in doctors and groups of doctors. Cochrane Database Systematic Reviews; 2014(3): CD004134.

Rouillon A. (1991). The Mutual Assistance Programme of the IUATLD. Development, contribution and significance. Bull Int Union Tuberc Lung Dis; 66: 159-72.

Roy SK, Roy SK, Bagchi S, Bajpayee A, Pal R, Biswas R. (2005). Study of KAP of the private medical practitioners about national disease control programmes. Indian J Public Health; 49: 256–57.

Sachdeva KS, Raizada N, Gupta RS, et al. (2015). The potential impact of up-front drug sensitivity testing on India's epidemic of multi-drug resistant tuberculosis. PLoS One; 10: e0131438.

Sam IC, Drobniewski F, More P, Kemp M, Brown T. (2006). Mycobacterium tuberculosis and rifampin resistance, United Kingdom. Emerging infectious diseases; 12: 752.

Sandelowski M. (2000). Whatever Happened to Qualitative Description? Research in Nursing & Health; 23: 334-340.

Sarpal SS, Goel NK, Kumar D, Janmeja AK (2014). Reasons for interruption of anti-tubercular treatment among the retreatment patients in category II of RNTCP in Chandigarh, north India. Indian Journal of Tuberculosis; 61(2):121-8.

Satti H, McLaughlin MM, Hedt-Gauthier B, Atwood SS, Omotayo DB, Ntlamelle L, Seung KJ. (2012). Outcomes of Multidrug-Resistant Tuberculosis Treatment with Early Initiation of Antiretroviral Therapy for HIV Co-Infected Patients in Lesotho. PLoS ONE;7.

Satyanarayana S, Kwan A, Daniels B, et al. (2016). Use of standardised patients to assess antibiotic dispensing for tuberculosis by pharmacies in urban India: a cross-sectional study. Lancet Infect Dis; 16: 1261–68.

Satyanarayana S, Nair SA, Chadha SS, Shivashankar R, Sharma G, Yadav S. (2011). From where are tuberculosis patients accessing treatment in India? Results from a cross-sectional community based survey of 30 districts. PLoS One; 6(9): e24160.

Selvam JM, Wares F, Perumal M, et al. (2007). Health-seeking behaviour of new smear-positive TB patients under a DOTS programme in Tamil Nadu, India, 2003. Int J Tuberc Lung Dis; 11: 161–67.

Sengupta S, Pungrassami P, Balthip Q, Strauss R, Kasetjaroen Y, Chongsuvivatwong V, & Van Rie A. (2004). Social impact of tuberculosis in southern Thailand: views from patients, care providers and the community. Int J Tuberc Lung Dis; 10(9): 1008-12.

Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Andreev YG, et al. (2006). Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia. Int J Tuberc Lung Dis;10:402-8.

Siddiqi N, Shamim M, Hussain S, Choudhary RK, Ahmed N, et al. (2002). Molecular Characterization of Multidrug-Resistant Isolates of Mycobacterium tuberculosis from Patients in North India. Antimicrob. Agents Chemother., 46(2) : 443-450. doi: 10.1128/aac.46.2.443-450.2002

Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, Kuntz KM. (2012). State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force - 3. Med Decis Making, 32, 690-700.

Simelela NP, Venter WDF. (2014). A brief history of South Africa's response to AIDS. S Afr Med J;104(3 Suppl 1):249-251.

Singla N, Sharma PP, Singla R, Jain RC. (1998). Survey of knowledge, attitudes and practices for tuberculosis among general practitioners in Delhi, India. Int J Tuberc Lung Dis; 2: 384–89.

Skordis-Worrall. (2010). Confusion, caring and tuberculosis diagnostic delay in Cape Town, South Africa. Int J Tuberc Lung Dis, 14(2), 171-180.

Smith E, Brugha R, Zwi A (2001).Working with Private Sector Providers for Better Health Care: an introductory guide. London School of Hygiene and Tropical Medicine & Options Consultancy Services Limited: London, UK.

South African National AIDS Council.(2011). National Strategic Plan on HIV, STIs and TB 2012–2016. Pretoria: South African National AIDS Council.

Speziale HJS, Carpenter DR. (2007). Qualitative Research in Nursing: Advancing the Humanistic Imperative (4th ed.). Philadelphia, Pennsylvania: Lippincott Williams & Wilkins.

Spiegelhalter DJ, Best NG. (2003). Bayesian approaches to multiple sources of evidence and uncertainty in complex cost-effectiveness modelling. Statistics in Medicine, 22: 3687-3709.

Sreeramareddy CT, Qin ZZ, Satyanarayana S, Subbaraman R, Pai M (2014). Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. International Journal of Tuberculosis and Lung Disease, 18: 255–66.

Stagg HR, Lipman MC, McHugh TD, and Jenkins HE (2017). Isoniazid resistant tuberculosis- a cause for concern? Int J Tuberc Lung Dis, 21(2): 129-39.

Statistics South Africa. (2014). Mortality and causes of death in South Africa, 2013: Findings from death notification. Pretoria, South Africa: Statistics South Africa.

Statistics South Africa. (2016). Mid-year population estimates 2016. Pretoria, South Africa: Statistics South Africa.

Sterne J, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. (2016). ROB-INS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ; 355:i4919.

Stop TB Partnership and WHO (2006). The global plan to stop TB, 2006-2015. World Health Organization: Geneva.

Strauss A & Corbin J. (1990). Basics of Qualitative Research. Newbury Park, CA: Sage Publications.

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GC, Rennie D, et al. (2000). Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting. JAMA; 283(15): 2008-12.

Suárez PG, Floyd K, Portocarrero J, Alarcón E, Rapiti E, Ramos G, et al. (2002). Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: A national cohort study in Peru. Lancet;359:1980-9.

Suen SC, Bendavid E, Goldhaber-Fiebert JD. (2014). Disease control implications of India's changing multi-drug resistant tuberculosis epidemic. PLoS One; 9: e89822.

Suganthi P, Chadha VK, Ahmed J, et al. (2008). Health seeking and knowledge about tuberculosis among persons with pulmonary symptoms and tuberculosis cases in Bangalore slums. Int J Tuberc Lung Dis; 12: 1268–73.

Tandon M, Gupta M, Tandon S, Gupta KB. (2002). Dots versus self-administered therapy (SAT) for patients of pulmonary tuberculosis: A randomised trial at a tertiary care hospital. Indian J Med Sci; 56: 19–21.

Taneja N, Chellaiyan VG, Daral S, Adhikary M, Das TK. (2017). Home Based Care as an Approach to Improve the Efficiency of treatment for MDR Tuberculosis: A Quasi-Experimental Pilot Study. J Clin Diagn Res;11:LC05-LC8.

Telenti, A., Imboden, P., Marchesi, F., Matter, L., Schopfer, K., Bodmer, T., et al. (1993). Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. Lancet, 341(8846): 647-651.

The World Bank. (2015). Country and Lending Groups. Retrieved 22 June, 2015, from http://data.worldbank.org/about/country-and-lending-groups

The World Bank. (2016). Death rate, crude (per 1,000 people). Washington, DC: The World Bank Group.

Thom DH, Campbell B. (1997). Patient-physician trust: an exploratory study. Journal of Family Practice, 44(2): 169-76.

Thomas A, Ramachandran R, Rehaman F, Jaggarajamma K, Santha T, Selvakumar N, et al. (2007). Management of multi drug resistance tuberculosis in the field: Tuberculosis Research Centre experience. Indian J Tuberc;54:117-24.

Toczek A, Cox H, du Cros P, Cooke G, Ford N (2013). Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis. International Journal of Tuberculosis and Lung Disease, 17(3): 299-307.

Udwadia, Z. F., Pinto, L. M., & Uplekar, M. W. (2010). Tuberculosis management by private practitioners in Mumbai, India: has anything changed in two decades? PLoS One, 5(8), e12023. doi: 10.1371/journal.pone.0012023

UNAIDS. UNAIDS 2018 estimates. (2018). Geneva, Switzerland: UNAIDS. Downloaded from http://aidsinfo.unaids.org/ on February 2, 2018.

Uplekar M, Juvekar S, Morankar S, Rangan S, Nunn P. (1998).Tuberculosis patients and practitioners in private clinics in India. Int J Tuberc Lung Dis; 2: 324–29.

Uplekar M, Pathania V, Raviglione M (2001). Private practitioners and public health: weak links in tuberculosis control. Lancet, 358(9285): 912-6.

Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. (2015).WHO's new End TB Strategy. Lancet, 385(9979): 1799-801.

Uplekar MW, Juvekar SK, Parande SD, et al.(1996). Tuberculosis management in private practice and its implications. Indian J Tuberc; 43: 19–22.

Vaghela JF, Kapoor SK, Aditi K, Dass RT, Ashwani K, Bhatnagar AK. (2015). Home based care to multi-drug resistant tuberculosis patients: a pilot study. Indian J Tuberc;62:91-6.

van der Hoeven, Marinka , Kruger, Annamarie, & Greeff, Minrie. (2012). Differences in health care seeking behaviour between rural and urban communities in South Africa. International Journal for Equity in Health, 11: 31.

van Hoorn R, Jaramillo E, Collins D, Gebhard A, van den Hof S. (2016). The Effects of Psycho-Emotional and Socio-Economic Support for Tuberculosis Patients on Treatment Adherence and Treatment Outcomes - A Systematic Review and Meta-Analysis. PLoS One,; 11(4):e0154095.

Van Rie, A., Warren, R., Mshanga, I., Jordaan, A. M., van der Spuy, G. D., Richardson, M., . . . Victor, T. C. (2001). Analysis for a limited number of gene codons can predict drug resistance of Mycobacterium tuberculosis in a high-incidence community. Journal of Clinical Microbiology, 39(2), 636-641.

Van Soolingen D, Borgdorff MW, de Haas PE, et al. (1999). Molecular epidemiology of tuberculosis in the Netherlands: a nationwide study from 1993 through 1997. J Infect Dis; 180: 726–36.

Van Wyk SS, Enarson DA, Beyers N, Lombard C, Hesseling AC (2011). Consulting private health care providers aggravates treatment delay in urban South African tuberculosis patients. Int J Tuberc Lung Dis, 15(8): 1069-76.

Vandan N, Ali M, Prasad R, Kuroiwa C. (2009). Assessment of doctors' knowledge regarding tuberculosis management in Lucknow, India: a public-private sector comparison. Public Health; 123: 484–89.

Vassall A, Siapka M, Foster N, Cunnama L, Ra L, Fielding K, et al. (2017). Cost-effectiveness of Xpert MTB/RIF for tuberculosis diagnosis in South Africa: a real-world cost analysis and economic evaluation. Lancet; 5(7): e710-19.

Vijay S, Kumar P, Chauhan LS, Vollepore BH, Kizhakkethil UP, Rao SG (2010). Risk factors ssociated with default among new smear positive TB patients treated under DOTS in India. PLoS One, 5(4):e10043.

Vijayan S, Khetarpal M, Datta M, et al. (2014). Chemists and less-than-fully-qualified providers dominate Mumbai's health provider universe (PD-647-30). Int J Tuberc Lung Dis; 18: S146–47.

Wan X, Wang W, Liu J, Tong T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol;14:135.

Weiss P, Chen W, Cook VJ, Johnston JC. (2014).Treatment outcomes from community-based drug resistant tuberculosis treatment programs: a systematic review and meta-analysis. BMC Infect Dis; 14:333.

Wells WA, Ge CF, Patel N, Oh T, Gardiner E, Kimerling ME. (2011). Size and usage patterns of private TB drug markets in the high burden countries. PLoS ONE, 6(5): e18964.

World Health Organization [WHO]. (2017a). Global tuberculosis report 2017. Geneva: WHO.

WHO. (2017b) Guidelines for treatment of drug-susceptible tuberculosis and patient care: 2017 update. WHO: Geneva.

WHO. (2010). Treatment of tuberculosis: guidelines for national programmes, 4th edition. Geneva: World Health Organization.

WHO. (2009). Global tuberculosis control: a short update to the 2009 report. Geneva: World Health Organization.

WHO. (2010). Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. Geneva: World Health Organization.

WHO. (2016). WHO treatment guidelines for drug-resistant tuberculosis: 2016 Update - October 2016 revision. Geneva, Switzerland: World Health Organization.

WHO. (2008). Anti-tuberculosis drug resistance in the world: fourth global report. Geneva: World Health Organization.

WHO. (2013). Global Tuberculosis Report 2013. Geneva: World Health Organization.

WHO. (2016). Global Tuberculosis Report 2016. Geneva: World Health Organization.

WHO. (2000). Guidelines for establishing DOTS-Plus projects for the management of multi-drug-resistant tuberculosis (MDR-TB). Geneva: WHO.

WHO. (2014). The End TB: Strategy Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: WHO.

WHO. (2018). WHO TB burden estimates. Geneva, Switzerland: WHO; 2018. Downloaded from http://www.who.int/tb/country/data/download/en/ on February 2, 2018.

Wirth T, Hildebrand F, Allix-Béguec, et al. (2008). Origin, Spread and Demography of the Mycobacterium tuberculosis Complex. PLoS Pathogen, 4(9): e1000160.

World Medical Association. (2013). WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Retrieved July 22, 2015, from http://www.wma.net/en/30publications/10policies/b3/

Yadav A, Garg SK, Chopra H, et al. (2012). Treatment practices in pulmonary tuberculosis by private sector physicians of Meerut, Uttar Pradesh. Indian J Chest Dis Allied Sci; 54: 161–63.

Yin J, Yuan J, Hu Y, Wei X. (2016). Association between Directly Observed Therapy and Treatment Outcomes in Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis. PLoS One; 11(3):e0150511.

Yu MC, Chen HY, Chien SH, Jou R. (2015). An integrated MDR-TB management programme results in favourable outcomes in northern Taiwan. Eur Respir J;45:272-5.

Zaman FA, Sheikh S, Das KC, Zaman GS, Pal R. (2014). An epidemiological study of newly diagnosed sputum positive tuberculosis patients in Dhubri district, Assam, India and the factors influencing their compliance to treatment. J Nat Sci Biol Med; 5: 415–20.

APPENDIX

The appendix is organized by the thesis studies.

Table of contents

STUDY 1: EMERGENCE OF DRUG RESISTANCE IN PATIENTS WITH TUBERCULOSIS CARED FOR BY THE INDIAN HEALTH-CARE SYSTEM: A DYNAMIC MODELLING STUDY

The following is a duplicate of the online supplement to the published article: Law S, Piatek AS, Vincent C, Oxlade O, Menzies D. Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study. Lancet Public Health, 2017;2(1):e47-e55.

Table S1: Details on Markov model

Type of model: Markov model with dynamic TB transmission
Cycle length*:* 1 year
About the model: We constructed a dynamic TB transmission Markov model using decision analysis software (TreeAge Professional, 2014). The Markov model consists of several Markov states (i.e. health states) as well as decision trees, which represent the probability framework for how individuals move between the different health states. At the base year (first year of the model), a hypothetical cohort representing the population of India was initially divided into the different TB-related health states in the model, including: uninfected with TB; having latent TB infection; and having current active TB disease (new and previously treated). Health states were further stratified by smear status (positive and negative), underlying drug resistance (drug sensitive, INH-resistant, and rifampicin-resistant/MDR), and health sector in which TB care is sought (public, private, chemist and informal). The time frame (cycle length) of the model is one-year. This means that during each year, a person could either remain in the present health state or transition into another health state. That is, at the end of each year, those who were uninfected with TB could stay uninfected or acquire infection, and those with TB infection could: remain without disease (with latent infection); develop active disease (this rate was higher in the first two years after infection) and seek treatment; acquire drug resistance; or remain as chronic TB cases if they were unsuccessful at receiving treatment after three treatment-seeking attempts.
Transition probabilities*:* How patients transition between states from year to year will depend on numerous probabilities. All of these probabilities will determine how patients move through the model within each yearly cycle, see main text for details on these probabilities.
Integration of dynamic TB transmission: We integrated a dynamic annual risk of TB infection that was calculated from the sum of the number of infections generated from untreated smear positive and negative cases in the population in each year. Infections were generated by both drug resistant and drug sensitive cases, dynamically affecting the drug sensitive or MDR annual risk of TB infection in subsequent years. Infectious cases that were drug resistant and untreated (or treated inadequately) generated drug resistant infections, but with a slight reduction in contagiousness (Table S1). The model used a dynamic population whereby new births or immigrants in the population replaced people who died as a consequence of their age, disease, or treatment, such that the population remained stable and the susceptible population did not become depleted over the modeling time horizon.

Table S2: Key input parameters – TB pathogenesis and natural history

	Probability or Number	95% CI or range	Source
General Parameters:			
Early reactivation (progression to disease in first two years)	3%	2- 5%	Sutherland, 1976[1]
Late reactivation (more than 2 years after infection)	0·24%*	0·1-0·3%	Comstock, Edwards & Livesay, 1974; Nolan & Elarth, 1988[2,3]
New TB Infections generated per year by untreated DS-TB, smear positive	10*	1 - 22	Styblo, Meijer, & Sutherland, 1969; Vynnycky & Fine, 1997[4,5]
New TB Infections generated per year by untreated DS-TB, smear negative	2*	0·2 - 4·4	Behr et al·, 1999; Van Geuns, Meijer, & Styblo, 1975[6,7]
Infectiousness of INH-resistant TB relative to DS-TB	98·6%	n/a	Denkinger, Pai, & Dowdy, 2014[8]
Infectiousness of MDR-TB relative to DS-TB	77·4%	n/a	Ibid·
Untreated Active Cases:			
Spontaneous cure - smear positive¶	18%	7-33%	Grzybowski, 1993; Tiemersma, van der Werf, Borgdorff, Williams, & Nagelkerke, 2011[9,10]
Spontaneous cure -smear negative¶	51%	46-57%	Grzybowski, 1993; Tiemersma, et al, 2011[9,10].
Annual Mortality - smear positive (First 10 years) †	19·0%	12·6-27·3%	Grzybowski, 1993; Tiemersma, et al, 2011[9,10]
Annual Mortality - smear positive (After 10 years) †	4·1%	2·1-19·3%	Grzybowski, 1993; Tiemersma, et al, 2011[9,10]
Annual Mortality - smear negative (First 10 years) †	5·6%	3·2-7·4%	Grzybowski, 1993; Tiemersma, et al, 2011[9,10]
Annual Mortality - smear negative (After 10 years) †	1·3%	1·2-1·5%	Grzybowski, 1993; Tiemersma, et al, 2011[9,10]

Note – The parameters in this table were not varied during probability sensitivity analyses as they were used to calibrate the model.

n/a – Not available

*Parameters were derived from the cited sources then adjusted during model calibration. These key pathogenetic parameters were uncertain and therefore were estimated through model calibration. These included the number of new TB infections generated in one year by a person with untreated smear positive

TB, and the risk of reactivation in a person with long-standing latent TB infection. We varied these key parameters until the model predicted a drug-sensitive TB epidemic that matched the 2012 WHO-estimated TB incidence and prevalence rates in India (see Table S2).[11] Parameters that affected emergence of drug resistance were not calibrated in this fashion.

¶ One-time spontaneous cure rates were estimated by multiplying sample size-weighted average of 10-year survival rates, stratified by smear status,[9] by 65%, which is the estimated proportion of survivors of untreated TB who become bacteriologically negative.[12]

† Fixed annual mortality rates for the first 10 years are estimated in order to match sample size-weighted average of 10-year survival rates, stratified by smear status.[9] Fixed annual mortality rates for after 10 years are estimated such that the total mortality rate between years 11 and 20 is 3·4% (out of total TB population), regardless of smear status·[9] Annual mortality rates from untreated TB include the background mortality rate of 0·8%.

Table S3: Reported Epidemiologic data for India, 2012

	Prevalence rate	**Incidence rate**	**Mortality rate**	**ARI***	**Prevalence of DR in new TB cases**
Reported data	230 per 100,000[11]	176 per 100,000[11]	25 per 100,000[11]	1·9	10·1% INH-resistance[13] 2·5% any RIF-resistance including MDR[11;13]

*The annual risk of infection (ARI) was estimated as the incidence rate of smear-positive pulmonary TB divided by 49.[4] The incidence rate of smear-positive pulmonary TB is estimated as total TB incidence rate (176 per 100,000) multiplied by 80% (proportion with pulmonary TB), and then by 66·5% (proportion of pulmonary TB that is smear-positive).[11]

Table S4: Health-seeking behaviour of TB patients in India*

	% of TB patients seeking care from each sector	% of TB patients referred out by chemists**	% of patients referred out by chemists who seek care from each sector**	% of TB patients seeking care from each sector after chemists' referrals	% of TB patients referred out by informal providers	% of patients referred out by informal providers who seek care from each sector**	% of TB patients seeking care from each sector after chemist and informal providers' referrals
Private	12·3		15.3 (0.7% of all TB patients)	13·0		26.1 (6·1% of all TB patients)	19·1%
Public	34·8		43.1 (2.1% of all TB patients)	36·9		73·9 (17·5% of all TB patients)	54·4%
Chemist	19·3	25·0 (4.8% of all TB patients)	-	14·5		0	14·5%
Informal	33·6		41.6 (2.0% of all TB patients)	35·6	66·2 (23.6% of all TB patients)	-	12·0%

*See Table 1 in main text for the sources used to obtain the probabilities of TB patients seeking care from each sector and of being referred out by informal providers. The purpose of this table is to show how the probabilities of TB patients seeking care from each sector shift after specific proportions of those who seek care from chemists and informal providers are referred out to other providers.

**We assumed chemists referred 25% of patients out to other providers (any type). However, informal doctors only referred out to private and public doctors. The distribution of referrals among the other providers is based on the initial distribution of TB patients seeking care from each sector (excluding the sector that is referring patients out).

Table S5. Probability of seeking care, and treated with TB drugs, in each sector at the end of three health-seeking attempts

Health Sector	Probability of seeking care (95%CI)	Probability of being treated with TB drugs (95%CI)
Private	17·3% (13.3-18.4%)	91·8% (79.6-96.2%)
Public	64·1% (64.1-68.4%)	96·4% (94.5-98.8%)
Chemist	3·3% (2.3-4.4%)	34.1 (28.2-43.9%)
Informal	15·4% (10.9-17.9%)	97.5% (91.4-99.5%)

Note: This table presents the final probabilities after a maximum of three attempts at seeking care. Each patient had a maximum of three attempts at receiving TB drugs. When a patient failed to get treated at their first or second attempt, they then sought care again from any of the sectors (based on the probabilities presented in Table 1 and Table S3). If they failed to get treated at their third attempt, then they became prevalent TB cases and no longer had opportunities at being treated. Overall, 93·7% would be treated across all sectors, after a maximum of three attempts. The 95%CIs were estimated based on the 95%CIs of: a) the probability of informal providers referring patients to public and private providers; and b) the probabilities of receiving TB drugs in the different sectors.

Table S6: Treatment outcomes after initial treatment by underlying drug resistance and type of initial treatment regimen received

Type of treatment regimen	**Underlying drug resistance**	**Treatment outcome after initial treatment (%)***					
		Failure (95% CI)	Acquire SDR after treatment failure (95% CI)	Acquire MDR after treatment failure (95% CI)	Relapse after cure§ (95% CI)	Acquire SDR after relapsing¶ (95% CI)	Acquire MDR after relapsing† (95% CI)
Correct Treatment	DS-TB	0·3 (0.1-0.4)[a]	25·3 (6.9-42.6)[b]	17·1 (12.7-28.8)[b]	3·7 (2.8-4.7)[a]	4·8 (2.4-11.3)[b]	2·2 (2.0-10.9)[b]
	SDR	14·3 (8.2-17.2)[b]	-	56·2 (46.3-71.5)[b]	11·4 (6.5-16.2)[a]	-	5·8 (0.6 - 17.2)[b]
	MDR	28.0 (15.0-44.8)[b]	-	-	14.0 (0.8-20.3)[b]	-	-
Too short	DS-TB	2·2 (1.4-2.5)[b]	44·7 (35.8-56.2)[b]	5·9 (0.2-20.2)[b]	8·3 (6.8-10.0)[b]	8·8 (4.8-9.5)[b]	0·2 (0-0.6)[b]
	SDR	20·4 (15.5-25.7)[b]	-	13·1 (4.2-20.4)[b]	14·9 (13.9-23.1)[b]	-	1·9 (0-10.2)[b]
	MDR	1-spont· Cure-death	-	-	1·3% per year[c]	-	
Low dose (Less than 450/650 mg)**	DS-TB	0·3 (0.1-0.4)[d]	25·3 (6.9-42.6)[d]	17·1 (12.7-28.8)[d]	12·1 (8.2-20.6)[b]	4·8 (2.4-11.3)[d]	2·2 (2.0-10.9)[d]
	SDR	14.3 (8.2-17.2)[d]	-	56·2 (46.3-71.5)[d]	12·5 (11.1-14.3)[b]	-	5·8 (0.6-17.2)[d]
	MDR	1-spont· Cure-death	-	-	1·3% per year[c]	-	-
Mono-therapy	DS	1-spont· Cure - death	100 (if treated with INH)[f]	100 (if treated with RIF)[f]	1·3% per year[c]	20 (if treated with INH)[g]	12·5 (if treated with RIF)[h]
	SDR	1-spont· Cure - death	-	100 (if treated with RIF)[f]	1·3% per year[c]	-	12·5 (if treated with RIF)[h]
Two drugs with INH and RIF	DS	1·8 (0.9-3.1)[b]	46.9 (9.1-79.1)[b]	12·5 (7.5-33.7)[b]	3.2 (2.1-5.0)[b]	0[7]	2·2 (2.0-10.9)[d]
	SDR	25·7 (14.2-43.3)[b]	-	100[b]	11.5 (0.6-29.7)[b]	-	12·5 (if treated with RIF)[h]
Two drugs with INH and any drug other than RIF	DS	11·8 (8.8-13.2)[b]	69·6 (53.3-75.3)[b]	-	10.7 (4.7-17.0)[b]	13·9 (10.7-15.1)[g]	-
	SDR	67·4 (48.9-82.0)[b]	-	-	1·3% per year[c]	-	-
Two drugs with RIF and any drug other than INH	DS	1·8 (0.9-3.1)[e]	-	12·5 (7.5-33.7)[e]	3.2 (2.1-5.0)[e]	-	2·2 (2.0-10.9)[d]
	SDR	10·3 (4.7-13.9)[b]	-	50 (18.4-78.7)[b]	5.1 (3.7-11.4)[b]	-	12·5 (if treated with RIF)[e]
Monotherapy or any two-drug therapy	MDR	1-spont· Cure - death	-	-	-	1·3% per year[c]	-

*Mortality rate 4% total for DS-TB or INH-resistant TB if treated with 2 drugs or more.[14] Mortality of all MDR, or all patients receiving mono-therapy: same as untreated TB = 19% annually for smear-positive TB and 5% annually for smear-negative TB. Our model assumed DST was not done on patients, therefore all patients received the same standard initial treatment or retreatment regimen regardless of their underlying drug-resistance profile in all sectors.
§ Proportion who relapse after stopping treatment early is 37·6% for any TB patients, regardless of underlying drug resistance.
¶ Probability of acquiring SDR if relapsed after stopping treatment early is 9·3% when correct treatment was received.
† No patients who received correct treatment acquired MDR if they relapsed after stopping treatment early.
** We assumed irregular adherence to treatment was equivalent to taking a suboptimal dosage of RIF in terms of treatment outcomes, including the risk of acquiring drug resistance.
[a] Estimate obtained from a 2009 systematic review by Menzies, et al.[15]
[b] Estimate is derived from a meta-analysis– using a DerSimonian & Laird (1986)[16] random-effects model – of data found in studies included in the 2009 systematic review by Menzies, et al.[15,17]
[c] Assumed same as relapsing after spontaneous cure from untreated TB. Estimate is derived from 1969 study by Horwitz.[18]
[d] Assumed the same probability as when treated with the correct regimen.
[e] Assumed the same probability as when treated with two-drug therapy containing INH and RIF.
[f] Model assumption.
[g] Assumed probability is 1/5th of acquired SDR rate after treatment failure.
[h] Assumed probability is 1/8th of acquired MDR rate after treatment failure.

Table S7: Treatment outcomes after retreatment in public sector by underlying drug resistance

Type of retreatment regimen	**Underlying drug resistance**	**Treatment outcome after retreatment**		
		Failure (95%CI or range)	**Default (95%CI or range)**	**Death (95%CI or range)**
Standard WHO-recommended retreatment (CAT-II)	DS	5·3 (1.3-17.2)[19-21]	14 (13.8-14.2)[14]	8 (7.9-8.1)[14]
	SDR	18·0 (14.3-26.6)[21-26]		
	MDR	48·4 (48.1-50.0)[20, 21]		

Table S8: Hypothetical scenarios: Major outcomes after 20 years if all patients accessed a single sector, without correction of problems identified in that sector

Hypothetical scenario	**Outcomes – per 100,000 population in 2032**			
	DS-TB Incidence	INH-resistance incidence	MDR incidence	Total mortality (all forms of DS and DR-TB)
The public sector treats all TB patients	134	23	15	29
The private sector treats all TB patients	142	29	14	41
Patients only seek care from chemists and informal providers**	142	51	8	62
Patients only seek care from chemists and informal providers, and these providers routinely prescribe RIF	116	35	37	54

Table S9: Full results for change in epidemiologic outcomes (ARI, Incidence, Prevalence, ADR and Mortality) in India after 20 years, when different health system and patient related model parameters are changed

	Sources of error contributing to ADR	DS (ARI)	SDR (ARI)	MDR (ARI)	DS-TB Incidence (per 100,000)	INH-resistant TB Incidence (per 100,000)	MDR-TB Incidence (per 100,000)	DS-TB Prev (per 100,000)	INH-resistant TB Prev (per 100,000)	MDR-TB Prev (per 100,000)	Acquired INH-resistant TB (per 100,000)	Acquired MDR-TB (per 100,000)	DS-TB Deaths	INH-resistant TB Deaths	MDR-TB Deaths
BASE CASE	n/a	1·52	0·37	0·30	136·75	26·65	14·08	319·56	59·12	49·57	3·30	4·61	21·24	5·90	7·53
CROSS SECTOR															
ALL SECTORS	**1·** Optimize Health sector accessed (ie· All go to public)	1·14	0·24	0·31	130·98	22·44	14·69	272·79	43·05	50·39	2·24	5·18	14·09	3·47	7·80
	2· Reduce number of diagnostic attempts to **one (i·e· all get diagnosed/treated at 1st attempt)***	1·28	0·36	0·29	132·28	26·65	13·73	285·94	58·05	47·47	3·86	4·44	18·05	5·94	7·27
	3· Improve drug quality at regulatory level	1·52	0·37	0·30	136·74	26·64	14·00	319·29	59·05	49·29	3·28	4·58	21·20	5·89	7·47

* In this scenario the probability of being diagnosed and treated is increased to 100% after a single attempt in any sector, and patient delay is reduced to 0 days from 19·4 days. Health system delay remains at 38·1 days, which is the total delay in this scenario.

	Sources of error contributing to ADR	DS (ARI)	SDR (ARI)	MDR (ARI)	DS-TB Incidence (per 100,000)	INH-resistant TB Incidence (per 100,000)	MDR-TB Incidence (per 100,000)	DS-TB Prev (per 100,000)	INH-resistant TB Prev (per 100,000)	MDR-TB Prev (per 100,000)	Acquired INH-resistant TB (per 100,000)	Acquired MDR-TB (per 100,000)	DS-TB Deaths	INH-resistant TB Deaths	MDR-TB Deaths
BASE CASE	n/a	1·52	0·37	0·30	136·75	26·65	14·08	319·56	59·12	49·57	3·30	4·61	21·24	5·90	7·53
	Error in Private Allopathic MDs														
PRIVATE	4· Improve rx (ie· always 3 drugs prescribed)	1·52	0·37	0·30	136·77	26·69	14·07	319·92	59·30	49·56	3·32	4·60	21·27	5·92	7·53
	5· All correct drugs prescribed	1·53	0·37	0·30	136·87	26·75	14·03	320·71	59·59	49·41	3·34	4·58	21·37	5·96	7·49
	Error in Private Chemist who fill private MD's Rx														
	6· Chemist refers to public sector for dispensing of drugs	1·50	0·36	0·30	136·51	26·43	14·05	317·17	58·14	49·44	3·22	4·62	20·94	5·77	7·50
	7· Chemist doesn't dispense daily/weekly (i·e· short)	1·50	0·36	0·30	136·51	26·46	14·05	317·28	58·29	49·42	3·22	4·62	20·95	5·79	7·50
	Patients treated in private sector														
	8· No default	1·41	0·33	0·30	135·33	25·52	13·97	306·23	54·23	48·86	2·85	4·69	19·54	5·26	7·40
	9· No monotherapy or 2-drug therapy due to patient	1·52	0·36	0·29	137·02	26·47	13·72	320·15	58·55	48·05	3·14	4·36	21·22	5·79	7·27
	10· No Irregular adherence	1·53	0·37	0·30	136·81	26·69	14·03	319·99	59·30	49·40	3·31	4·59	21·29	5·93	7·50

	Sources of error contributing to ADR	DS (ARI)	SDR (ARI)	MDR (ARI)	DS-TB Incidence (per 100,000)	INH-resistant TB Incidence (per 100,000)	MDR-TB Incidence (per 100,000)	DS-TB Prev (per 100,000)	INH-resistant TB Prev (per 100,000)	MDR-TB Prev (per 100,000)	Acquired INH-resistant TB (per 100,000)	Acquired MDR-TB (per 100,000)	DS-TB Deaths	INH-resistant TB Deaths	MDR-TB Deaths
BASE CASE	n/a	1·52	0·37	0·30	136·75	26·65	14·08	319·56	59·12	49·57	3·30	4·61	21·24	5·90	7·53
Error in Private Chemist who dispense without Rx															
CHEMIST	11· Chemist refers all to other providers for diagnosis	1·36	0·33	0·31	134·03	25·49	14·27	295·34	53·68	49·82	3·29	4·75	18·27	5·17	7·62
	12· No TB drugs given in 1st round of treatment	1·53	0·37	0·30	136·94	26·58	14·10	321·45	59·03	49·73	3·25	4·63	21·37	5·87	7·55
	13· All correct drugs prescribed (If prescribed)	1·51	0·35	0·31	136·65	26·15	14·23	318·27	57·16	50·31	3·25	4·67	20·96	5·63	7·62
	14· Chemist doesn't dispense daily/weekly	1·52	0·37	0·30	136·75	26·65	14·08	319·56	59·12	49·57	3·30	4·61	21·24	5·90	7·53
	Patients errors in taking meds following Chemist dispensing **without prescription –** not modelled because in base case no chemists dispensed a correct regimen without prescription, and errors could not be compounded (ie only one type of error possible.														

	Sources of error contributing to ADR	DS (ARI)	SDR (ARI)	MDR (ARI)	DS-TB Incidence (per 100,000)	INH-resistant TB Incidence (per 100,000)	MDR-TB Incidence (per 100,000)	DS-TB Prev (per 100,000)	INH-resistant TB Prev (per 100,000)	MDR-TB Prev (per 100,000)	Acquired INH-resistant TB (per 100,000)	Acquired MDR-TB (per 100,000)	DS-TB Deaths	INH-resistant TB Deaths	MDR-TB Deaths
BASE CASE	n/a	1·52	0·37	0·30	136·75	26·65	14·08	319·56	59·12	49·57	3·30	4·61	21·24	5·90	7·53
	Error in Public sector MDs														
PUBLIC	15· All correct tx	1·51	0·37	0·29	136·74	26·60	13·66	318·10	58·77	48·00	3·23	4·45	21·04	5·86	7·18
	Patients treated in public sector														
	16· No default	1·48	0·36	0·30	136·19	26·26	13·99	314·63	57·53	48·97	3·09	4·63	20·57	5·68	7·45
	17· No Irregular adherence	1·50	0·36	0·28	136·71	26·55	13·26	316·50	58·41	46·55	3·17	4·30	20·83	5·82	6·84
INFORMAL SECTOR	Error in Informal sector														
	18· Refers to public/private providers for diagnosis	1·47	0·31	0·32	136·28	24·59	14·55	317·47	52·45	51·32	2·64	4·95	19·64	4·72	7·83
	19· No TB drugs prescribed	1·70	0·35	0·32	140·13	25·79	14·41	351·84	58·31	51·69	2·58	4·81	23·79	5·50	7·80
	Error in Private Chemist who fill informal practitioners Rx														
	20· Refers to public sector for dispensing*	1·52	0·37	0·30	136·75	26·65	14·08	319·56	59·12	49·57	3·30	4·61	21·24	5·90	7·53
	21· Chemist doesn't dispense daily/weekly	1·52	0·37	0·30	136·75	26·65	14·08	319·56	59·12	49·57	3·30	4·61	21·24	5·90	7·53
	Patients treated in informal sector - Patients errors in taking meds when prescribed by informal sector – not modelled, because in base case informal sector did not prescribe any correct regimens, and errors could not be compounded (ie only one type of error possible).														

*Same drugs given as prescribed by informal, but dispensing errors can only happen when correct prescription is given, which never happens in the informal sector. Since only one source of error can be estimated at a time, the effect of chemist dispensing incorrectly could not be estimated in the informal sector, furthermore, it was not possible to estimate what the effect would be if chemists were to refer to the public sector for dispensing drugs.

Table S10: Sequential removal of sources of Acquired Drug Resistance (by treatment outcome and health sector)
(DATA TO SUPPORT FIGURE 2 in main manuscript)

Parameter affected (each adds to previous)	**Acquired INH-resistant TB (per 100,000)**	**Acquired MDR-TB (per 100,000)**	**DS-TB Deaths**	**INH-resistant TB Deaths**	**MDR-TB Deaths**	**DS-TB Incidence (per 100,000)**	**INH-resistant TB Incidence (per 100,000)**	**MDR-TB Incidence (per 100,000)**
Base case (after 20 years)	3·30	4·61	21·24	5·90	7·53	136·75	26·65	14·08
REMOVE ADR FROM DEFAULT (during initial and retx)								
Remove ADR from default in **private sector only**·	2·93	4·57	21·39	5·72	7·49	137·10	26·28	14·03
Remove ADR from default in **private and public sectors**	2·69	4·54	21·51	5·59	7·47	137·36	26·03	14·00
Remove ADR from default in **all sectors**·	2·69	4·54	21·51	5·59	7·47	137·36	26·03	14·00
REMOVE ADR FROM IRREGULAR ADHERENCE (during initial and retx)								
Remove ADR from failure/relapse after **irregular adherence** in **private sector only**	2·68	4·47	21·54	5·60	7·39	137·41	26·06	13·90
Remove ADR from failure/relapse after **irregular adherence** in **private and public sectors**	2·40	3·09	21·98	5·85	6·06	138·43	26·60	12·10
Remove ADR from failure/relapse after **irregular adherence** in **all sectors**	2·40	3·09	21·98	5·85	6·06	138·43	26·60	12·10
REMOVE ADR FROM RELAPSE (during initial and retx)								
Remove ADR from relapse (unrelated to irregular adherence) in **private sector only**	2·37	3·02	22·02	5·85	5·99	138·51	26·59	12·00
Remove ADR from relapse (unrelated to irregular adherence) in **private and public sectors**·	2·24	2·56	22·22	5·84	5·55	138·98	26·60	11·40
Remove ADR from relapse in **all sectors**	2·10	2·55	22·29	5·76	5·54	139·12	26·45	11·39
REMOVE ADR FROM FAILURE AFTER **INITIAL** TREATMENT								
Remove ADR from fail in **initial** treatment in **private sector only**	1·92	2·19	22·43	5·76	5·21	139·46	26·46	10·95
Remove ADR from fail in **initial** treatment in **private and public sectors**	1·18	0·62	22·91	5·80	3·83	140·78	26·57	9·06
Remove ADR from fail in **initial** treatment in **all sectors**	0·39	0·59	23·21	5·40	3·79	141·47	25·82	9·01
REMOVE ADR FROM FAILURE **AFTER** RETREATMENT								
Remove ADR from fail in **retreatment** in **private sector only**	0·36	0·53	23·26	5·40	3·71	141·57	25·82	8·90
Remove ADR from fail in **retreatment** in **private and public sectors**	0·12	0·00	23·69	5·45	3·06	142·40	25·90	8·01
Remove ADR from fail in **retreatment** in **all sectors**	0·00	0·00	23·81	5·32	3·06	142·64	25·66	8·01

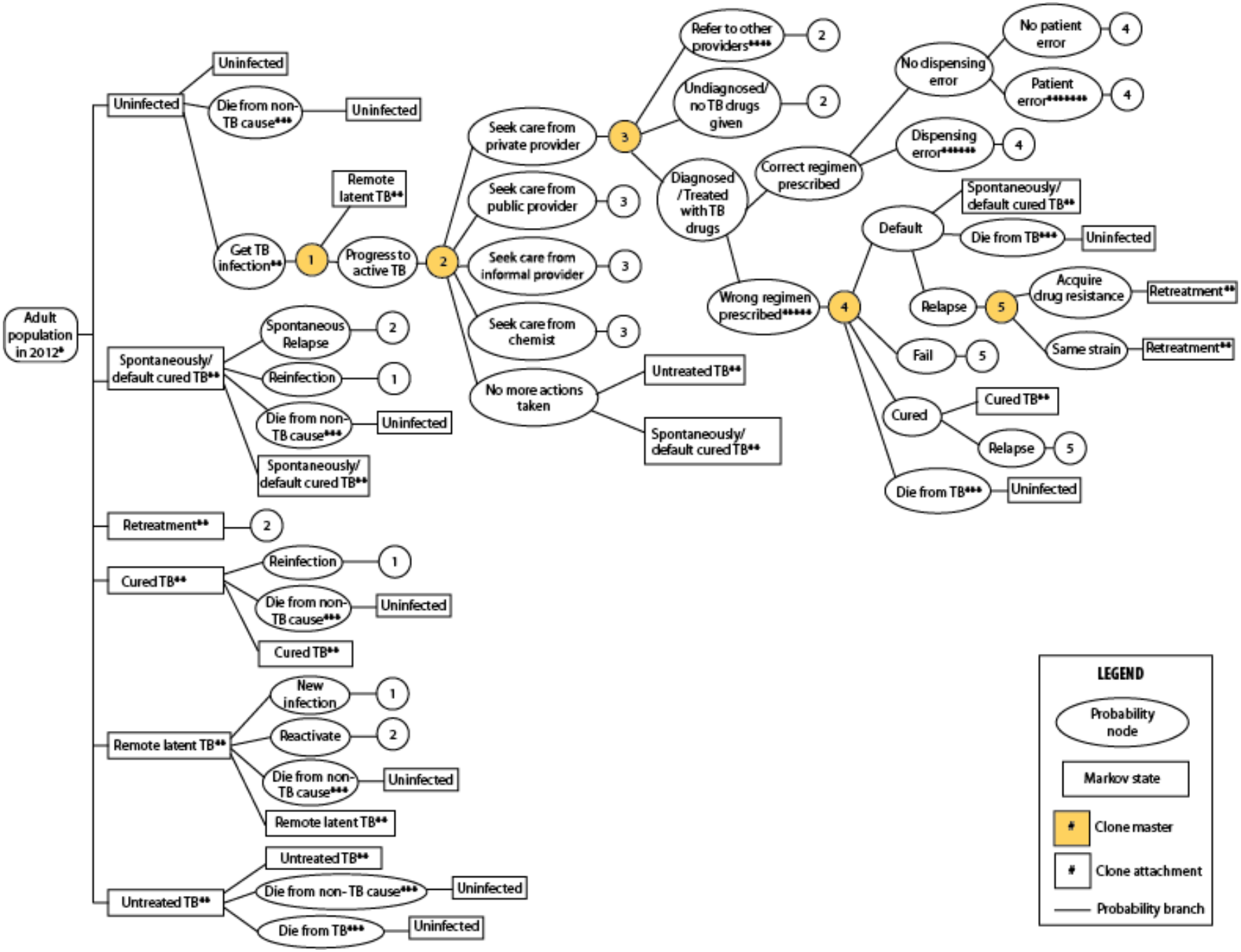
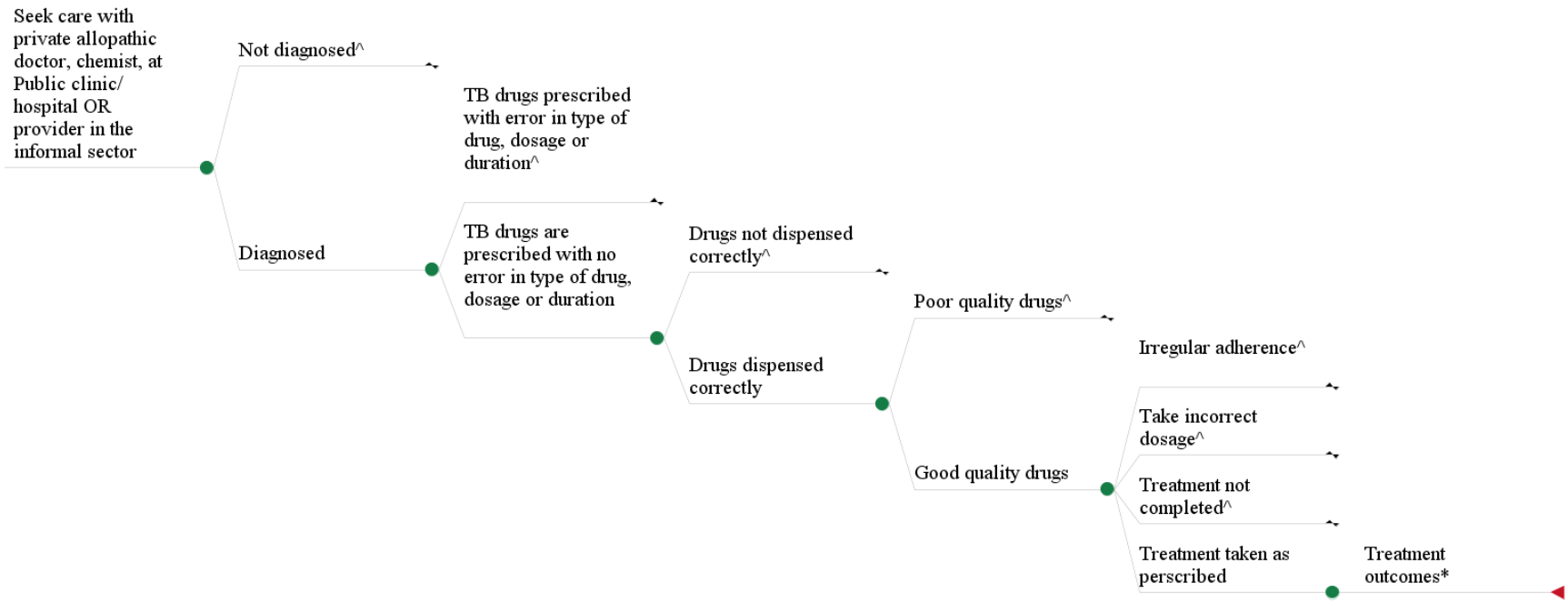


Figure S1. Schematic of Markov model.

The cycle-length is one year. Each year, the population moves through probability trees, which redistributes the population the Markov states for following year. *For the first model cycle, the population is distributed among the different Markov states based on parameters calibrated to 2012 figures specific to India.**These states/probability nodes are further split according to drug-resistance profile: 1) drug-susceptible TB; 2) non-MDR drug-resistant TB; and 3) MDR-TB (Not shown here due to space limitations.) ***Whenever an individual died, a new individual was entered into the model as uninfected. ****The probabilities for referring to other providers differed based on provider type. *****Types of prescription errors not explicitly shown in this schematic due to space limitations. ******Types of dispensing errors not shown here. *******Types of patient errors not shown here.

Fig S2: Simplified schematic of decision analytic tree representing the healthcare system with respect to TB care in India



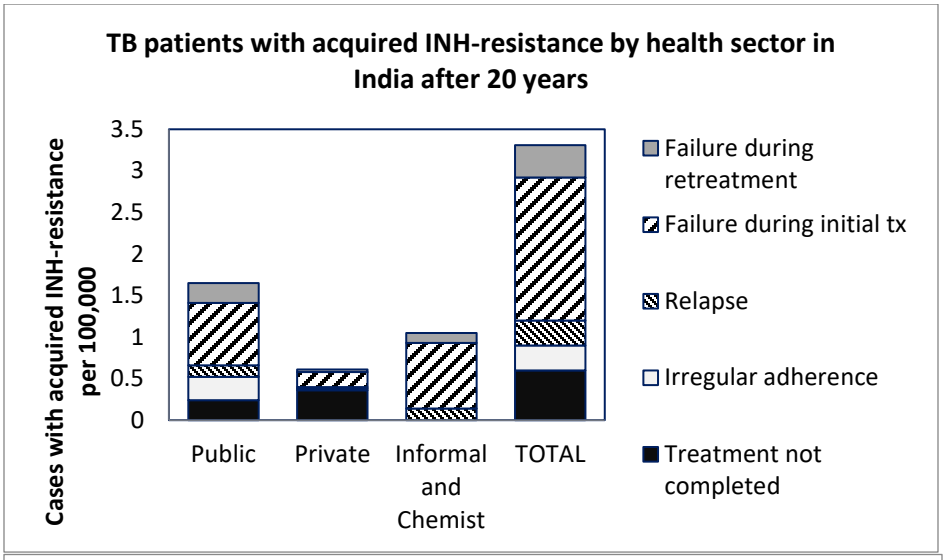
This simplified schematic summarizes the different types of barriers included in our model that a TB patient can encounter as they are diagnosed and treated for active TB. Prior to being diagnosed the patient may delay seeking care (not shown in sketch). There may also encounter delays through the health system prior to starting treatment (not shown). An individual seeking care can only encounter a single type of barrier as they move through the health system. If they don't have any barriers at a particular stage, they can still encounter barriers in subsequent steps as they move through the system (see to text for more detail).

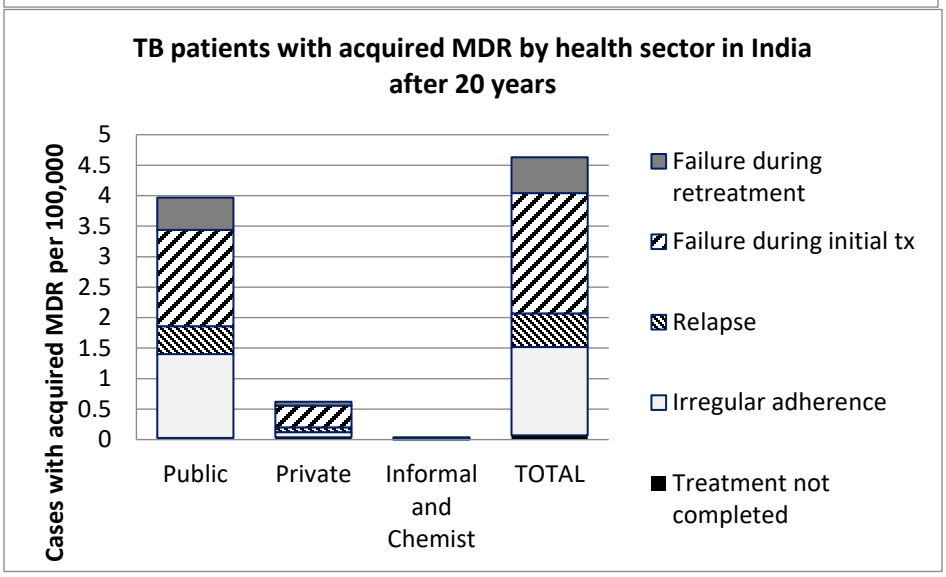
Footnotes:

^ Subsequent possible events and outcomes are the same as those that follow the other branch below. Poor quality drugs refer to substandard quality drugs, which could include counterfeit drugs, that may contain lower-than-accepted dosages, and drugs that may have lost its potency due to poor storage conditions.

* Different treatment outcomes can occur depending on underlying drug resistance· Outcomes include treatment completion, failure, relapse, death and acquired drug resistance.

Figure S3: TB patients with acquired INH-resistance or MDR by health sector in India in 2032





References

1. Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. *Advances in tuberculosis research Fortschritte der Tuberkuloseforschung Progres de l'exploration de la tuberculose* 1976; **19**: 1-63.
2. Nolan CM, Elarth AM. Tuberculosis in a cohort of Southeast Asian refugees: a five-year surveillance study. *The American review of respiratory disease* 1988; **137**: 805-9.
3. Comstock GW, Edwards LB, Livesay VT. Tubercuosis morbidity in the US Navy: its distribution and decline. *The American review of respiratory disease* 1974; **110**: 572-80.
4. Styblo K, Meijer J, Sutherland I. Tuberculosis Surveillance Research Unit Report No. 1: the transmission of tubercle bacilli; its trend in a human population. *Bulletin of the International Union against Tuberculosis* 1969; **42**: 1-104.
5. Vynnycky E, Fine PE. The annual risk of infection with Mycobaterium tuberculosis in England and Wales since 1901. *The international journal of tuberculosis and lung disease* 1997; **1**(5): 389-96.
6. Behr MA, Warren SA, Salamon H, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacill. *Lancet* 1999; **353**(9151): 444-9.
7. Van Geuns HA, Meijer J, Styblo K. Results of contact examination in Rotterdam, 1967-1969. *Bulletin of the International Union against Tuberculosis* 1975; **50**: 107-21.
8. Denkinger CM, Pai M, Dowdy DW. Do we need to detect isoniazid resistance in addition to rifampicin resistance in diagnostic tests for tuberculosis? *PloS one* 2014; **9**(1): e84197.
9. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural History of Tuberculosis Duration and Fatality of Untreated Pulmonary Tuberculosis in HIV Negative Patients: A Systematic Review. *PloS one* 2011; **6**(4): e17601.
10. Grzybowski S. Drugs are not enough. Failure of short-course chemotherapy in a district in India. *Tubercle and lung disease* 1993; **74**(3): 145-6.
11. World Health Organization. Global Tuberculosis Report 2013. Geneva, Switzerland: World Health Organization, 2013.
12. Grzybowski S, Enarson DA. The fate of cases of pulmonary tuberculosis under various treatment programmes. *Bulletin of the International Union against Tuberculosis* 1978; **53**(2): 70-4.
13. World Health Organization. Anti-tuberculosis Drug Resistane in the World: Fourth Global Report. Geneva, Switzerland: World Health Organization, 2008.

14. Central TB Division. TB India 2014: Revised National TB Control Programme Annual Status Report. New Delhi, India: Directorate General of Health Services, Ministry of Health and Family Welfare, 2014.
15. Menzies D, Benedetti A, Paydar A, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. *PLoS medicine* 2009; **6**(9): e1000146.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**(3): 177-88.
17. Menzies D, Benedetti A, Paydar A, et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. *PLoS medicine* 2009; **6**(9): e1000150.
18. Horwitz O. Public health aspects of relapsing tuberculosis. *The American review of respiratory disease* 1969; **99**: 183-93.
19. Churchyard GJ, Corbett EL, Kleinschmidt I, Mulder D, De Cock KM. Drug-resistant tuberculosis in South African gold miners: incidence and associated factors. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2000; **4**(5): 433-40.
20. Sevim T, Atac G, Gungor G, et al. Treatment outcome of relapse and defaulter pulmonary tuberculosis patients. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2002; **6**(4): 320-5.
21. Espinal MA, Kim SJ, Suarez PG, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA : the journal of the American Medical Association* 2000; **283**(19): 2537-45.
22. Narayanan PR. Split-drug regimens for the treatment of patients with sputum smear-positive pulmonary tuberculosis -- a unique approach. *Tropical medicine & international health : TM & IH* 2004; **9**: 551-8.
23. Seung KJ, Gelmanova IE, Peremitin GG, et al. The effect of initial drug resistance on treatment response and acquired drug resistance during standardized short-course chemotherapy for tuberculosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2004; **39**(9): 1321-8.
24. Santha T, Garg R, Frieden TR, et al. Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District, South India, 2000. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2002; **6**(9): 780-8.
25. Kimerling ME, Kluge H, Vezhnina N, et al. Inadequacy of the current WHO re-treatment regimen in a central Siberian prison: treatment failure and MDR-TB. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 1999; **3**(5): 451-3.

26. Pardeshi GS, Deshmukh D. A comparison of treatment outcome in re-treatment versus new smear positive cases of tuberculosis under RNTCP. *Indian journal of public health* 2007; **51**(4): 237-9.

STUDY 2: "I REALLY NEEDED THEM TO TRUST ME, BUT THEY DIDN'T": HOW THE PRESENCE OR ABSENCE OF PATIENT-PROVIDER TRUST INFLUENCES TUBERCULOSIS TREATMENT OUTCOMES

This is the appendix for the manuscript prepared for submission to Social Science & Medicine. It includes additional findings not found in the main text, as well as consent forms, interview guides, and copies of ethics approval from the McGill University and University of Cape Town IRBs, and the City of Cape Town.

Treatment-seeking behaviours

The majority of patients (n=20; 61%) noticed their TB symptoms and sought care on their own for their first TB episode, of whom nearly half went to a public clinic or hospital (n=9; 45%), and the others either bought non-TB medication from the chemist (n=6; 30%) or went to see a private doctor (n=5; 25%). On the other hand, patients who did not recognize or ignored their TB symptoms were all advised by peers or family members to directly seek care from public clinics or hospitals (n=13; 29%).

Many patients had a difficult time ascertaining how long they waited before seeking medical attention for their TB symptoms. However, among those who could provide an estimated delay before seeking care, patients who sought care on their own after noticing the symptoms often reported shorter delays compared to those who were advised by others. One patient mentioned receiving some education on TB at school: "I suspected it was TB because everyone knows about TB outside…Because the people went into our schools and gave us lessons about TB and teach us everything and tell all the stories (P9; one-week delay before going to the clinic during first episode of TB)."

Although all patients knew about TB, some were unfamiliar with TB symptoms and often confused the symptoms with a flu or attributed the symptoms to their lifestyle, such as regular smoking or drinking, and some doubted the possibility they could get TB because nobody close to them have had it. These patients were more likely to visit chemists or private doctors rather than TB clinics or public hospitals: "The time I was coughing, I thought it was just the flu, I didn't

know…I went to the private doctor, and then the doctor said nothing, and he just gave me the flu something (P20; one-month delay before going to a private doctor)." Furthermore, patients perceived private clinics to be more convenient and to have shorter queues: "I do go to the chemist because I was lazy to wake up in the morning to go the clinic, and I go to the special [private] doctor… Because of queueing, a lot of time there, you spending the whole day in there, that's why I didn't want to go to the clinic at that time (P14; one-month delay before testing for TB at a clinic)."

Patients who have previously completed full courses of TB treatment often went immediately to the clinic as soon as TB symptoms resurfaced. However, some delayed going to the clinic even if they suspected it was TB, citing denial or non-acceptance of needing retreatment as primary reasons: "I didn't want to tell myself that I have TB, because I don't want to have TB, because I know the treatment you see, that is why, you see, I end up go late to the clinic (P20; five-week delay before going to clinic during second episode of TB)." A couple patients opted to seek alternative diagnoses from private providers to avoid testing for TB due to their denial.

Many health care providers suggested people with TB symptoms might delay seeking care due to stigma associated TB and the lack of privacy at public clinics. "They are scared to come to the clinic because they see someone at the clinic who live in their community with her, that's why you don't like to come to the clinic (HCP17)." This was echoed by private providers who often see patients who are reluctant to be seen going to TB clinics. Furthermore, TB is highly associated with HIV, which remains stigmatized in many communities: "People think that if you have TB, afterwards you're going to get AIDS or something, that's what people say (HCP19)."

None of the patients interviewed reported seeing traditional healers. However, healthcare providers – including traditional healers – shared experiences with TB patients who prefer traditional medicine, and may either mix traditional and Western anti-TB medication, or in rare cases, refuse to seek treatment at Western medical clinics altogether: "I explain there are limitations to how I can help them. Some agree [to go to the clinic] and then just go to a different healer, and then you hear they have passed away. Some already know they have TB they just won't accept it, so they think I will be able to heal them (HCP35)." In some cases, patients might

never get diagnosed for TB or get diagnosed too late: "[My brother] was glad about the traditional healers, he didn't believe about the clinics. But while he come to the clinic and find out that he got a TB, it was too late for him. Yes, he didn't make it (P15)."

Some patients had exceptional circumstances that led to lengthy treatment delays. One patient (P32) interrupted HIV antiretroviral treatment for a year during which her health deteriorated. She intentionally delayed returning to the clinic to seek care, but eventually tested positive for TB: "Because my aunt died, she was supposed to look after me, my treatment buddy, and she died. After that, my father died. My uncle died. And I just think, I also can die, just take life." Another patient (P9) developed TB symptoms while in prison for two months, and he only got tested for TB after his release.

Diagnostic and treatment delays

Patients who did not go directly to a public TB clinic or hospital experienced delays in getting diagnosed and in starting effective treatment. For example, those who went to a chemist would take pain and flu tablets for weeks to months before attending a clinic. Those who sought care from private doctors might receive multiple rounds of ineffective treatment for other conditions, before being diagnosed at a TB clinic or hospital: "I went to a private doctor as well…they gave me antibiotics, and they gave me stuff for the chest, and none of those seem to have helped. Twice, I went to the same doctor and afterwards, I went to another one to see what he had to say…And all of them couldn't pick up nothing (P22 – two-month delay before getting diagnosed at a TB clinic)." Although none of the patients who sought care from private doctors were successfully diagnosed, public TB doctors said they often get TB referrals from private doctors, where patients will arrive at the public clinic with x-rays or sputum test results in hand.

Knowledge and practices around TB testing and treatment, and subsequent diagnostic or treatment delays, varied among private general practitioners interviewed (see Table 3). One general practitioner prescribed anti-TB medication to patients who test positive for TB: "Put them on Rifafour [combination first-line TB drug], I say, at least you got something until you get something at the clinic (HCP32)." All private general practitioners said they would refer the

patient to the local TB clinic for treatment, recognizing that the state is responsible for TB management. The majority of TB patients in South Africa do not have the financial resources or medical aid to seek testing and treatment in the private doctors. However, for patients who insist on receiving treatment in the private sector and who have the financial capacity, it is possible to be treated privately by pulmonologists at private hospitals. In some cases, patients might start treatment privately but would then switch to a public clinic when they have drained their financial resources: "They realize that either the medical aid doesn't pay, or the TB tablets cost too much, or whatever else, and then they request to go to public [clinics] (HCP29)." There is no formal follow-up after patients are referred to public clinics, and private providers do not receive any feedback from public clinics or hospitals.

There are some individuals in the communities who will seek treatment from multiple traditional healers, increasing delays to getting tested and treated for TB. For example, one healer spoke of one patient she recently saw: "He told me he had been seeking treatment for a long time, he told me he has three izangoma, and he's still not okay (HCP35)." All but one healer interviewed would refer the patient directly to a clinic or hospital to seek testing and treatment, and wouldn't treat TB (Table 3). The one exception was a healer who said: "I can't take my knowledge, which is also my source of income, and pass it on to a doctor (HCP36)." Although this healer would not stop a TB patient from continuing anti-TB treatment if they come see him, he would treat TB with his own medication because he believes sometimes TB patients are not in fact sick with TB: "Idliso (poison) can be seen as TB in a person, but you find that it cannot be treated at the hospital and when they come to me, I see it (HCP36)." Healers who are familiar with TB symptoms and treatment spoke poorly of other healers who treat TB patients with traditional medicines: "I think other traditional healers, whereby they don't have the information, they give any everything. Yah, they'll treat them, and then the patients, after that, all those patients are dead (HCP34)."

Public providers all noted how the scale-up of GeneXpert MTB/RIF in public clinics have drastically reduced delays in testing and initiation of treatment, as well as decreased lost-to-follow-up between testing and receiving results. However, due to the heavy reliance on sputum-

based testing, patients who fail to produce sputum or who have extrapulmonary TB are often missed. Private providers commented on how these patients sometimes end up seeking their help: "If it's [pleural] effusion though, it's sputum negative, but you pick it up on the X-ray and the fusion won't be diagnosed at the clinic on the sputum. So you will have those patients that will come here for that. And there are patients who refuse to produce sputum at the clinic, there is an element of reluctance to produce sputum (HCP28)." Furthermore, although diagnostic delays have shortened to two to five days in public clinics, interviews with patients and public providers suggest the delay between testing and receiving results are still approximately two weeks at public hospitals: "Most of our delays happens in that group of clients, because some day hospitals, they'll say, come back in 2 weeks for your results, not necessarily come back in two days. So already that's a two-week delay in terms of initiating treatment (HCP27)." Additionally, public (day) hospitals only performing TB testing and do not provide treatment. Thus after testing positive, patients will then have to take their test results and attend a local clinic, potentially leading to even lengthier delays to initiating treatment.

Informed Consent Form for Health Care Providers of TB patients in and around Cape Town

Project Title: Exploring patient movement within TB care

Researchers

Stephanie Law (PhD Candidate)
Dr. Dick Menzies (PhD Supervisor)
McGill University
Department of Epidemiology
stephanie.law@mail.mcgill.ca
dick.menzies@mcgill.ca

Dr. Keertan Dheda
Professor of Respiratory Medicine Head of the
Lung Infection and Immunity Unit
Department of Medicine,
University of Cape Town
keertan.dheda@uct.ac.za

This Informed Consent Form has two parts:

- Information Sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you choose to participate)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

You are invited to join a study that aims to learn about the experiences of individuals seeking care for tuberculosis in and around Cape Town. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

Please ask to stop as we go through the information if you have any questions. If you have questions later, you can ask them of me or of another researcher.

Why is this study being done?

Tuberculosis (TB) is making many people sick in your community. We want to find ways stop this from happening. We believe you can help by telling us about your experiences with providing care to TB patients. We want to learn what people who have TB do when they first become sick, and who they go to for treatment or diagnosis. We want to learn about the different types of health care providers people with TB get care from, and what kind of care they receive. We also want to know how you think care for TB could be made better, because

this knowledge might help us learn to improve treatment for tuberculosis and to better control it in this community.

Why are you being asked to take part?

We are inviting you to take part in this study because we feel that your experience as somebody who provides care for TB patients can help us understand TB patients' care-seeking and treatment-taking behaviours, the interactions between health care providers and TB patients, as well as the types of care and services provided to TB patients (as well as potential TB patients) by different healthcare providers.

What will happen if you decide to take part in the study

If you accept to take part in this study, we will ask you to participate in a one-on-one interview with Stephanie Law. The interview will take about one hour.

During the interview, the interviewer will sit down with you in a comfortable, private place at your clinic. If you do not wish to answer any of the questions during the interview, you may say so and the interviewer will move on to the next question. No one else but the interviewer will be present unless you would like someone else to be there. If needed, a translator will be present during the interview.

In the interview, some personal information will be collected, including: age, sex, ethnicity and occupation. We will also ask you questions about:

- Your health/clinical practice, such as: how long have you been working at this facility? On average, how many patients do you see each day? What types of patients do you see? How often do potential TB patients come to your clinic? How many TB patients do you currently provide care to?

- Your experiences with diagnosing TB: can you describe what you do when you think a patient might have TB? Have you had patients not come back for their diagnoses? If so, why do you think they don't come back?

- Your experiences with treating TB: what kind of care do you provide TB patients? Do you prescribe any treatment or drugs to the patients? Have you had patients leave your care or the clinic while still ill with TB? If so, why do you think they leave? Have you had patients come to you after receiving care from another clinic or health care provider? If so, do you know why?

- Potential improvements to services and care: do you have any suggestions for changes or improvements at this clinic (or other health care facilities that provide care to TB patients) to help patients complete their diagnostic processes or treatment?

What if you refuse to take part?

Your participation in this research is entirely voluntary. It is your choice whether to participate or not, and you can stop at any time during the interview. You have the right to withdraw from the study at any time. You do not have to talk about anything you do not want to, and can refuse to answer questions for any reason. If you refuse to participate or withdraw from the interview, this will not affect your job or job-related evaluations in any way. I will give you an opportunity at the end of the interview to review your remarks, and you can ask to modify or remove portions of those, if you do not agree with my notes or if I did not understand you correctly.

Who will see the information collected about you during the study?

The information recorded is confidential. Only researchers directly involved in this study (Stephanie Law, Dr. Amrita Daftary, Dr. Keertan Dheda and Dr. Dick Menzies) will have access to the information documented during your interview. The entire interview will be tape-recorded, but no-one will be identified by name on the tape. The tape and any other materials will be kept in a secure locked cabinet. The information recorded is confidential, and no one else except Stephanie Law will have access to the tapes. The tapes will be destroyed seven years after the study has ended.

We will not be sharing information about you to anyone outside of the research team. The information that we collect from this project will be kept private. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key.

How many people will take part in the study?

We will be interviewing 20 to 30 TB patients and 10 to 20 healthcare providers who provide care to TB patients.

What are the risks and discomforts of this study?

We are asking you to share with us some of your personal experiences with the care and services you have provided for tuberculosis treatment, and you may feel uncomfortable talking about some of the topics. You do not have to answer any question or take part in the interview if you don't wish to do so, and that is also fine. You do not have to give us any reason for not responding to any question, or for refusing to take part in the interview.

Are there any benefits to you for being in the study?

There will be no direct benefit to you, but your participation might help us improve the care and services provided to people who have or might have tuberculosis.

Who will the results be shared with?

Nothing that you tell us today will be shared with anybody outside the research team, and nothing will be attributed to you by name. The knowledge that we get from this research will

be shared with you and with healthcare providers in your community before they become widely. Each participant will receive a summary of the results if they would like.

Following the presentations and meetings with local healthcare providers, we will publish the results so that other interested people may learn from the research. The results will be presented to the academic community through international conferences and scholarly journal articles and shared through local and national community conferences, and reports. During all public presentations, and in any publication of results, your identity will not be revealed.

Will you receive any reward (money or food vouchers) for taking part in this study?

You will be given R50 for your time. No other incentive or reward will be provided for taking part in an interview.

Who do I speak to (or contact) if I have any questions about the study?

If you have any questions, you can ask them now or later. If you wish to ask questions later, you may contact Stephanie Law at +27 (82) 421 2246.

The UCT's Faculty of Health Sciences Human Research Ethics Committee can be contacted on 021 406 6338 in case participants have any questions regarding their rights and welfare as research subjects on this study. You can also ask those questions to the ethics officer at McGill University, Ilde Lepore (+1 514 398 8302; ilde.lepore@mcgill.ca).

This study has been reviewed and approved by the human research ethics committees at McGill University and University of Cape Town, and by the City of Cape Town, which are committees whose task it is to make sure that research participants are protected from harm.

Part II: Certificate of Consent

Participant:

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study. I do not waive any of my rights by signing this consent.

Print Name of Participant_____
Signature of Participant _____
Date _____
Day/month/year

If participant is illiterate then a witness (other than the researcher) must sign below:

I have witnessed the accurate reading of the consent form to or by the potential participant, and the individual has had the opportunity to ask questions. I confirm the individual has given consent freely.

Print name of witness_____
Signature of witness _____
Date _____
Day/month/year

Statement by the interviewer

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Some personal information will be collected (age, sex, ethnicity and occupation);
2. A one-on-one interview with the researcher (and a translater, if needed) in a private place in the clinic (or another private place agreed upon) that will last approximately one hour; and
3. The interview will be tape-recorded. The tape will be kept in a secure, locked cabinet and can only be accessed by the researcher Stephanie Law.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print Name of interviewer _____
Signature of interviewer _____
Date _____
Day/month/year

Informed Consent Form for Tuberculosis Patients in and around Cape Town

Project Title: Exploring patient movement within TB care

Researchers

Stephanie Law (PhD Candidate)
Dr. Dick Menzies (PhD Supervisor)
McGill University
Department of Epidemiology
stephanie.law@mail.mcgill.ca
dick.menzies@mcgill.ca

Dr. Keertan Dheda
Professor of Respiratory Medicine Head of the Lung Infection and Immunity Unit
Department of Medicine,
University of Cape Town
keertan.dheda@uct.ac.za

This Informed Consent Form has two parts:

- Information Sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you choose to participate)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

You are invited to join a study that aims to learn about the experiences of individuals seeking care for tuberculosis in and around Cape Town. You do not have to decide today whether or not you will participate in the study. Before you decide, you can talk to anyone you feel comfortable with about the study.

This consent form may contain words that you do not understand. Please ask to stop as we go through the information if you have any questions. If you have questions later, you can ask them of me or of another researcher.

Why is this study being done?

Tuberculosis (TB) is making many people sick in your community. We want to find ways stop this from happening. We believe you can help by telling us about your experiences with TB and about the health care you have received. We want to learn what people who have TB do when they first become sick, and who they go to for treatment or diagnosis. We want to learn about the different types of health care providers people with TB get care from, and what kind of care they receive. We also want to know how you think your care for TB could be made better, because this knowledge might help us learn to improve treatment for tuberculosis and to better control it in this community.

Why are you being asked to take part?

We are inviting you to take part in this study because we feel that your experience as somebody who has received or is receiving care for TB can help us understand what TB patients do when they first become sick, and their opinions of the care they receive for TB.

What will happen if you decide to take part in the study

If you accept to take part in this study, we will ask you to participate in a one-on-one interview with Stephanie Law. The interview will take about one hour.

During the interview, the interviewer will sit down with you in a comfortable, private place at the clinic (or at another private place at your suggestion). If you do not wish to answer any of the questions during the interview, you may say so and the interviewer will move on to the next question. No one else but the interviewer will be present unless you would like someone else to be there. If needed, a translator will be present during the interview.

In the interview, some personal information will be collected, including: age, sex, living status (for example, are you living alone or with roommates or family?), ethnicity and occupation. We will also ask you questions about:

- Your general health, such as: how do you feel about your current health? How was your health before you became sick with tuberculosis?
- Your health-seeking behaviours, such as: who/where do you go to first usually when you get sick? Do you have a regular doctor?
- Past experiences with health care and medications, such as: have you had to take medications for longer periods of time in the past? Have you ever had problems with your health care provider or at the clinic?
- Services and care received for tuberculosis: Where did you go first when you thought you might be sick or had tuberculosis? What was your experience like when you found out you had tuberculosis? Did you go see different providers before you started on treatment? What were your experiences with your providers for your TB care like? What could have made your care for TB better?

What if you refuse to take part?

Your participation in this research is entirely voluntary. It is your choice whether to participate or not, and you can stop at any time during the interview. You have the right to withdraw from the study at any time. You do not have to talk about anything you do not want to, and can refuse to answer questions for any reason. If you refuse to participate or withdraw from the interview, this will not affect the care, treatment, or service you receive at this health facility, or from any healthcare provider. I will give you an opportunity at the end of the interview to review your remarks, and you can ask to modify or remove portions of those, if you do not agree with my notes or if I did not understand you correctly.

Who will see the information collected about you during the study?

The information recorded is confidential. Only researchers directly involved in this study (Stephanie Law, Dr. Amrita Daftary, Dr. Keertan Dheda and Dr. Dick Menzies) will have access to the information documented during your interview. The entire interview will be tape-recorded, but no-one will be identified by name on the tape. The tape and any other materials will be kept

in a secure locked cabinet. The information recorded is confidential, and no one else except Stephanie Law will have access to the tapes. The tapes will be destroyed seven years after the study has ended.

We will not be sharing information about you to anyone outside of the research team. The information that we collect from this project will be kept private. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key.

How many people will take part in the study?

We will be interviewing 20 to 30 TB patients and 10 to 20 healthcare providers who provide care to TB patients.

What are the risks and discomforts of this study?

We are asking you to share with us some of your personal experiences with the care and services you have received for tuberculosis treatment, and you may feel uncomfortable talking about some of the topics. You do not have to answer any question or take part in the interview if you don't wish to do so, and that is also fine. You do not have to give us any reason for not responding to any question, or for refusing to take part in the interview.

Are there any benefits to you for being in the study?

There will be no direct benefit to you, but your participation might help us improve the care and services provided to people who have or might have tuberculosis.

Who will the results be shared with?

Nothing that you tell us today will be shared with anybody outside the research team, and nothing will be attributed to you by name. The knowledge that we get from this research will be shared with you and with healthcare providers in your community before they become widely. Each participant will receive a summary of the results if they would like.

Following the presentations and meetings with local healthcare providers, we will publish the results so that other interested people may learn from the research. The results will be presented to the academic community through international conferences and scholarly journal articles and shared through local and national community conferences, and reports. During all public presentations, and in any publication of results, your identity will not be revealed.

Will you receive any reward (money or food vouchers) for taking part in this study?

You will not be provided any incentive or reward to take part in an interview. However, we will give you R50 for your time.

Who do I speak to (or contact) if I have any questions about the study?

If you have any questions, you can ask them now or later. If you wish to ask questions later, you may contact Stephanie Law at 082 421 2246. The UCT's Faculty of Health Sciences Human Research Ethics Committee can be contacted on 021 406 6338 in case participants have any questions regarding their rights and welfare as research subjects on this study. You can also ask

those questions to the ethics officer at McGill University, Ilde Lepore (+1 514 398 8302; ilde.lepore@mcgill.ca).

This study has been reviewed and approved by the human research ethics committees at McGill University and University of Cape Town, and by the City of Cape Town, which are committees whose task it is to make sure that research participants are protected from harm.

Part II: Certificate of Consent

Participant:

I

have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study. I do not waive any of my rights by signing this consent.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If participant is illiterate then a witness (other than the researcher) must sign below:

I have witnessed the accurate reading of the consent form to or by the potential participant, and the individual has had the opportunity to ask questions. I confirm the individual has given consent freely.

Print name of witness_____

Signature of witness _____

Date _____

Day/month/year

Statement by the interviewer

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Some personal information will be collected (age, sex, living status (e.g.: alone, with roommates or family, or homeless), ethnicity and occupation);
2. A one-on-one interview with the researcher (and a translater, if needed) in a private place in the clinic (or another private place agreed upon) that will last approximately one hour; and
3. The interview will be tape-recorded. The tape will be kept in a secure, locked cabinet and can only be accessed by the researcher Stephanie Law.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print Name of interviewer _____

Signature of interviewer _____

Date _____

Day/month/year

Guide for semi-structured interviews with providers

The one-hour interviews are open-ended. The following guide provides topics that need to be covered, along with suggested questions for each topic. The comfort of participants is of utmost important. If at any point a question is making a participant uncomfortable (or a participant is having difficulty responding to it), move on to another question, and revisit it at a later point. You can say, "How about we come back to this question later?" Always trying to keep the interviewing flowing, and remember that a participant can refuse to answer a question for any reason. Before beginning the interview, make sure the participant is comfortable, and the setting is private and quiet. Also, remind them that participation in the interview and study is voluntary, they can refuse to answer any question, and can end the interview or withdraw from the study at any time.

1. Self-introduction:
    a. Tell me a little about your work here at this clinic/facility
2. Medical/healing practice:
    a. How long have you been working here?
    b. How long have you been seeing people with TB?
    c. How many people with TB do you currently care for?
    d. Do you get many people coming here with TB symptoms looking to be diagnosed, and for TB treatment? How many per week or month?
    e. What types of patients do your clinic serve (only TB? Mostly non-TB?)? How many patients (any kind) do you see per day?
    f. How would you describe the workload? (Do you feel overworked? Do you feel like the clinic is understaffed?) Does the workload affect your interactions with patients (for example, limit the amount of time per patient)?
    g. How do you think patients perceive your practice and the facilities? (Any improvements?)
    h. Why do patients come? Where else could they go? Do they go? Why do they choose to come here? Go elsewhere? Why do you think they do not come?
3. Diagnosing TB:
    a. Can you describe what you do when you think a patient might have TB?
    b. If you provide diagnostic services for TB, what do you do when a patient was confirmed to have TB?
    c. Do you know of patients not coming back for diagnoses? Why do you think they don't? How do you think things can be changed in order to keep more patients?
    d. Do you find there is a difference between genders? Between those with HIV and those without? Between different social classes or race/ethnicity?

    e. Is there anything you would change to the diagnostic process? How and why?
4. Treating TB:
    a. When you have a patient with TB, what sort of care/services do you provide them? Do you prescribe any treatment and drugs? If so, what do you prescribe?
    b. How do you describe the treatment to the patient? Is there any support provided for the patient during treatment from you or someone else? Is there treatment monitoring?
    c. Do you refer TB patients to other providers? Why? Give examples
    d. How do you think patients perceive the care and services provided at this clinic/facility? How do you think the care here differs from that given by other providers (list the different types of providers one by one: private, public, traditional, pharmacy, others)?
    e. Have you had patients come to you after receiving care from another clinic or health care provider? If so, do you know why they have switched care providers?
    f. Have you had patients leave your care or the clinic while still ill with TB? Why do you think they leave? How would you change the care provided at the facility to help retain patients? What solutions do you suggest?
    g. Have you had patients stop treatment while still under your care? If so, why do you think this happens?
    h. In general, why do you think some patients might stop treatment when they are still sick? And why do you think some patients switch healthcare providers?
    i. Have you had patients acquire drug resistance during or after treatment? Why do you think it happens? What do you think patients should do differently? What can you or the clinic/facility change in order to prevent it? What other solutions do you suggest?
    j. How do you think the facility/clinic and its management should change in order to improve care and patient retention? (Prompts: privacy, wait times, drug stock-outs, workload, case management, staffing, facility maintenance and appearances)
5. Possible solutions:
    a. Do you have additional reflections on possible solutions to: Improve patient retention in care, and also to help patients successfully complete treatment?; To increase diagnosis rate?; To increasing number of people seeking diagnosis or treatment for TB?
    b. Any changes you see in the near future to make those improvements? What would it take in terms of money, staff and training?

Guide for semi-structured interviews with patients

The one-hour interviews are open-ended. The following guide provides topics that need to be covered, along with suggested questions for each topic. The comfort of participants is of utmost important. If at any point a question is making a participant uncomfortable (or a participant is having difficulty responding to it), move on to another question, and revisit it at a later point. You can say, "How about we come back to this question later?" Always trying to keep the interviewing flowing, and remember that a participant can refuse to answer a question for any reason. Before beginning the interview, make sure the participant is comfortable, and the setting is private and quiet. Also, remind them that participation in the interview and study is voluntary, they can refuse to answer any question, and can end the interview or withdraw from the study at any time.

1. Self-introduction:
    a. Tell me a little about yourself (What do you like to do? Work? Family? Children? Free time?)
    b. Tell me a little about your health
2. General health & health-seeking behaviours:
    a. How would you describe your general health prior to getting TB? (Do you often get sick?)
    b. When you get sick, where do you usually go first for care? Do you have a regular doctor?
    c. (If they have family or children) Where does your family go for care? (If women) Where did you go for care related to your pregnancies?
    d. In the past when you were sick (or with HIV), have you had any problems taking prescribed medicines? If so, can you describe those problems?
        e. Was there anybody around you who had TB? If so, did they receive treatment? Where?
3. Seeking diagnosis for TB:
    a. When you first thought you were sick or have TB, what did you do first? Where did you go first? (Prompts: friend, pharmacy, traditional healer, private doctor, public doctor)
    b. Why did you do or go there (first)?
    c. What happened at this first visit? Was it helpful? How did you feel about it?
    d. What was good about the visit? What was bad about the visit?
    e. Were you diagnosed at this visit? Did you trust the results?
    f. How was the whole experience of receiving the diagnosis like? How do you feel you were treated? Why?

g. How could it be better?
h. Did you stay with that provider or go somewhere else? If you went somewhere else, why? What were the differences in the care you received? What made one better than the other?
i. (If they did not complete the diagnostic process, ask why they didn't and what would have helped them complete the process, if anything)
j. Repeat above for all subsequent visits, if any. Make sure to record where diagnosis was received (and accepted) and after how many visits.

4. (If applicable) Seeking treatment for TB:
    a. When you got diagnosed, did you seek treatment? If so, where did you go first?
    b. How was your experience of learning about the treatment? Did you have any concerns about it? Did anybody help with your concerns? What could have made this better?
    c. Did you start treatment? Why or why not?
    d. Did you go anywhere to seek treatment after? If yes, why? What were the differences in the care you received? What made one better than the other?
    e. (If they never started treatment even after seeking it, ask why they didn't and what could have helped them start treatment)
    f. Repeat above for all subsequent visits, if any. Make sure to record where treatment was started and after how many visits.
5. (If applicable) Receiving treatment for TB:
    a. Where were you treated? How was your experience of the treatment?
    b. What did you think of the care you received during treatment? What could have been better?
    c. Did you finish treatment?
        i. If yes: what kept you on track with treatment? (Prompts: work, family/children, the provider, the nurses or health care workers, feeling better) Was there any point at which you thought you might stop? If so, why did you think that?
        ii. If no: what led to you stopping treatment? (Prompts: work, family, provider attitudes or practices, switching provider, personal circumstances, money, travel, trust, feeling lack of control or autonomy over treatment)
    d. Did you receive treatment at more than one place? If so, why did you decide to do that? What were the differences in the care you received? What made one better than the other?
6. (For anybody who did not complete the diagnostic or treatment process) What could have changed so that you could complete the diagnostic or treatment process? (Prompts: community attitudes (stigma), health worker or clinic attitudes and practices, facilities and services, more knowledge or control/autonomy.)
7. Any additional reflections on your experience as a TB patient: improvements to services received for TB; improvements to the facilities; improvements to provider attitudes or training; differences between providers from whom care was received.

McGill University, Faculty of Medicine, IRB Approval

McGill

Faculty of Medicine
1655 Promenade Sir William Osler #633
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler #633
Montréal, QC H3G 1Y6

Fax/Télécopieur: (514) 398-3870
Tél/Tel: (514) 398-3124

CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board (IRB) is a registered University IRB working under the published guidelines of the Tri-Council Policy Statement, in compliance with the Plan d'action ministériel en éthique de la recherche et en intégrité scientifique (MSSS, 1998), and the Food and Drugs Act (17 June 2001); and acts in accordance with the U.S. Code of Federal Regulations that govern research on human subjects. The IRB working procedures are consistent with internationally accepted principles of Good Clinical Practices.

At a full Board meeting on 14 September 2015, the Faculty of Medicine Institutional Review Board, consisting of:

Alain Brunet, PhD	Kelly Davison, MD
Geoffrey Conrad, BCL, LLB,	Patricia Dobkin, PhD
Carolyn Ells, PhD	Paula LaPierre, PhD
Kathleen Montpetit, M.Sc.	Roberta Palmour, PhD

Lucille Panet-Raymond, B.A.

Examined the research project **A09-M44-15B** titled: *Exploring patient movement within healthcare and its role in the MDR-TB epidemic: a mixed methods study*

As proposed by: Dr. Dick Menzies (Applicant) to _____ (Granting Agency, if any)

And consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

17 November 2015 (Date) — Chair, IRB — Dean of Faculty

Institutional Review Board Assurance Number: FWA 00004545

University of Cape Town, Faculty of Health Sciences, IRB Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

05 November 2015

HREC REF: 606/2015

Dr K Dheda
Division of Pulmonology
H46.41
OMB

Dear Prof Dheda

PROJECT TITLE: EXPLORING PATIENT MOVEMENT WITHIN HEALTHCARE AND ITS ROLE IN THE MDR-TB EPIDEMIC: A MIXED METHODS STUDY (MMed-candidate-S Law)

Thank you for your response letter dated 26 October 2015, addressing the issues raised by the Human Research Ethics Committee (HREC).

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

Approval is granted for one year until the 30th November 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student: Stephanie Law is also involved in this project.

Please quote the HREC reference no in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

pp T Burges)

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

City of Cape Town Approval

CITY OF CAPE TOWN
ISIXEKO SASEKAPA
STAD KAAPSTAD

CITY HEALTH

Dr Hélène Visser
Manager: Specialised Health

T: 021 400 3981 **F:** 021 421 4894 **M:** 083 298 8718
E: Helene.Visser@capetown.gov.za

2015-12-07

Re: Research Request: Exploring patient movement within healthcare and its role in the MDR-TB epidemic: A mixed methods study (6590) (ID No: 10532)

Dear Prof Dheda,

Your research has been approved as per your request.

Mitchells Plain Sub District: Contact People	**Mzamomhle and Phumlani Clinics** Mrs S Elloker (Sub District Manager) Tel: (021) 391-5012/ 084 222 1478 Mrs N Nqana (Head: PHC & Programmes) Tel: (021) 391-0175/ 084 2221489
Klipfontein Sub District: Contact People	**Guguletu Clinic** Mr K Nkoko (Sub District Manager) Tel: (021) 630-1667/ 082 433 1332 Mrs T Nojaholo (Head: PHC & Programmes) Tel: (021) 630-1626/ 084 220 0133

Please note the following:

1. All individual patient information obtained must be kept confidential.
2. Access to the clinics and its patients must be arranged with the relevant Managers such that normal activities are not disrupted.
3. A copy of the final report must be sent to the City Health Head Office, P O Box 2815 Cape Town 8001, within 6 months of its completion and feedback must also be given to the clinics involved.
4. Your project has been given an ID Number (10532) Please use this in any future correspondence with us.
5. No monetary incentives to be paid to clients on the City Health premises.

Thank you for your co-operation and please contact me if you require any further information or assistance.

Yours sincerely

pp DR VISSER.

DR G H VISSER
MANAGER: SPECIALISED HEALTH

cc. Mrs Elloker & Ms Nqana
Mr Nkoko & Mrs Nojaholo
Dr de Azevedo & Mrs Patel Abrahams

STUDY 3: INTERVENTIONS TO IMPROVE RETENTION-IN-CARE AND TREATMENT ADHERENCE AMONG PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS: A SYSTEMATIC REVIEW

The following is a duplicate of the online supplement to an upcoming article currently in press: Law S, Daftary A, O'Donnell M, Padayatchi N, Calzavara L, Menzies D. Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review. Eur Resp J: in press.

Table of Contents

Table 1. Search strategy

OVID Database: EMBASE, MEDLINE, Global Health, PsycINFO, Social Work Abstracts
1. exp tuberculosis, multidrug resistant/ 2. (mdrtb or xdrtb).mp. 3. (mdr or xdr or ((multidrug or drug) adj resistan*)).mp. 4. (tuberculosis or tb).mp. 5. 3 and 4 6. 1 or 2 or 5 7. exp patient compliance/ 8. (dropout* or drop out*).mp. 9. cash.mp. 10. reimburse*.mp. 11. refund*.mp. 12. reward*.mp. 13. incentiv*.mp. 14. voucher*.mp. 15. reminder*.mp. 16. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 17. (penal* or punish*).mp. 18. (nonadheren* or adheren* or abscond* or attrition* or complian* or noncomplian* or default* or fail* or stop* or refus* or incomplet* or interrupt*).mp. 19. 16 or 17 or 18 20. 6 and 19 21. limit 20 to yr="2000 -Current"
Cochrane CENTRAL
MeSH descriptor: [Tuberculosis, Multidrug-Resistant] explode all trees (MDR or XDR) (multidrug or drug) next (resistan*) (#2 or #3) and (tuberculosis or TB) #1 or #4 MeSH descriptor: [Patient Compliance] explode all trees dropout or (drop out) cash reimburse* refund* reward* incentiv* voucher* reminder* #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 penal* or punish* nonadheren* or adheren* or abscond* or attrition* or complian* or noncomplian* or default* or fail* or stop* or refus* or incomplet* or interrupt* #15 or #16 or #17 #5 and #18 #19 Publication Year from 2000
Web of Science
12. #11 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2000-2017* 11. #5 AND #10 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*

10. #6 OR #7 OR #8 OR #9
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
9. TS=(nonadheren* OR adheren* OR abscond* OR attrition* OR complian* OR noncomplian* OR default* OR fail* OR stop* OR refus* OR incomplet* OR interrupt*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
8. TS=(reimburs* OR refund* OR reward* OR incentiv* OR voucher* OR reminder* OR monitor* OR penal* OR punish*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
7. TS=(cash)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
6. TS= (dropout* or drop out*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
5. #1 OR #4
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
4. #2 AND #3
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
3. TS=(TB OR Tuberculosis)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
2. TS=(mdr OR xdr OR ((multidrug OR drug) NEAR (resistan*)))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
1. TS= (mdrtb OR xdrtb)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

Scopus

((TITLE-ABS-KEY (droput* OR "drop out*" OR cash OR reimburs* OR refund* OR reward* OR incentiv* OR voucher* OR reminder* OR monitor* OR penal* OR punish* OR nonadheren* OR adheren* OR abscond* OR attrition* OR complian* OR noncomplian* OR default* OR fail* OR stop* OR refus* OR incomplet* OR interrupt*)) AND ((TITLE-ABS-KEY (mdrtb OR xdrtb)) OR ((TITLE-ABS-KEY ((mdr OR xdr OR ((multidrug OR drug) W/3 resistan*)))) AND (TITLE-ABS-KEY (tb OR tuberculosis))))) AND (PUBYEAR > 2000)

Table 2. Characteristics of included study cohorts in pooled analyses

Author, Year (Cohort group/Trial arm)	Study period (years)	Country	N	HIV (%)	XDR (%)	Previously Treated (%)	
						Any	SLD
*Studies with two or more cohorts**							
Baral 2014 (Arm 1)	2008	Nepal	33	n/a†	n/a	n/a	n/a
Baral 2014 (Arm 2)	2008	Nepal	42	n/a†	n/a	n/a	n/a
Huerga 2017 (Homa Bay)^^	2006-2012	Kenya	28	17 (60.7)	0	24 (85.7)	n/a
Huerga 2017 (Mathare)^^	2006-2012	Kenya	70	15 (21.4)	0	63 (90.0)	n/a
Huerga 2017 (Nairobi)^^	2006-2012	Kenya	71	11 (15.5)	0	67 (94.4)	n/a
Loveday 2015 (Site 1)	2008-2010	South Africa	125	96/124 (77.4)	0	87 (69.6)	6 (4.8)
Loveday 2015 (Site 2 & 3)	2008-2010	South Africa	350	235/333 (70.6)	0	217 (62.0)	33 (9.4)
Loveday 2015 (Site 4)	2008-2010	South Africa	261	197/235 (83.8)	0	107(41.0)	14 (5.4)
Mohr 2017 (SAT)¥	2010-2014	South Africa	244	180 (73.8)	0	146 (59.8)	33 (13.5)
Mohr 2017 (SOC)¥	2010-2014	South Africa	160	112 (70.0)	0	122 (76.3)	19 (11.9)
Taneja 2017 (Control)	2014	India	50	0	0	50 (100)	0
Taneja 2017 (Intervention)	2014	India	50	0	0	50 (100)	0
Studies with a single cohort							
Alene 2017	2011-2014	China	481	0	10 (2.1)	417 (86.7)	n/a
Bastard 2015	2002-2010	Armenia/ Georgia	393	n/a†	15/247 (6.1)	304 (77.4)	115 (29.3)
Cox 2007	2003-2005	Uzbekistan	87	n/a†	0 (0)	87 (100)	57 (65.5)
Escudero 2006øø	1998-2000	Spain	25	0	1 (4.0)	22 (88.0)	n/a
Gelmanova 2011§	2006-2008	Russia	38	0	2 (5.3)	21 (55.3)	10 (26.3)
Isaakidis 2011	2007-2011	India	58	58 (100)	3/50 (6.0)	51 (87.9)	26 (44.8)
Joseph 2011	2006-2007	India	38	0	0	38 (100)	0
Keshavjee 2008	2000-2004	Russia	608	5/604 (0.8)	29 (4.8)	605 (99.5)	n/a
Kliiman 2009	2003-2005	Estonia	289	11 (3.8)	54 (18.7)	139 (48.1)	n/a

Meressa 2015	2009-2014	Ethiopia	612	133/612 (21.7)	6/612 (1.0)#	603 (98.5)	n/a
Mitnick 2003	1996-1999	Peru	75	1/65 (1.5)	5 (6.7)	75 (100)	n/a
Mitnick 2008§§	1999-2002	Peru	651	9/635 (1.4)	48 (7.4)	649 (99.7)	420/648 (64.5)
Mohr 2015~	2008-2012	South Africa	853	605 (70.9)	39 (4.6)	576 (67.5)	0
Satti 2012ø	2008-2009	Lesotho	134	94 (70.2)	n/a	129 (96.3)	18 (13.4)
Shin 2006	1998-2000	Russia	244	0	n/a	239 (98.0)	n/a
Suarez 2002	1997-1999	Peru	298	n/a†	n/a	298 (100)	n/a
Thomas 2007	1999-2003	India	66	n/a†	1/33 (3.0)	66 (100)	n/a
Vaghela 2015	2009-2010	India	101	2 (2.0)	n/a	n/a	n/a
Yu 2015 ~	2007-2009	Taiwan	124	n/a†	n/a	60 (48.4)	n/a

*Studies with more than one arm/cohort – each arm shown separately.
#Presumed XDR-TB
~Includes 190 patients with mono-RR-TB.
^^In the full sample (from all three study sites), resistance to second-line drugs were as follows: CPM 1/63 (1.6%), KM 1/63 (1.6%), and OFX 3/47 (6.4%).
¥ Includes unknown number of patients with mono-RR-TB. Of 244 in the SAT cohort, 67 patients had recorded outcomes before end of 6 months (16 LTFU; 33 died; 1 failure; 17 were transferred out). Of the 160 in the DOT cohort, 42 had recorded outcomes before end of 6 months (19 LTFU; 13 died; 2 failures; 8 were transferred out). These patients were excluded from analysis in the published study, however, they were included in this analysis (except those transferred out/not evaluated).
†The estimated prevalence of HIV among TB patients: 6.3% in Armenia; 3.5% in Uzbekistan; 6% in Peru; 2.2% in Georgia; 4.7% in Nepal; 3% in India (WHO 2017); and 2.4% in Taiwan.

Table 3. Treatment outcomes at end of study of cohorts included in pooled analyses*

Author, Year (Cohort group)	Sample size (n)	Outcomes at end of study					
		Lost to follow-up (%)	Success (%)	Failure (%)	Death (%)	Transferred out/not evaluated (%)	Still on treatment** (%)
Studies with two or more cohorts							
Baral 2014 (Arm 1)	33	2 (6.1)	28 (84.8)	2 (6.1)	1 (3.0)	0 (0)	0 (0)
Baral 2014 (Arm 2)	42	6 (14.3)	32 (76.2)	2 (4.8)	2 (4.8)	0 (0)	0 (0)
Huerga 2017 (Homa Bay)	28	0 (0.0)	16 (57.1)	0 (0)	5 (17.9)	7 (25.0)	0 (0)
Huerga 2017 (Mathare)	70	6 (8.6)	52 (74.3)	0 (0)	4 (5.7)	8 (11.4)	0 (0)
Huerga 2017 (Nairobi)	71	6 (8.5)	43 (60.6)	1 (1.4)	12 (16.9)	9 (12.7)	0 (0)
Loveday 2015 (Site 1)	125	9 (7.2)	90 (72.0)	7 (5.6)	17 (13.6)	2 (1.6)	0 (0)
Loveday 2015 (Site 2 & 3)	350	70 (20.0)	202 (57.7)	23 (6.6)	47 (13.4)	8 (2.3)	0 (0)
Loveday 2015 (Site 4)	261	28 (10.7)	135 (51.7)	19 (7.3)	69 (26.4)	10 (3.8)	0 (0)
Mohr 2017 (SAT)	244	47 (19.3)	99 (40.6)	8 (3.3)	48 (19.7)	42 (17.2)	0 (0)
Mohr 2017 (SOC)	160	44 (27.5)	66 (41.3)	7 (4.4)	19 (11.9)	24 (15.0)	0 (0)
Taneja 2017 (Control)	50	21 (42.0)	14 (28.0)	3 (6.0)	7 (14.0)	5 (10.0)	0 (0)
Taneja 2017 (Intervention)	50	22 (44.0)	20 (40.0)	1 (2.0)	6 (12.0)	1 (2.0)	0 (0)
Studies with a single cohort							
Alene 2017	481	130 (27.0)	275 (57.2)	63 (13.1)	13 (2.7)	0 (0)	0 (0)
Bastard 2015	393	127 (32.3)	171 (43.5)	56 (14.2)	39 (9.9)	0 (0)	0 (0)
Cox 2007	87	12 (13.8)	54 (62.1)	8 (9.2)	13 (14.9)	0 (0)	0 (0)
Escudero 2006	25	2 (8.0)	21 (84.0)	0 (0)	0 (0)	2 (8.0)	0 (0)
Gelmanova 2011	38	6 (15.8)	27 (71.1)	2 (5.3)	2 (5.3)	1 (2.6)	0 (0)
Isaakidis 2011	58	7 (12.1)	13 (22.4)	2 (3.4)	13 (22.4)	0 (0)	23 (39.7)
Joseph 2011	38	5 (13.2)	25 (65.8)	5 (13.2)	3 (7.9)	0 (0)	0 (0)
Keshavjee 2008	608	119 (19.6)	400 (65.8)	58 (9.5)	31 (5.1)	0 (0)	0 (0)
Kliiman 2009	289	48 (16.6)	165 (57.1)	35 (12.1)	48 (16.6)	0 (0)	0 (0)
Meressa 2015	612	36 (5.9)	481 (78.6)	10 (1.6)	85 (13.9)	0 (0)	0 (0)
Mitnick 2003	75	5 (6.7)	55 (73.3)	1 (1.3)	14 (18.7)	0 (0)	0 (0)
Mitnick 2008	651	65 (10.0)	429 (65.90)	18 (2.8)	134 (20.6)	4 (0.6)	1 (0.2)
Mohr 2015	853	227 (26.6)	359 (42.1)	48 (5.6)	123 (14.4)	96 (11.3)	0 (0)
Satti 2012	134	1 (0.7)	83 (61.9)	1 (0.7)	46 (34.3)	3 (2.2)	0 (0)
Suarez 2002	298	34 (11.4)	136 (45.6)	96 (32.2)	32 (10.7)	0 (0)	0 (0)
Shin 2006	244	28 (11.5)	188 (77.0)	16 (6.6)	12 (4.9)	0 (0)	0 (0)
Thomas 2007	66	16 (24.2)	25 (37.9)	17 (25.8)	8 (12.1)	0 (0)	0 (0)
Vaghela 2015	101	7 (6.9)	72 (71.3)	4 (4.0)	17 (16.8)	1 (1.0)	0 (0)
Yu 2015	124	0 (0.0)	106 (85.5)	2 (1.6)	16 (12.9)	0 (0)	0 (0)

*Results for studies with more than one patient cohort are shown separately for each study arm or cohort.
**These are patients who have not yet completed the study's standard treatment duration, and who do not have a final treatment outcome recorded by the end of study.

Table 4. Summary of quality assessment of non-randomized studies (based on Robins-I Tool)

Author, Year	Overall risk of confounding bias	Overall Risk of selection bias	Overall risk due to intervention classification	Overall risk due to deviations from interventions	Overall risk of bias due to missingness	Overall risk of outcome measurement bias	Overall Risk of reporting bias	OVERALL BIAS
Cohort studies without comparison groups								
Alene 2017	n/a	Low	n/a	No information	Low	Low	Low	No information
Bastard 2015	n/a	Low	n/a	No information	Moderate	Low	Low	No information
Cox 2007	n/a	Low	n/a	Low	Low	Low	Low	Low
Escudero 2006	n/a	Low	n/a	Low	Moderate	Low	Low	Moderate
Gelmanova 2011	n/a	Low	n/a	Low	Low	Low	Low	Low
Isaakidis 2011	n/a	Low	n/a	Low	Low	Low	Low	Low
Joseph 2011	n/a	Low	n/a	No information	Low	Low	Low	No information
Keshavjee 2008	n/a	Low	n/a	Low	Low	Low	Low	Low
Kliiman 2009	n/a	Low	n/a	Low	Low	Low	Low	Low
Meressa 2015	n/a	Low	n/a	Low	Low	Low	Low	Low
Mitnick 2003	n/a	Low	n/a	Low	Low	Low	Low	Low
Mitnick 2008	n/a	Low	n/a	Low	Low	Low	Low	Low
Mohr 2015	n/a	Low	n/a	Low	Moderate	Low	Low	Moderate
Satti 2012	n/a	Low	n/a	Low	Low	Low	Low	Low
Shin 2006	n/a	Low	n/a	Low	Low	Low	Low	Low
Suarez 2002	n/a	Low	N/a	Low	Low	Low	Low	Low
Thomas 2007	n/a	Low	n/a	Moderate	Low	Low	Low	Moderate
Vaghela 2015	n/a	Low	n/a	Low	Low	Low	Low	Low
Yu 2015	n/a	Low	n/a	Low	Low	Low	Low	Low
Cohort studies with 2 or more interventions								
Mohr 2017	Serious	Low	Low	Low	Low	Low	Low	Serious
Loveday 2015	Serious	Low	Low	Low	Low	Low	Low	Serious
Cox 2014	Serious	Low	Low	Low	Moderate	Low	Low	Serious
Huerga 2017	Serious	Low	Low	Low	Moderate	Low	Low	Serious

Table 5. Summary of quality assessment of cluster randomized trials

Author, Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting? (reporting bias)	Other bias
Baral 2014	Low	Low	High	Low	Low	Low	Serious risk of confounding bias
Taneja 2017	Low	Low	High	Low	Low	Low	Serious risk of confounding bias

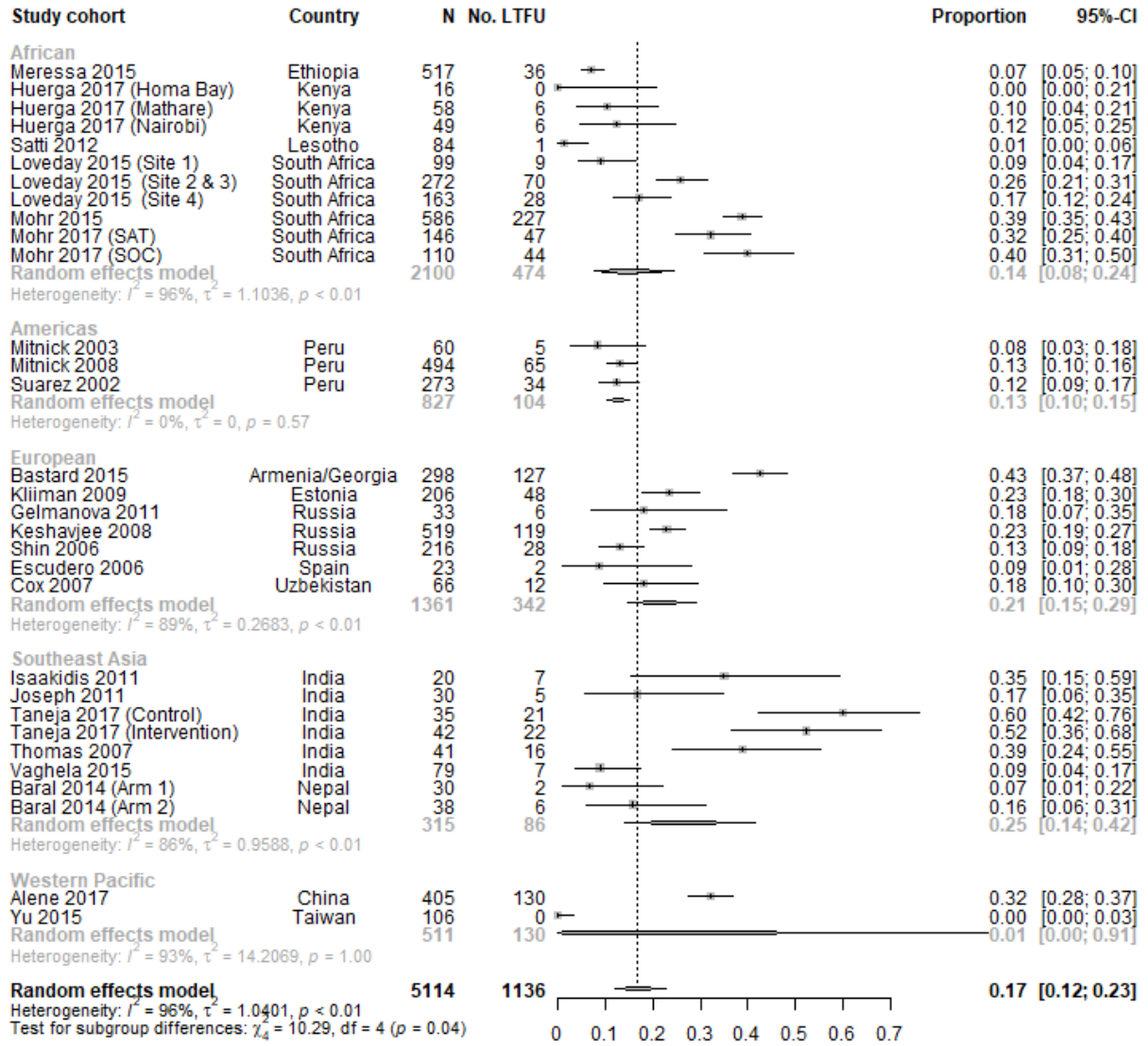


Figure 1. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by WHO region.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

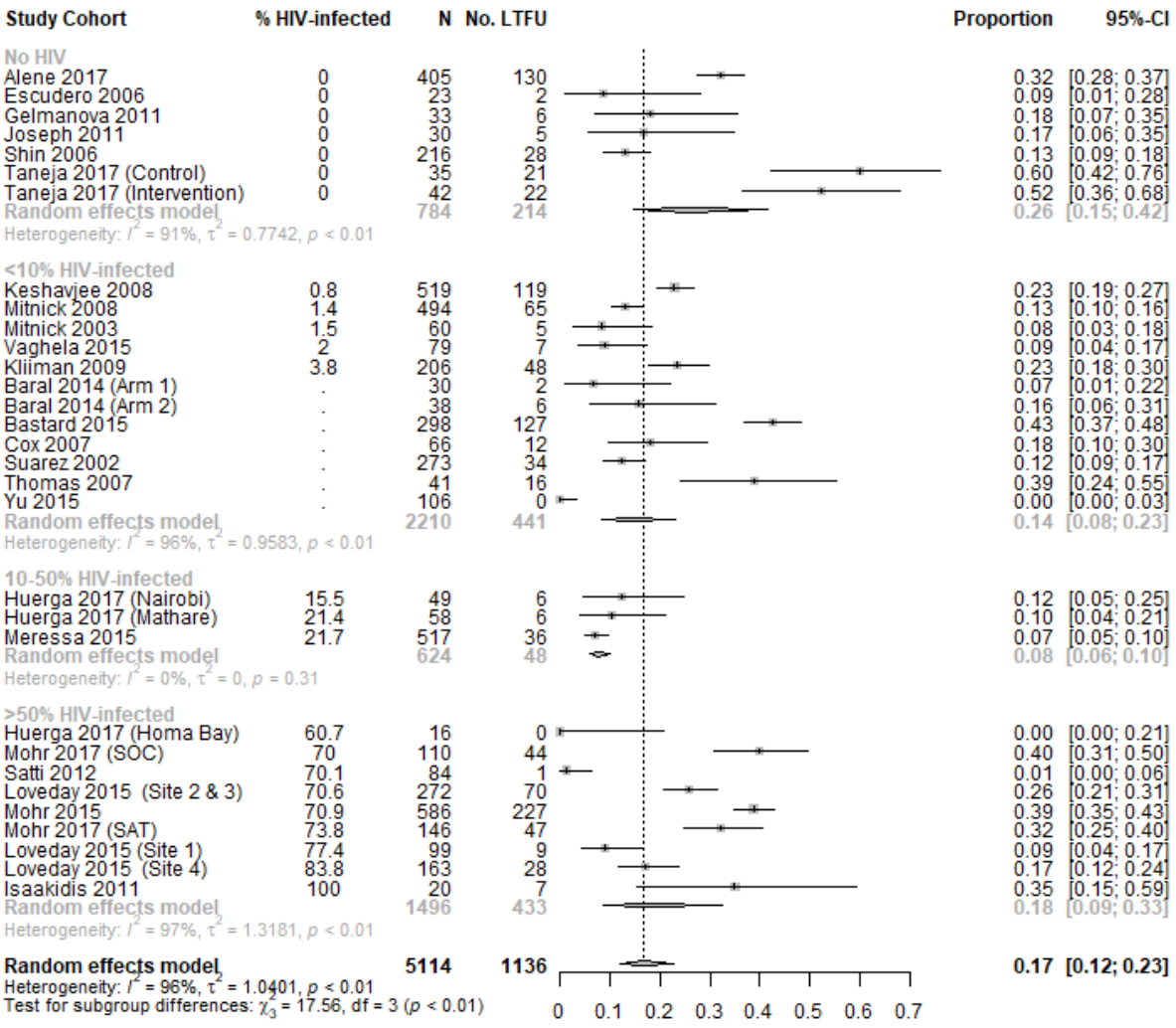


Figure 2. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by HIV prevalence.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. For studies that did not report HIV prevalence, all were assumed to have <10% HIV prevalence according to country-level estimates of HIV prevalence among TB patients (see Supplement Table 3). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

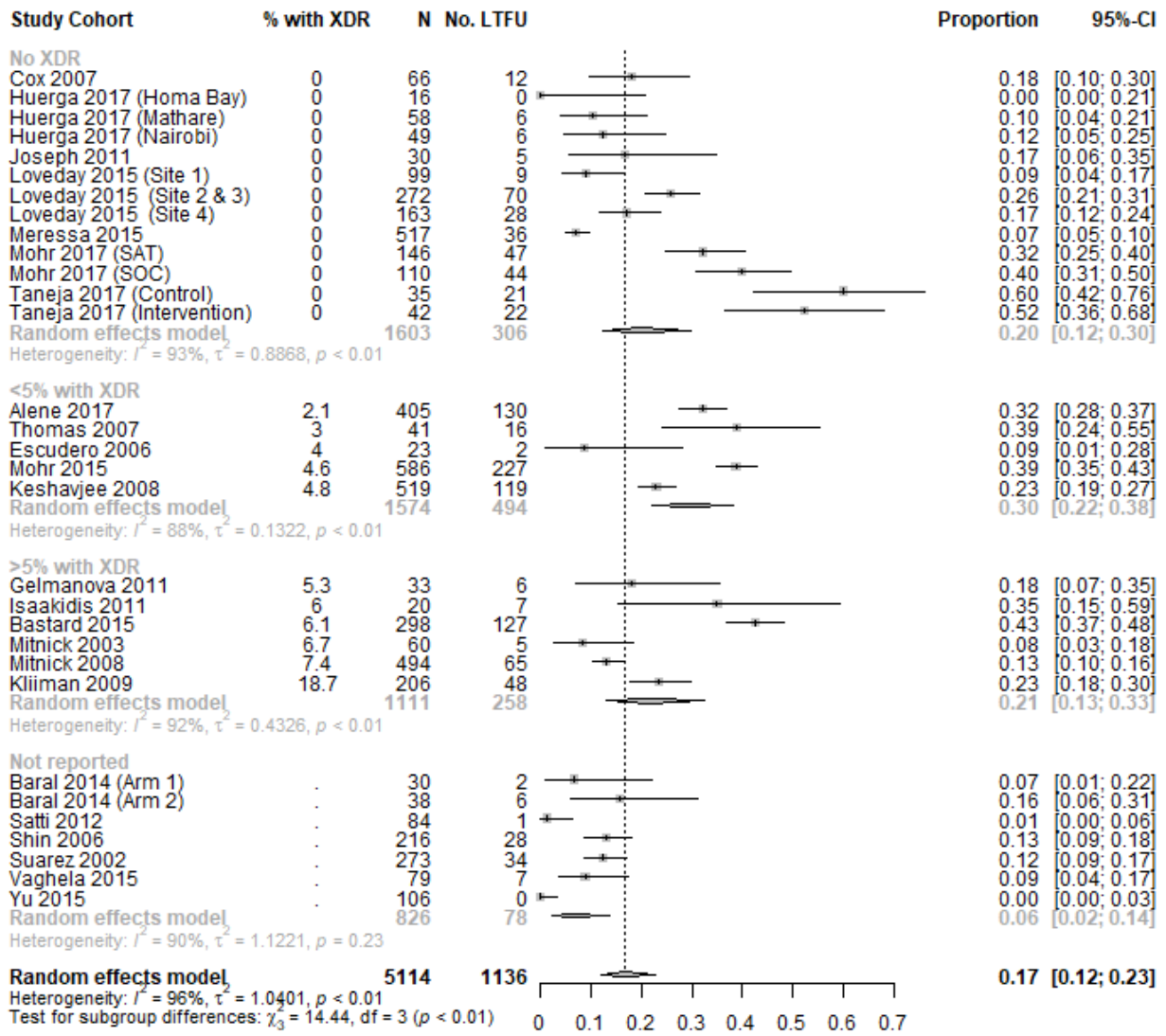


Figure 3. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by XDR status.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; XDR = extensively drug-resistant TB.

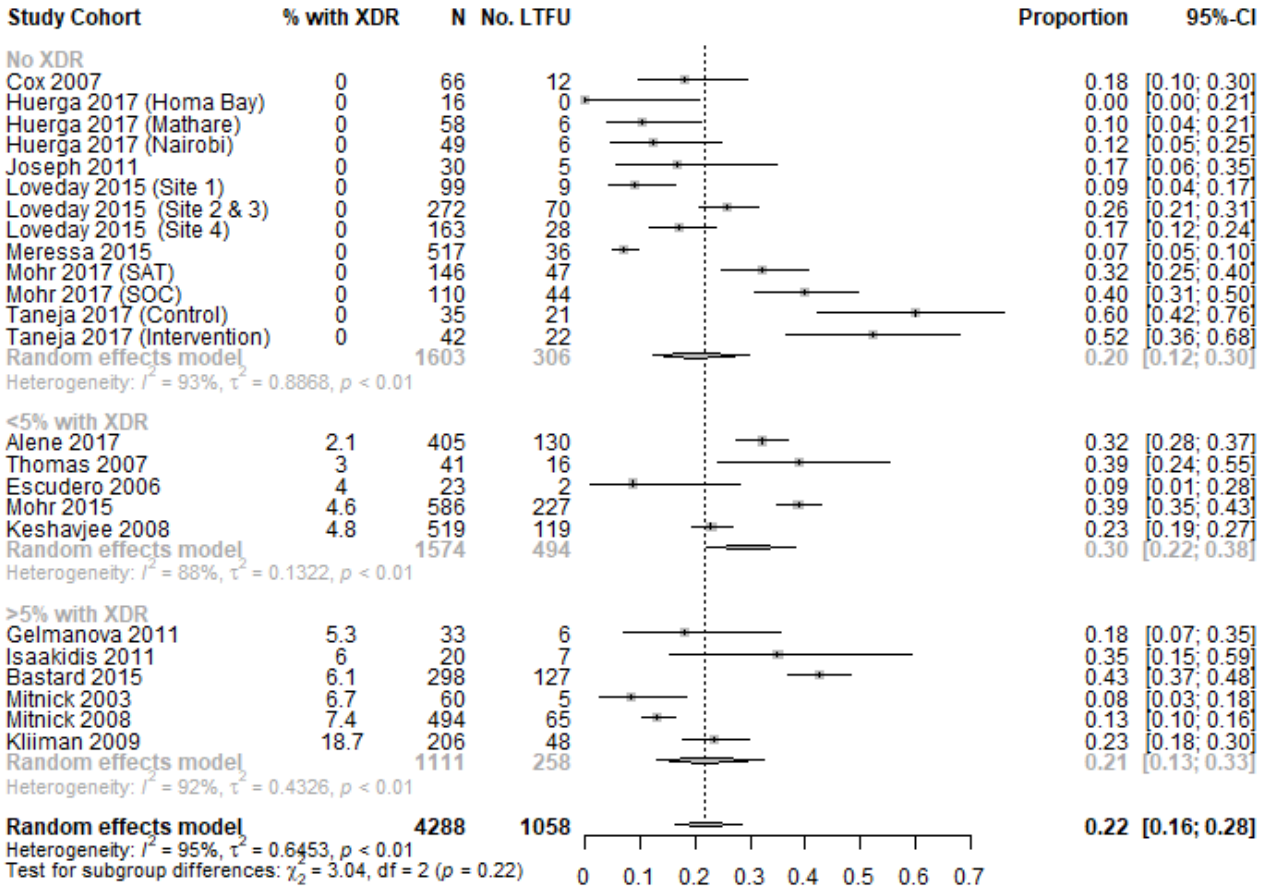


Figure 4. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by XDR status.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Study cohorts that did not report XDR status among patients were excluded (n=7). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; XDR = extensively drug-resistant TB.

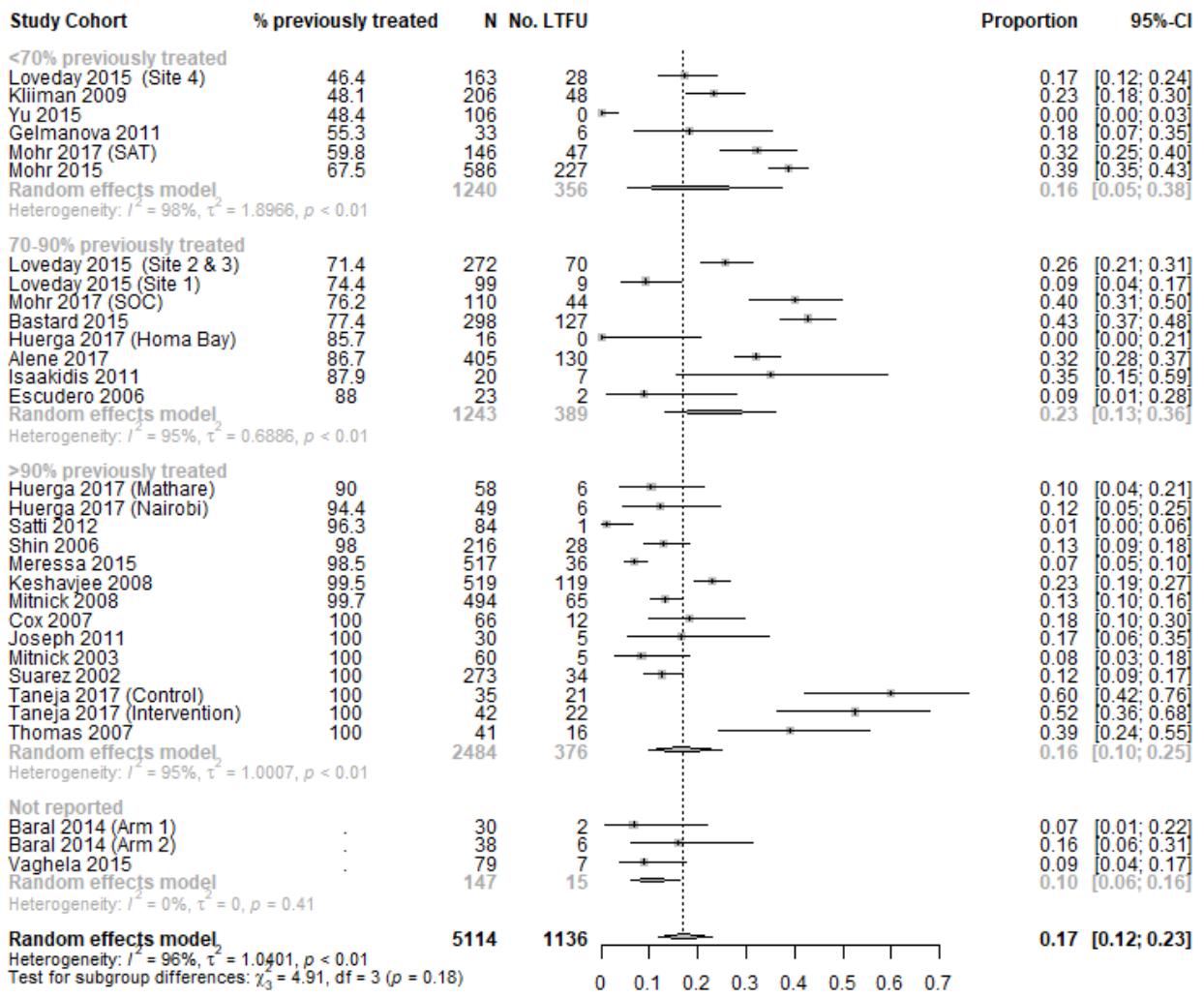


Figure 5. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by proportion previously treated for any type of TB.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

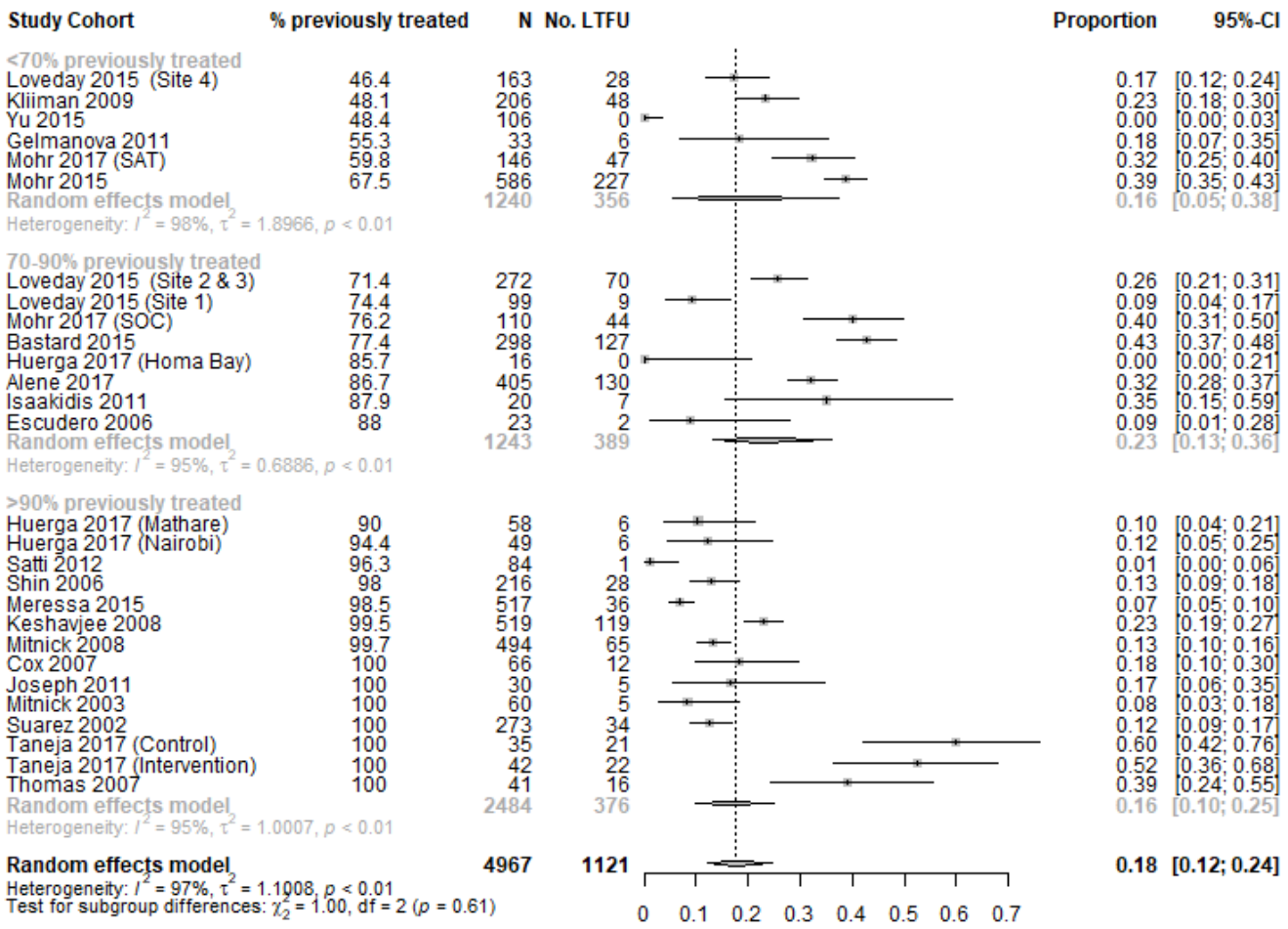


Figure 6. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by proportion previously treated for any type of TB.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Study cohorts that did not report proportions with any previous TB treatment were excluded (n=3). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

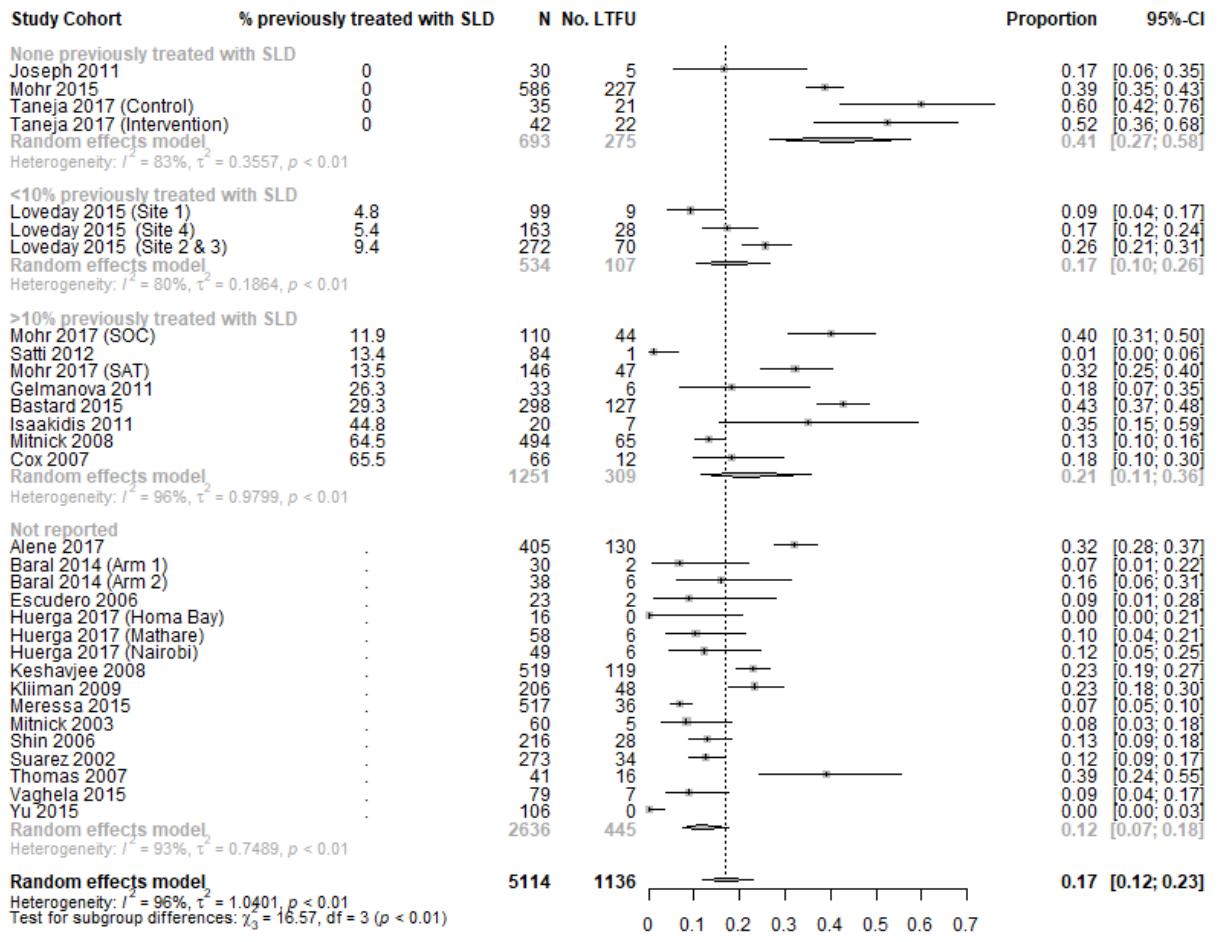


Figure 7. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by proportion previously treated with second-line TB drugs.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; SLD = second-line drugs.

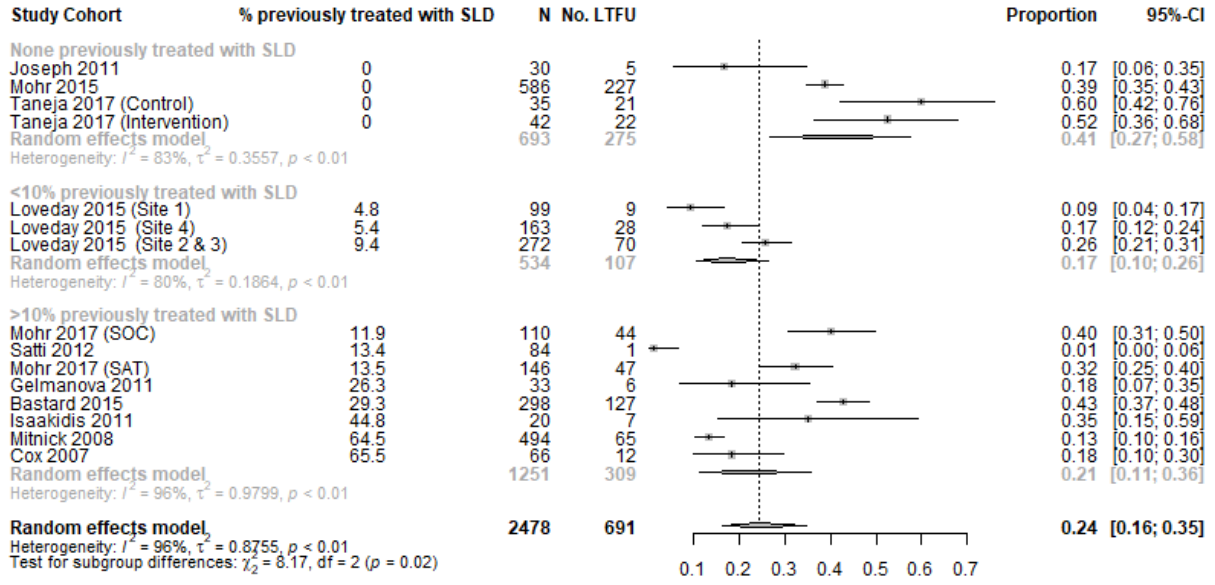


Figure 8. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by proportion previously treated with second-line TB drugs.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Study cohorts that did not report proportions with any previous treatment with second-line drugs were excluded (n=16). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; SLD = second-line drugs.

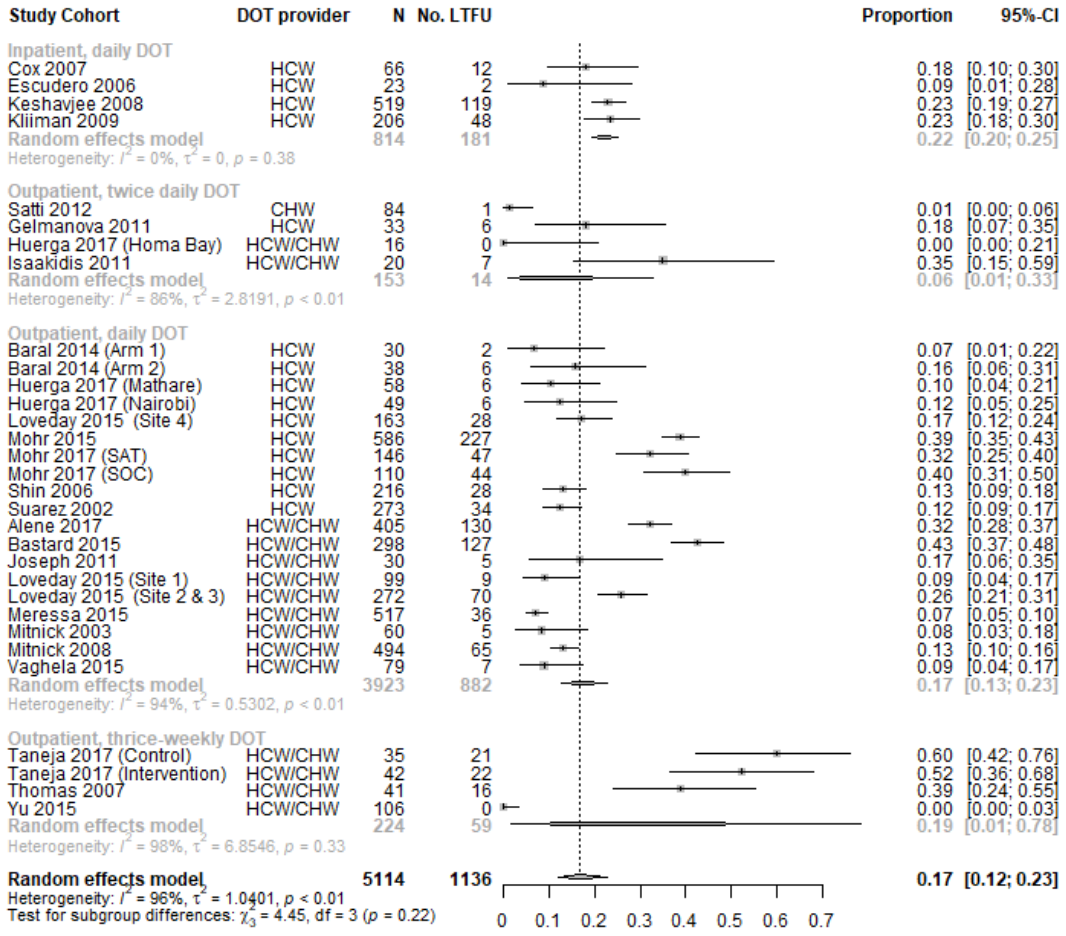


Figure 9. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by DOT frequency method during the intensive phase.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; HCW = health care worker; CHW = community health worker; DOT = daily observed therapy.

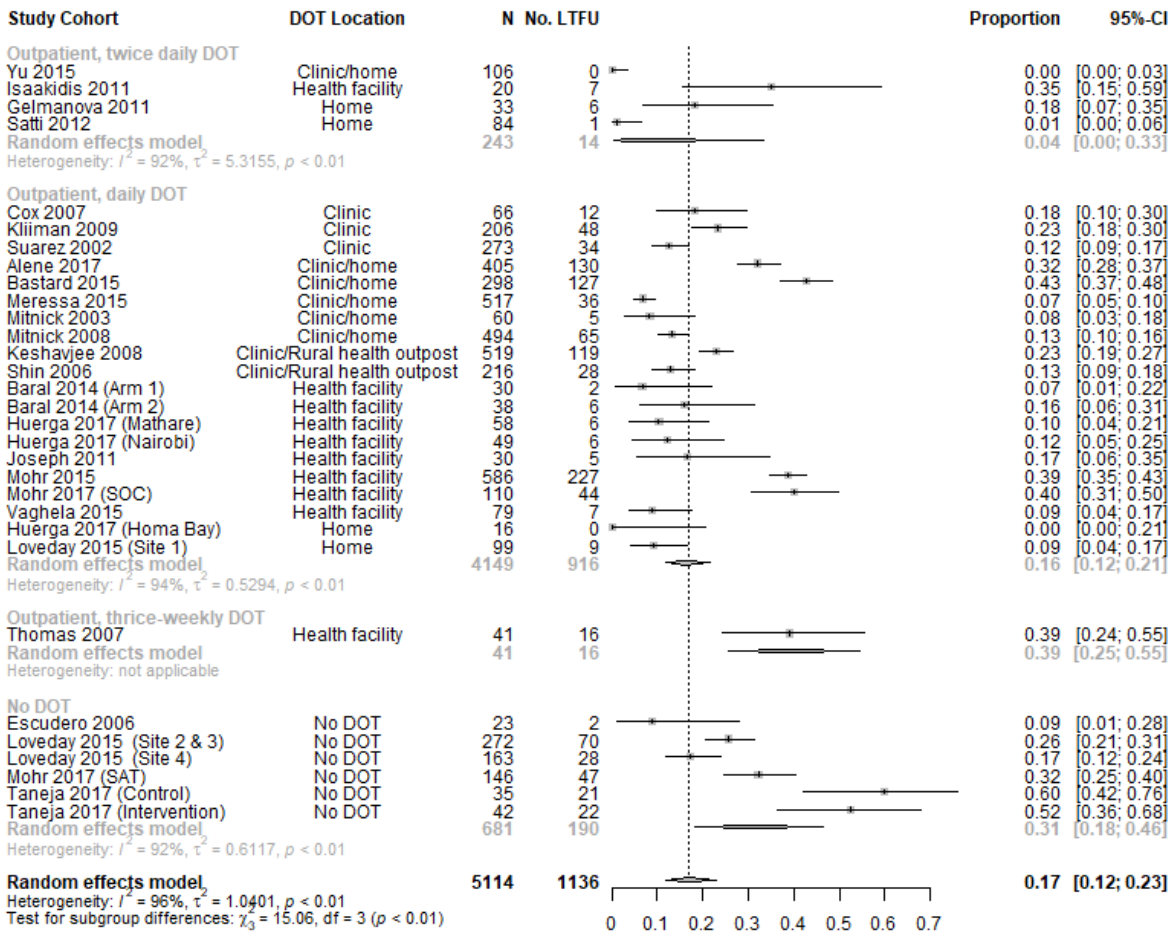


Figure 10. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by DOT frequency during the continuation phase.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; HCW = health care worker; CHW = community health worker; DOT = daily observed therapy.

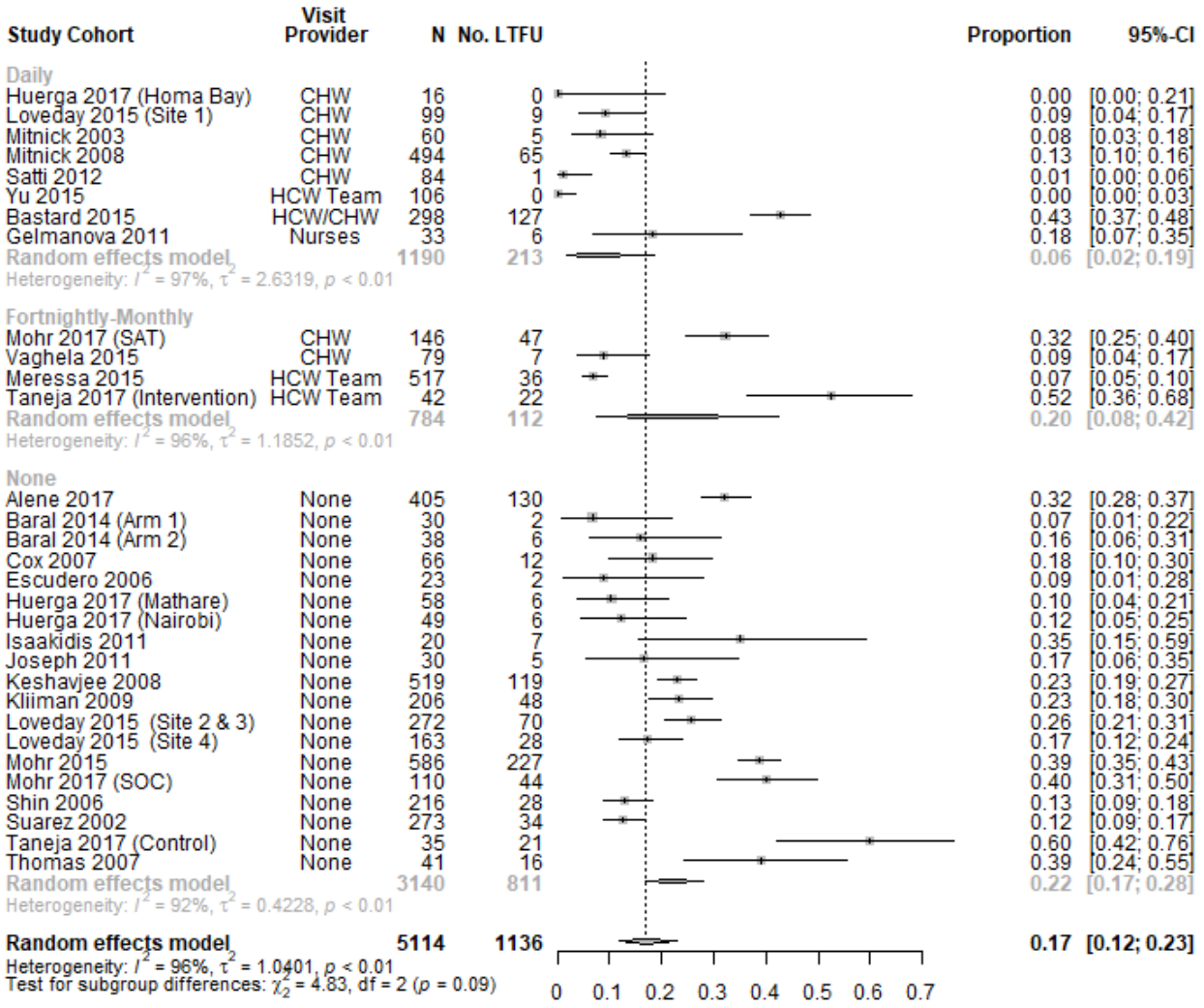


Figure 11. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by frequency of home visits throughout treatment.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. The statistical heterogeneity in subgroup with daily home visits was decreased to I^2=90% when Bastard 2015 was excluded, with a pooled proportion LTFU of 4% (95%CI 1 to 13%), or when both Bastard 2015 and Gelmanova 2011 were excluded, with a pooled proportion LTFU of 3% (95% CI 1 to 12%). Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; HCW = health care worker; CHW = community health worker.

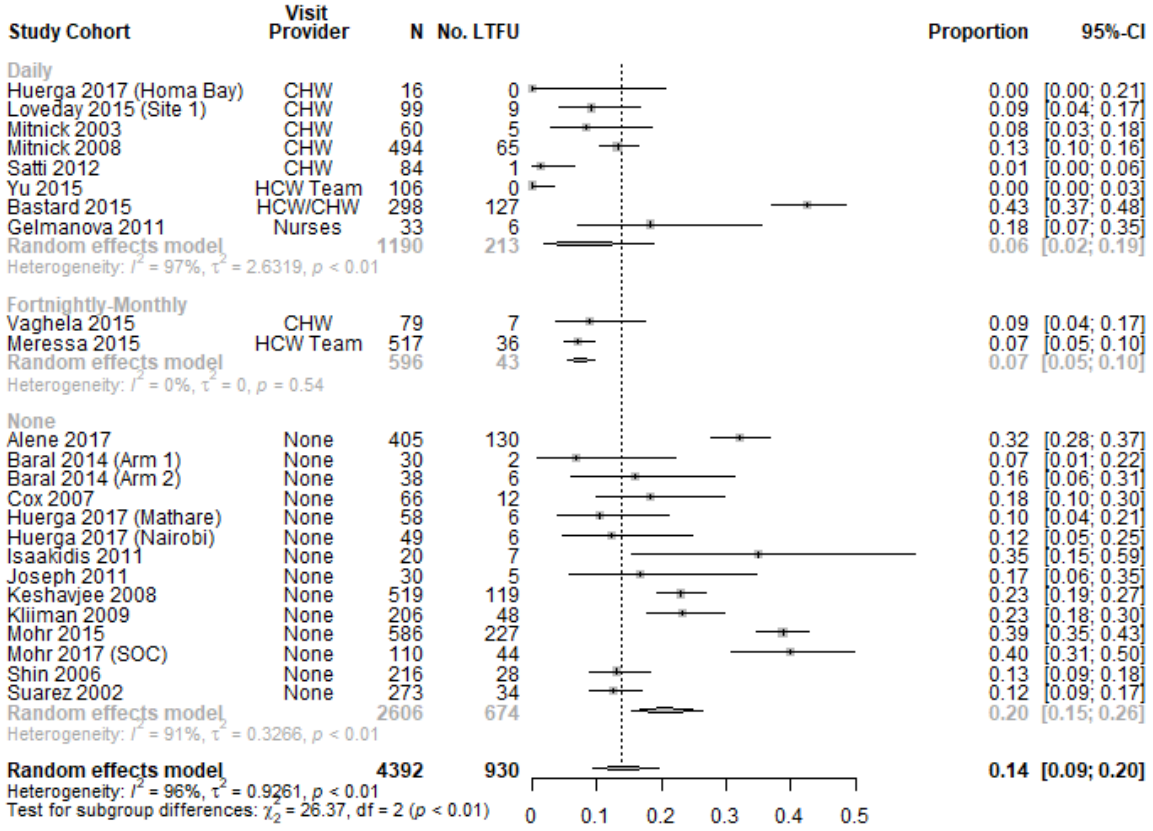


Figure 12. Forest plot of proportions lost to follow-up (LTFU) stratified by frequency of home visits throughout treatment, among study cohorts that received twice-daily or daily DOT.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval; HCW = health care worker; CHW = community health worker.

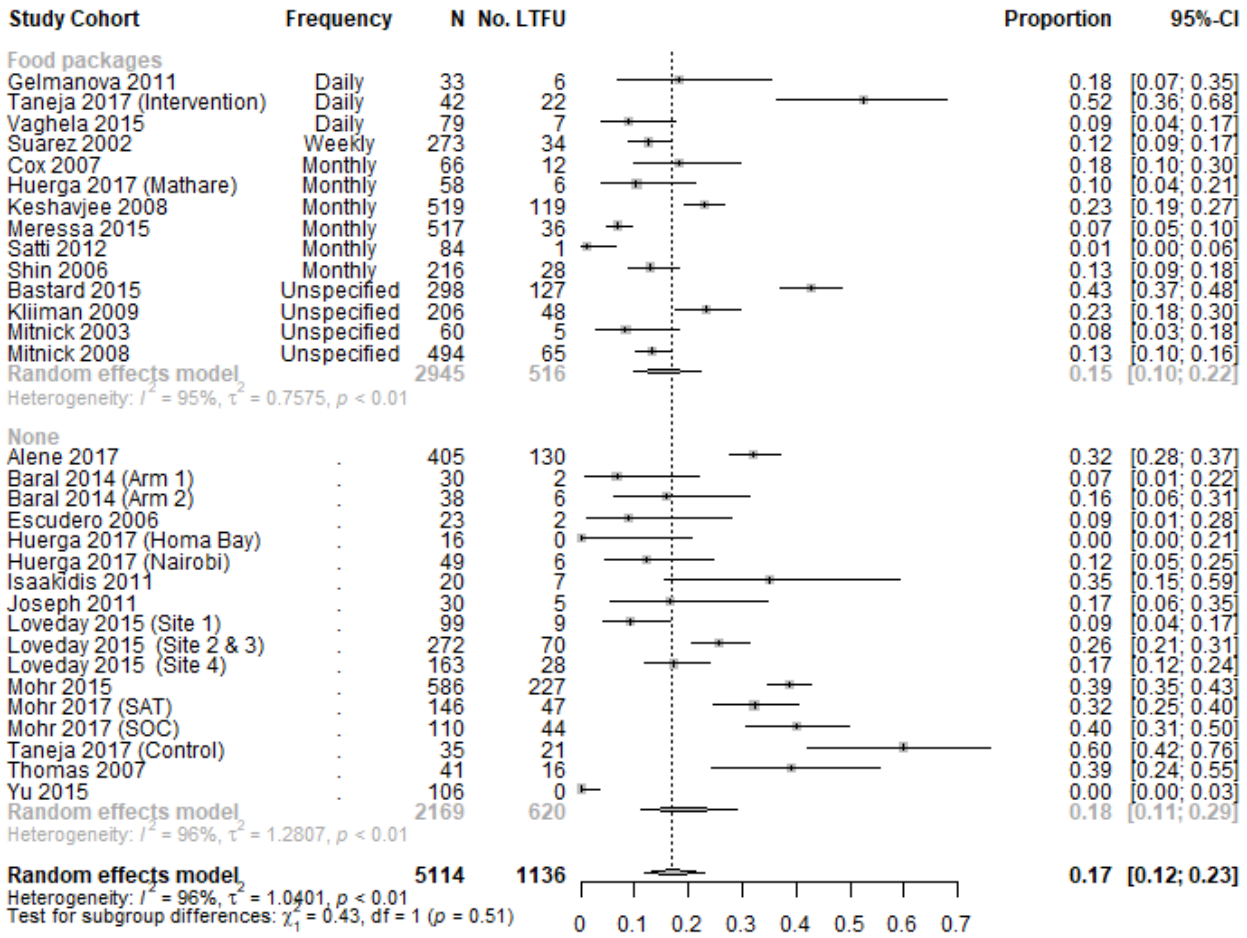


Figure 13. Forest plot of proportions lost to follow-up (LTFU) across all study cohorts stratified by whether of food was provided during treatment.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

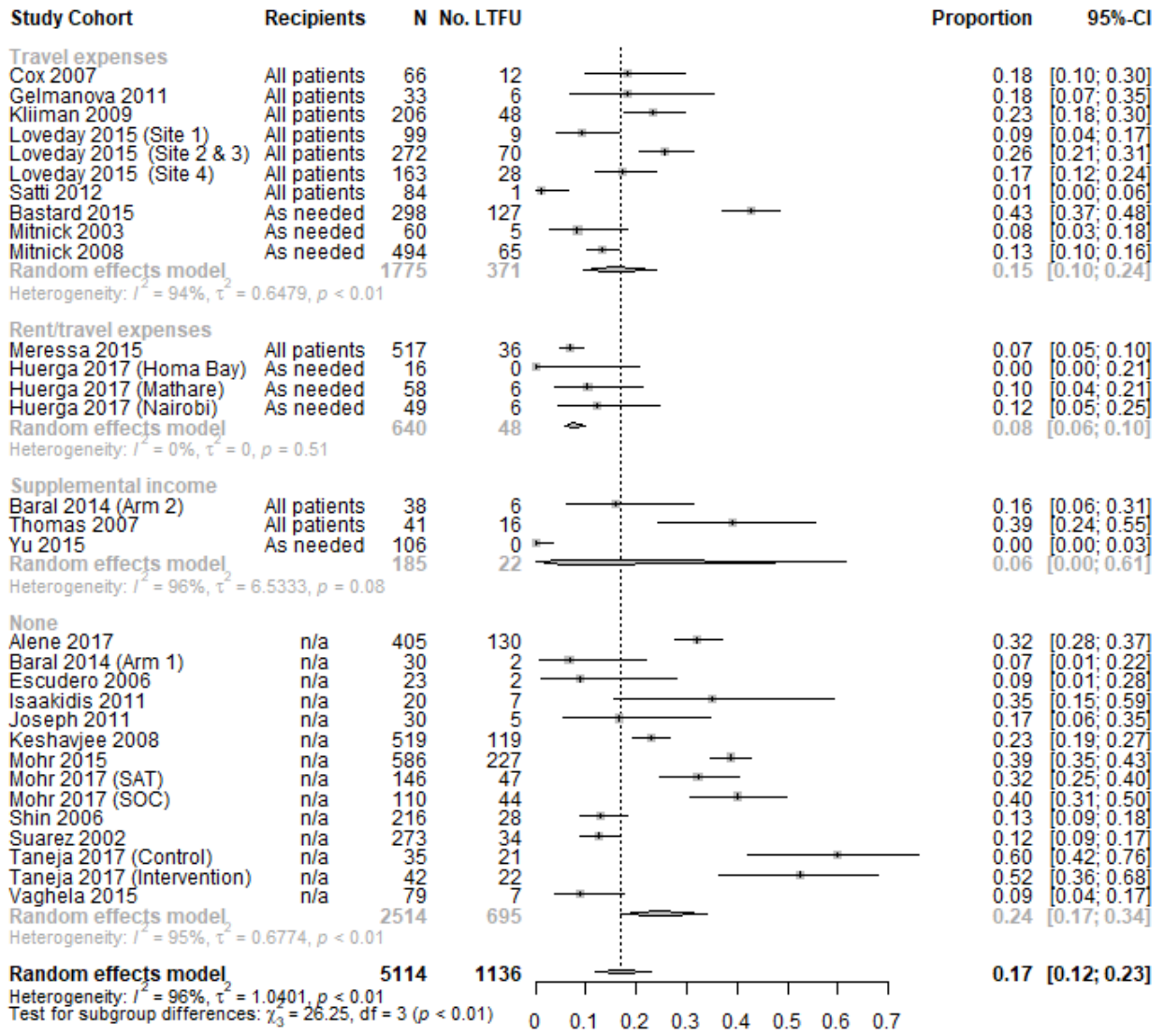


Figure 14. Forest plot of proportions lost to follow-up across all study cohorts stratified by type of financial support provided during treatment.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

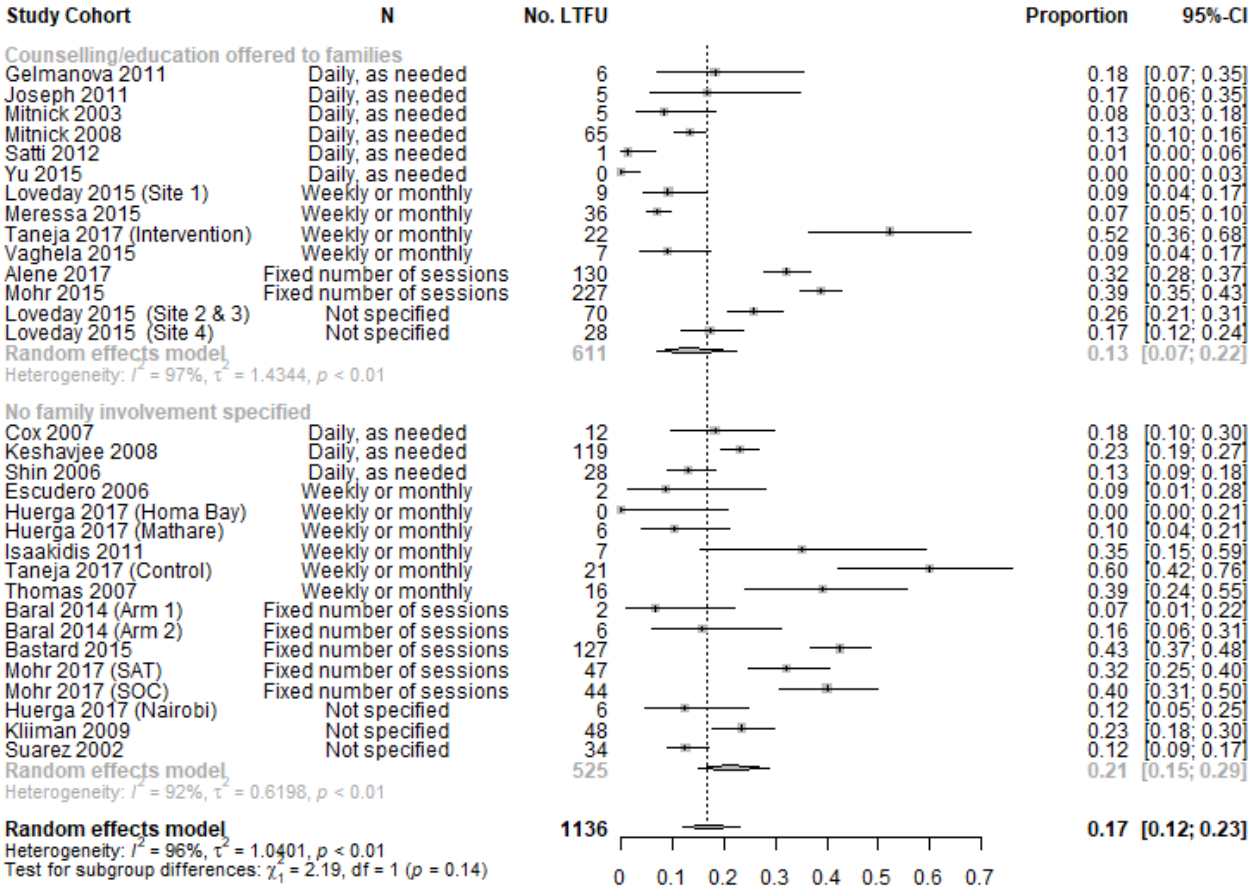


Figure 15. Forest plot of proportions lost to follow-up across all study cohorts stratified by whether families were offered counselling and education.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

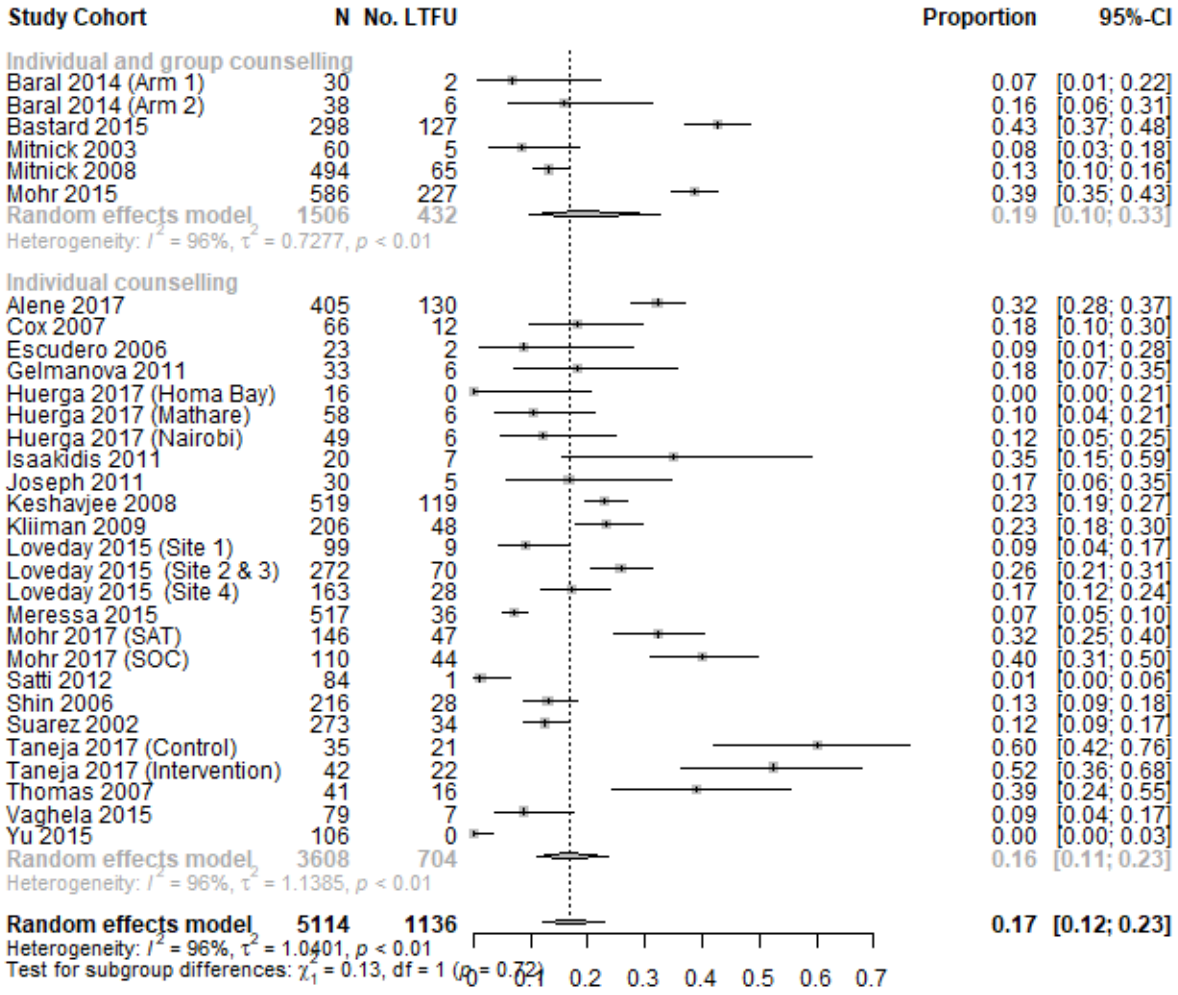


Figure 16. Forest plot of proportions lost to follow-up across all study cohorts stratified by whether group counselling was offered in addition to individual counselling.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

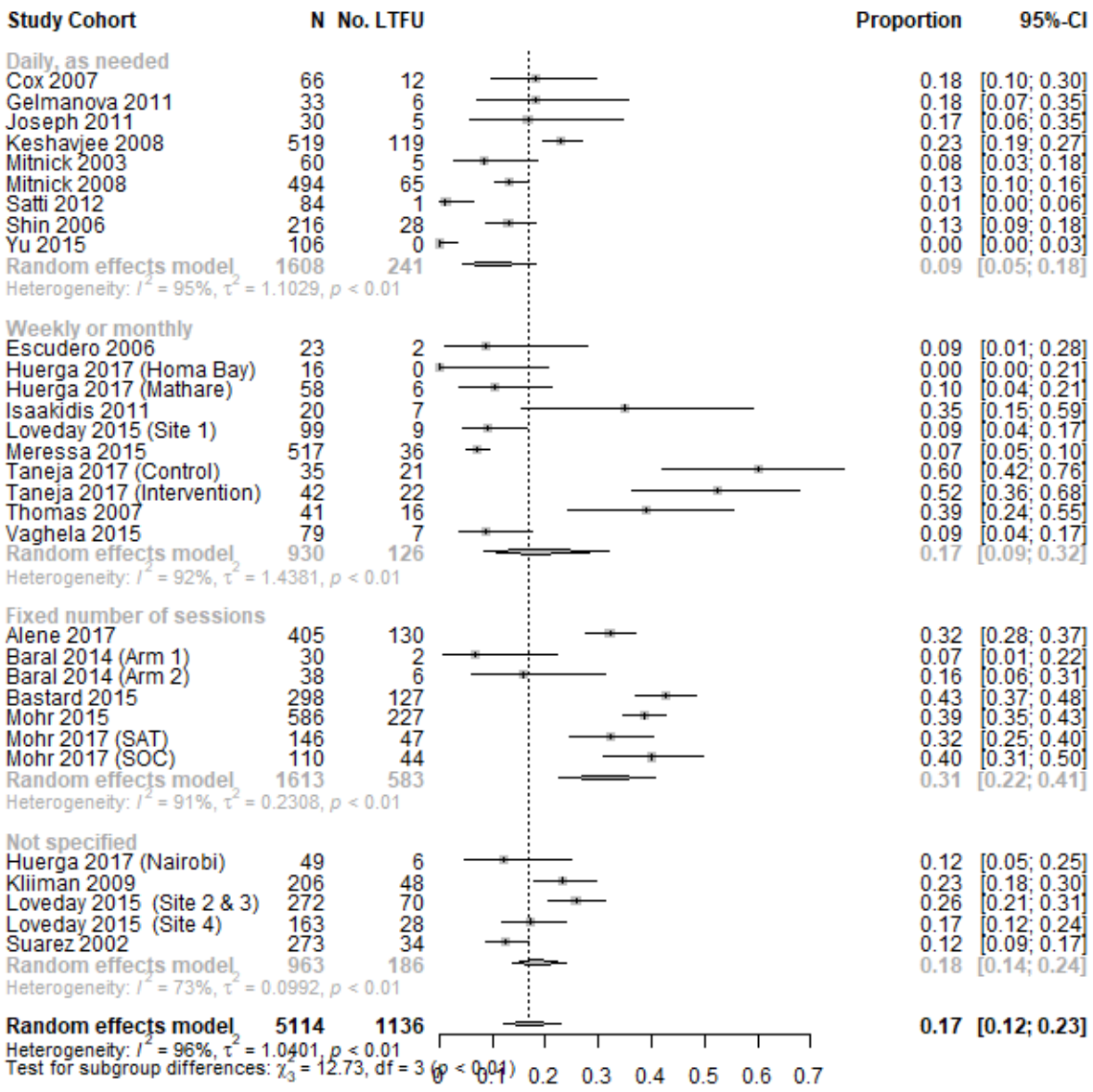


Figure 17. Forest plot of proportions lost to follow-up across all study cohorts stratified by frequency of individual counselling provided during treatment.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

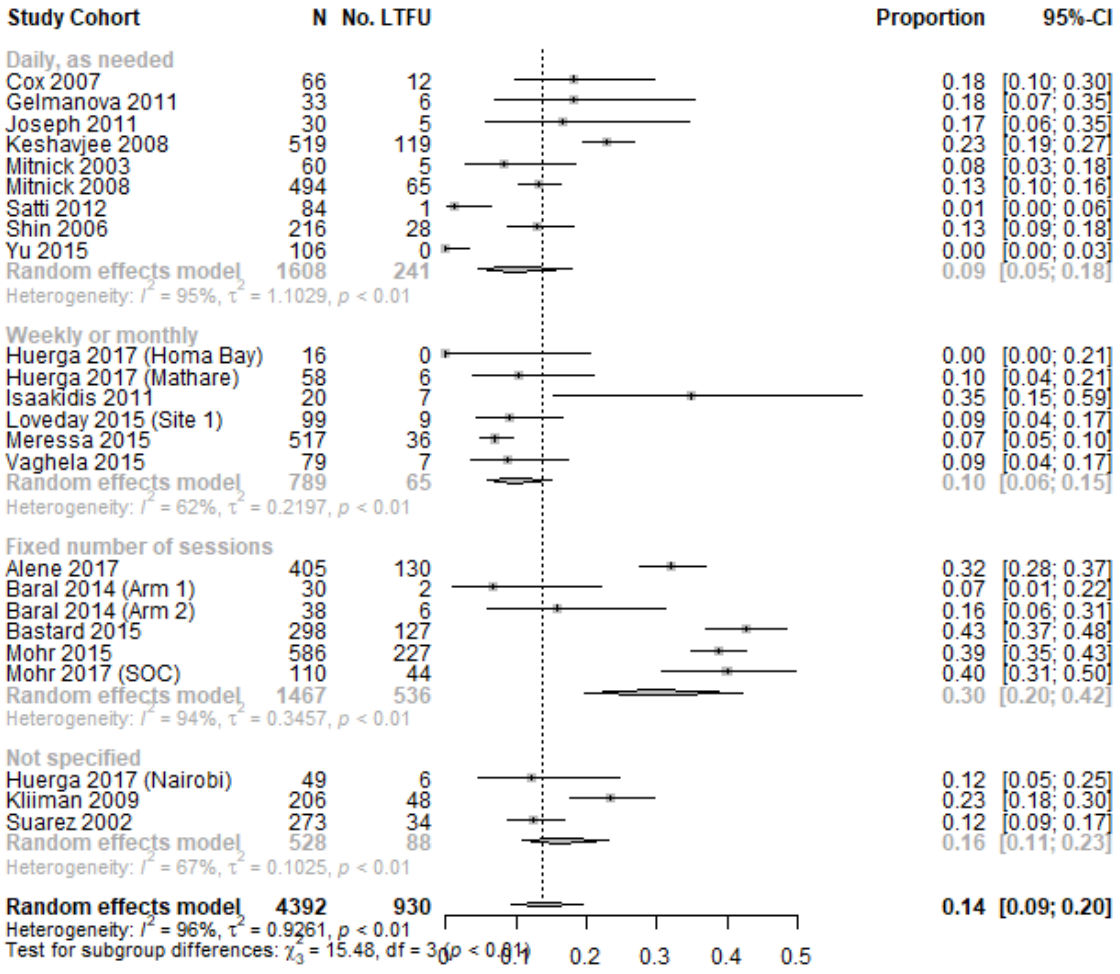


Figure 18. Forest plot of proportions lost to follow-up stratified by frequency of individual counselling provided during treatment, among study cohorts that received twice-daily or daily DOT.

Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

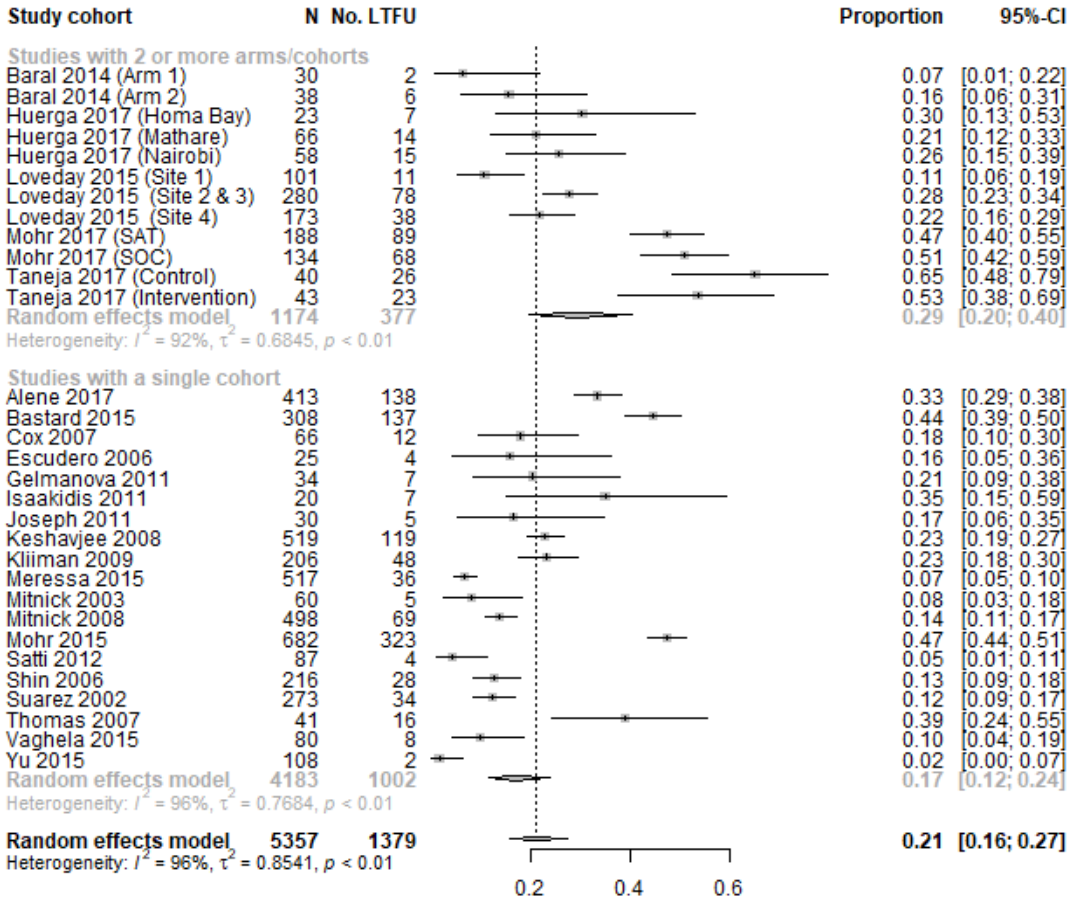


Figure 19. Forest plot of proportions lost to follow-up (LTFU), including those who transferred out or without reported final outcomes, across all study cohorts.

Patients who died or failed treatment were excluded. Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

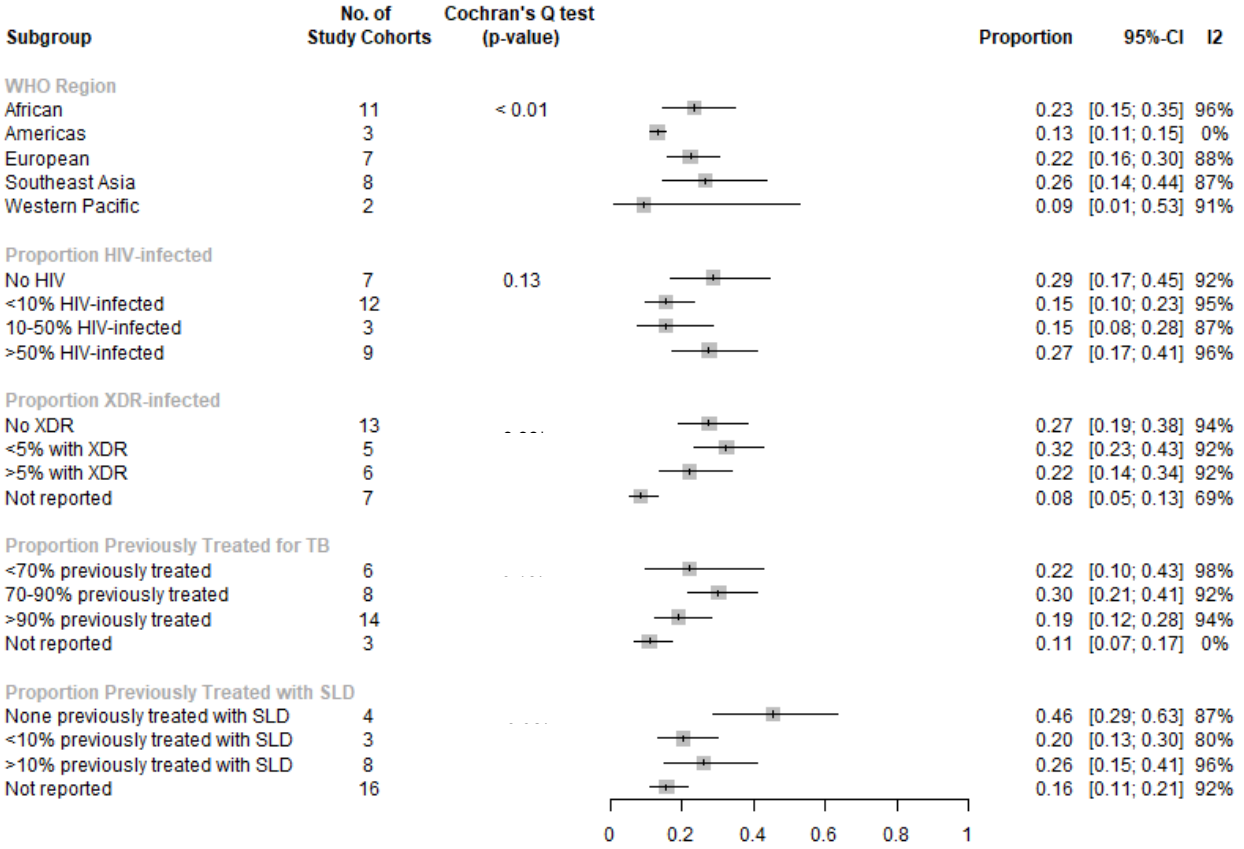


Figure 20. Forest plot of pooled proportions lost to follow-up, including those who transferred out or whose treatment outcome was not evaluated, across all study cohorts, stratified by study cohort characteristics.

Patients who died or failed treatment were excluded. *Study cohorts that did not report this parameter were excluded from the Cochran's Q test for subgroup differences.

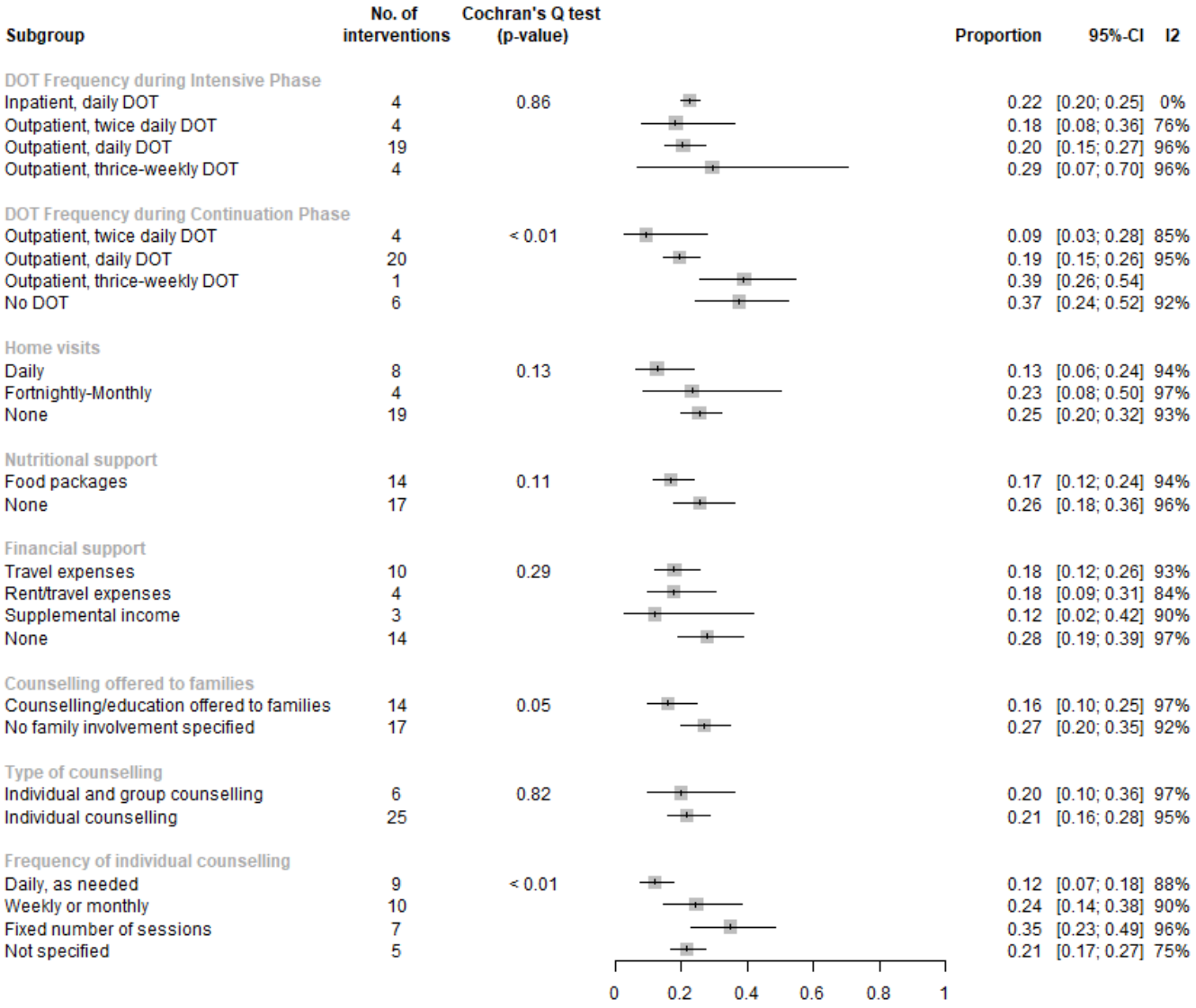


Figure 21. Forest plot of pooled proportions lost to follow-up, including those who transferred out or whose treatment outcome was not evaluated, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died or, failed treatment were excluded.

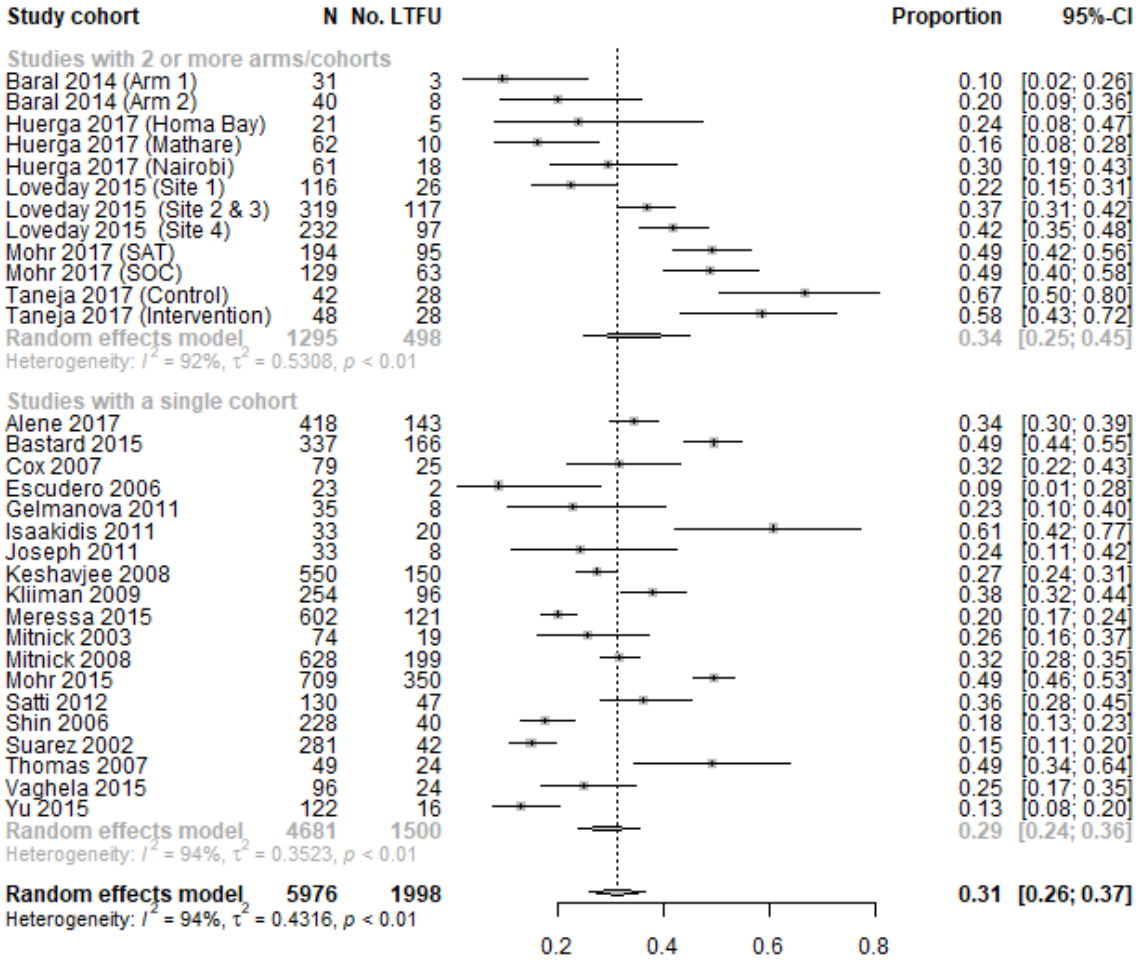


Figure 22. Forest plot of proportions lost to follow-up (LTFU), including those who died, across all study cohorts.

Patients who failed treatment, transferred out or whose treatment outcome was not evaluated, were excluded.
Abbreviations: SAT = self-administered therapy; SOC = standard of care; CI = confidence interval.

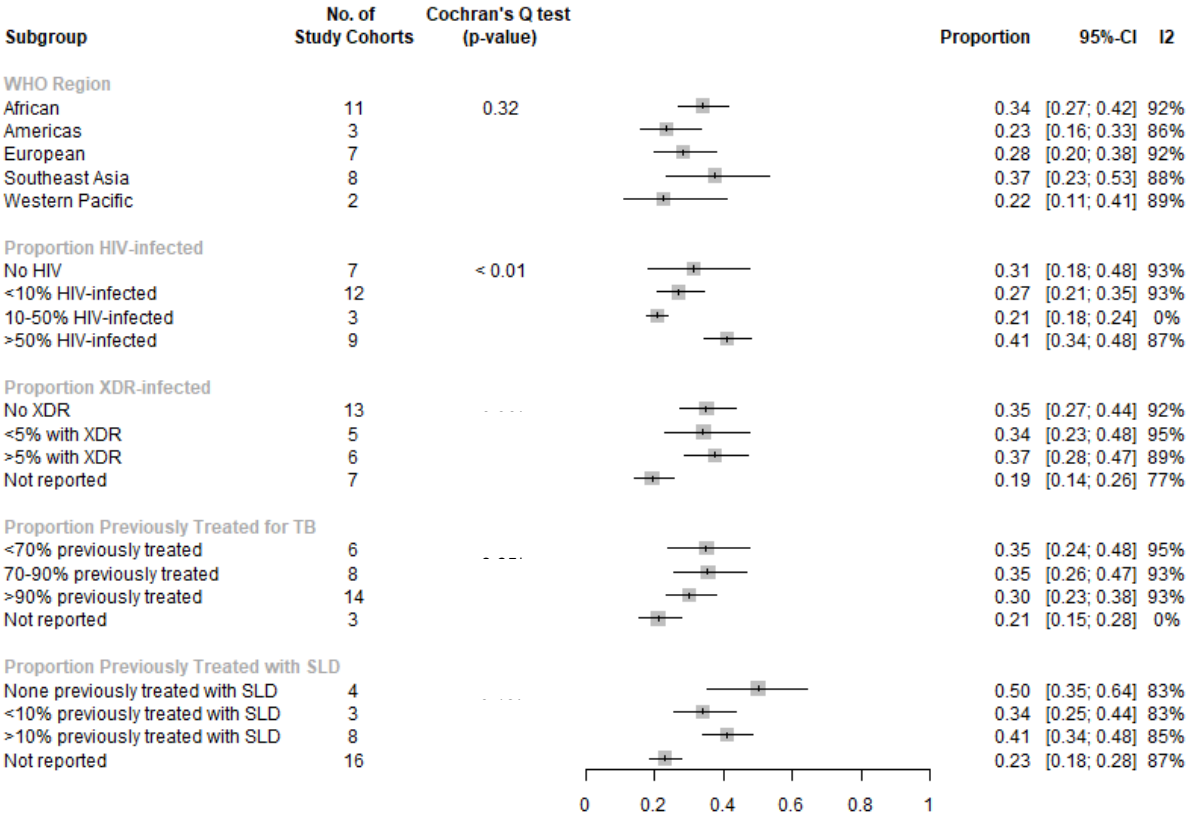


Figure 23. Forest plot of pooled proportions lost to follow-up, including those who died, across all study cohorts, stratified by study cohort characteristics.

Patients who failed treatment, who transferred out or whose treatment outcome was not evaluated, were excluded. *Study cohorts that did not report this parameter were excluded from the Cochran's Q test for subgroup differences.

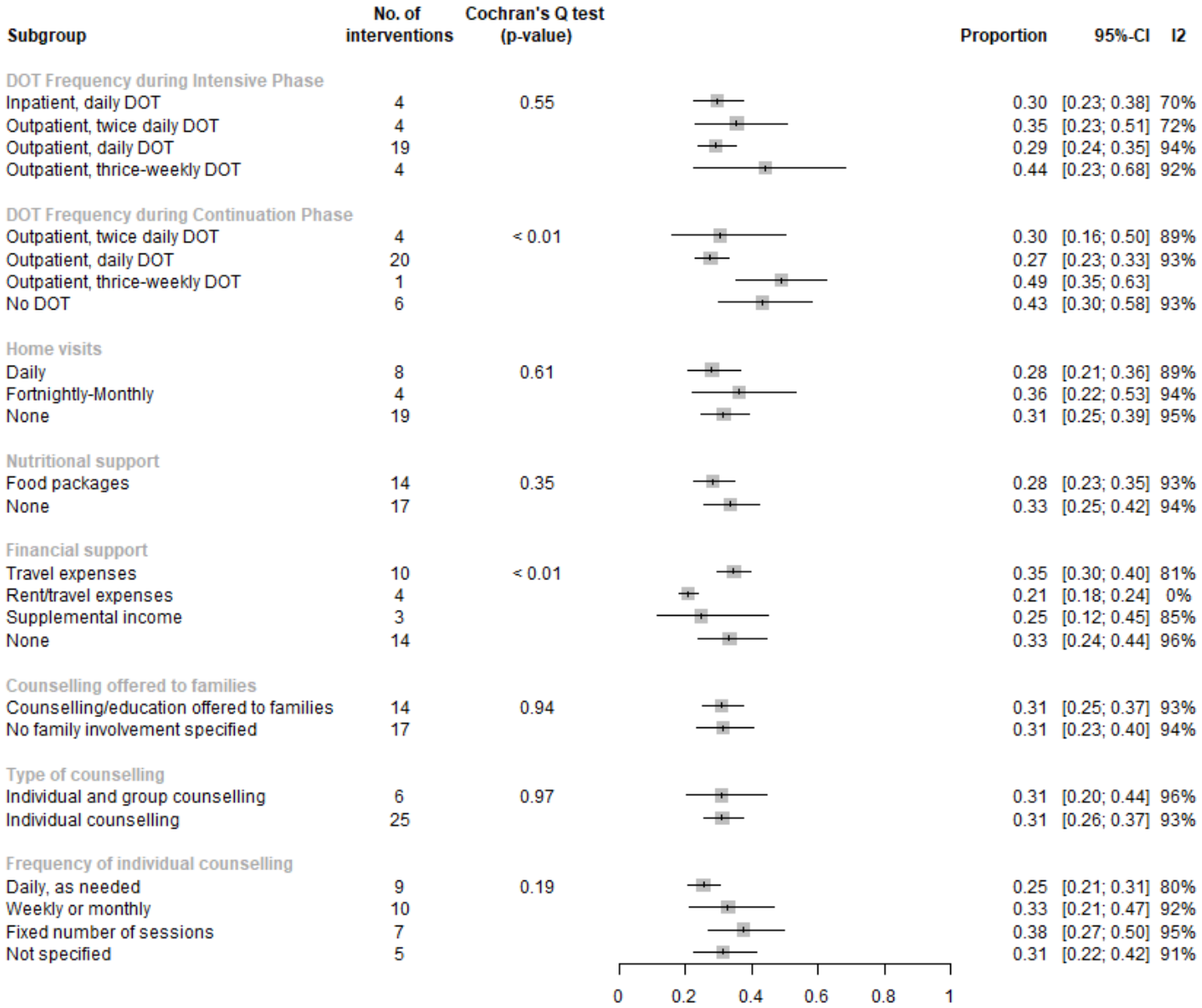


Figure 24. Forest plot of pooled proportions lost to follow-up, including those who died, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

No HIV

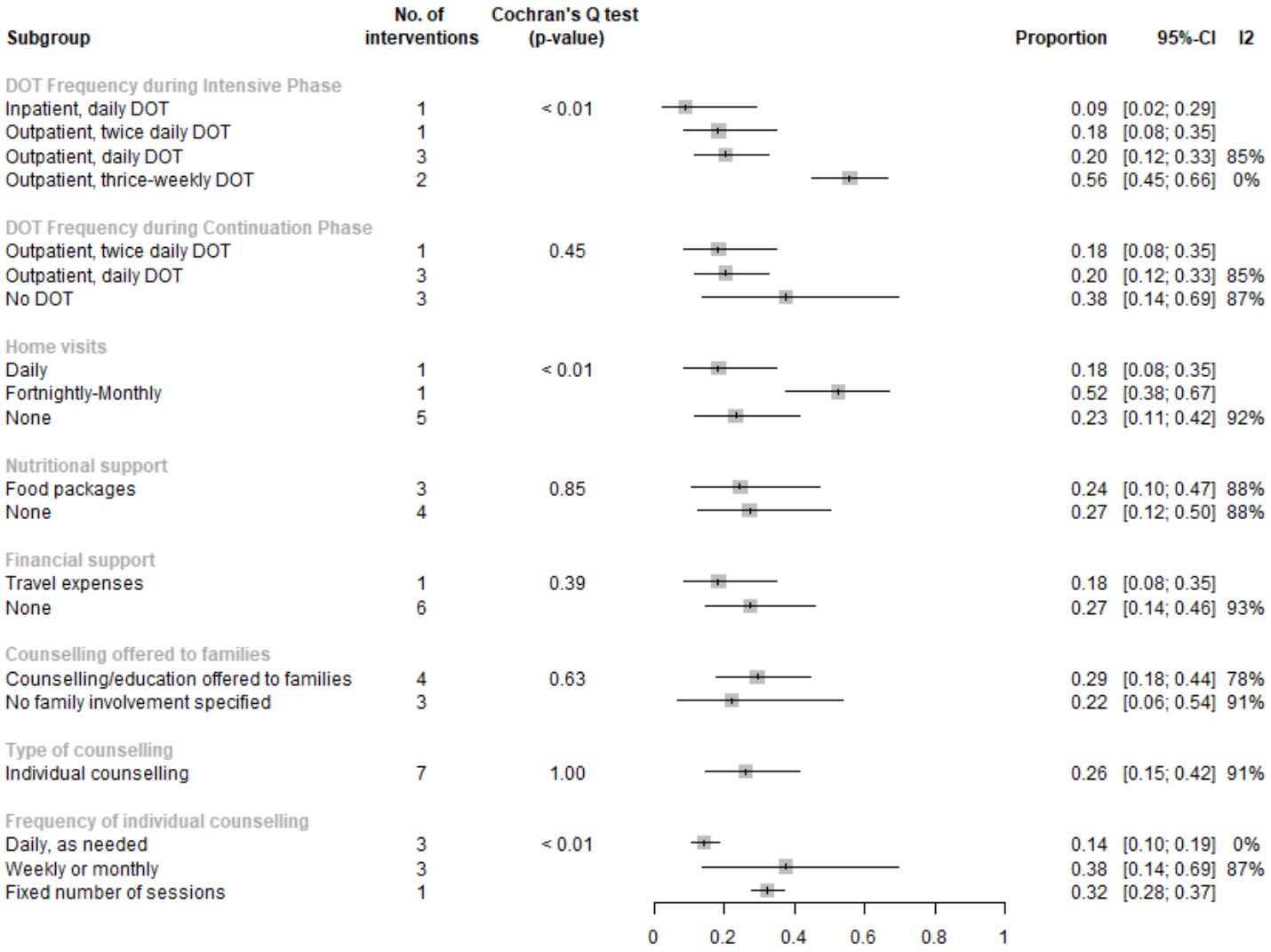


Figure 25. Forest plot of pooled proportions lost to follow-up among study cohorts with no reported HIV, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

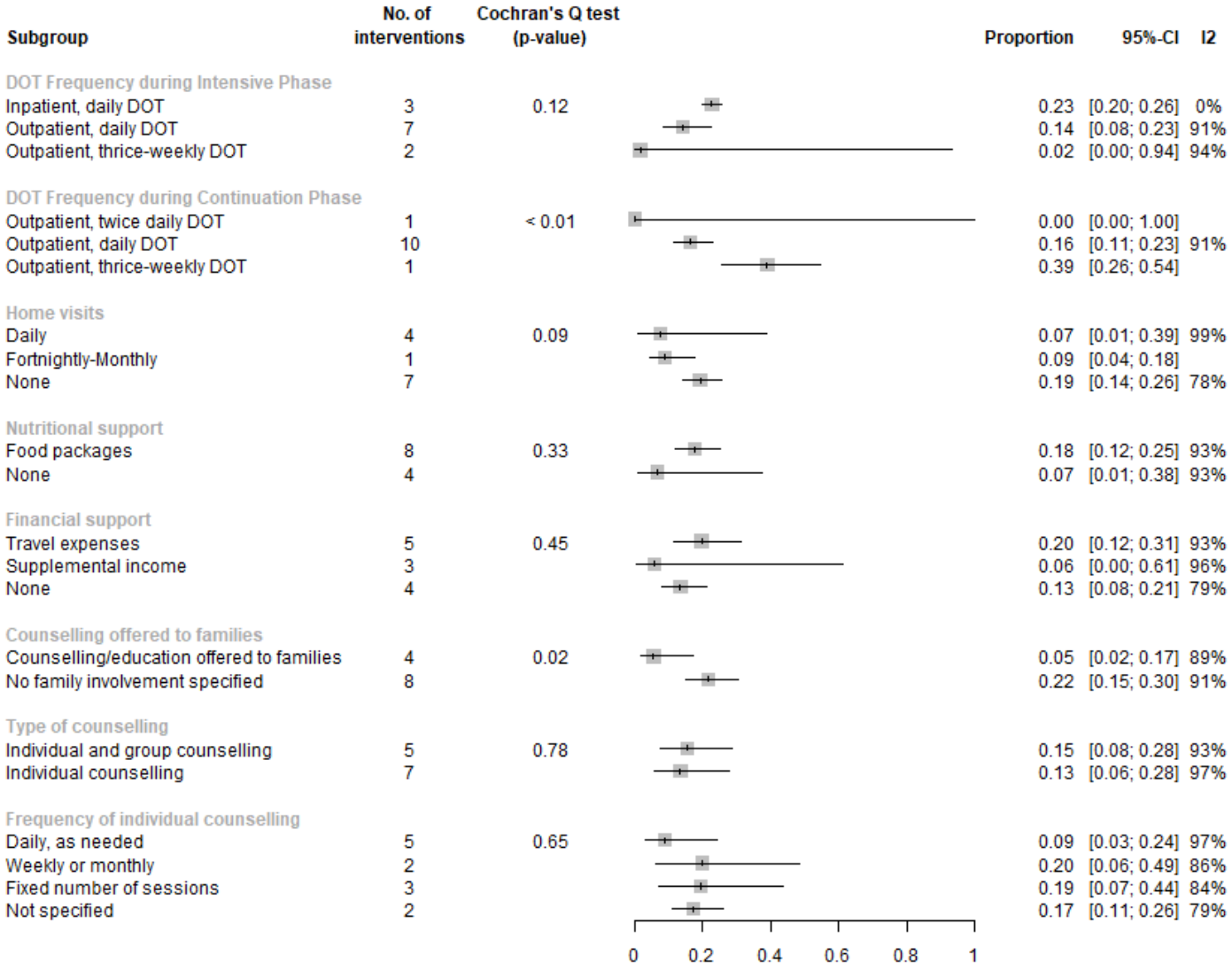


Figure 26. Forest plot of pooled proportions lost to follow-up among study cohorts with less than 10% HIV prevalence, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

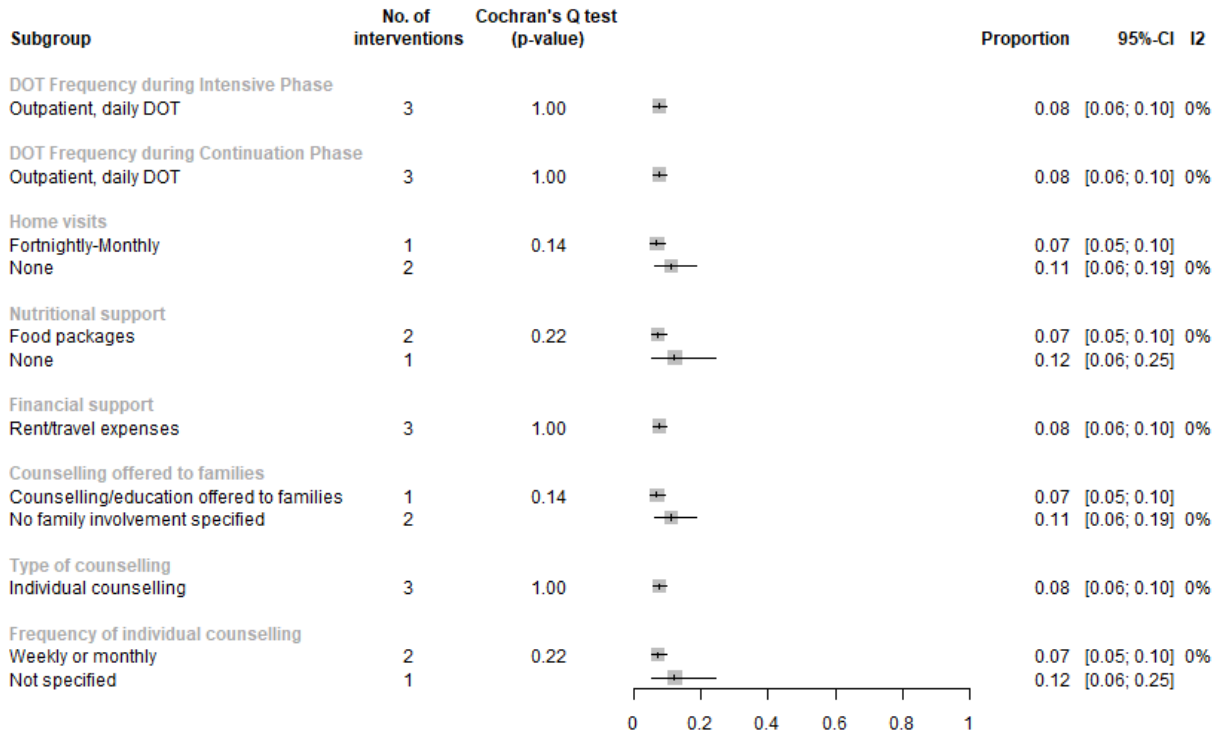


Figure 27. Forest plot of pooled proportions lost to follow-up among study cohorts with 10 to 50% HIV prevalence, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

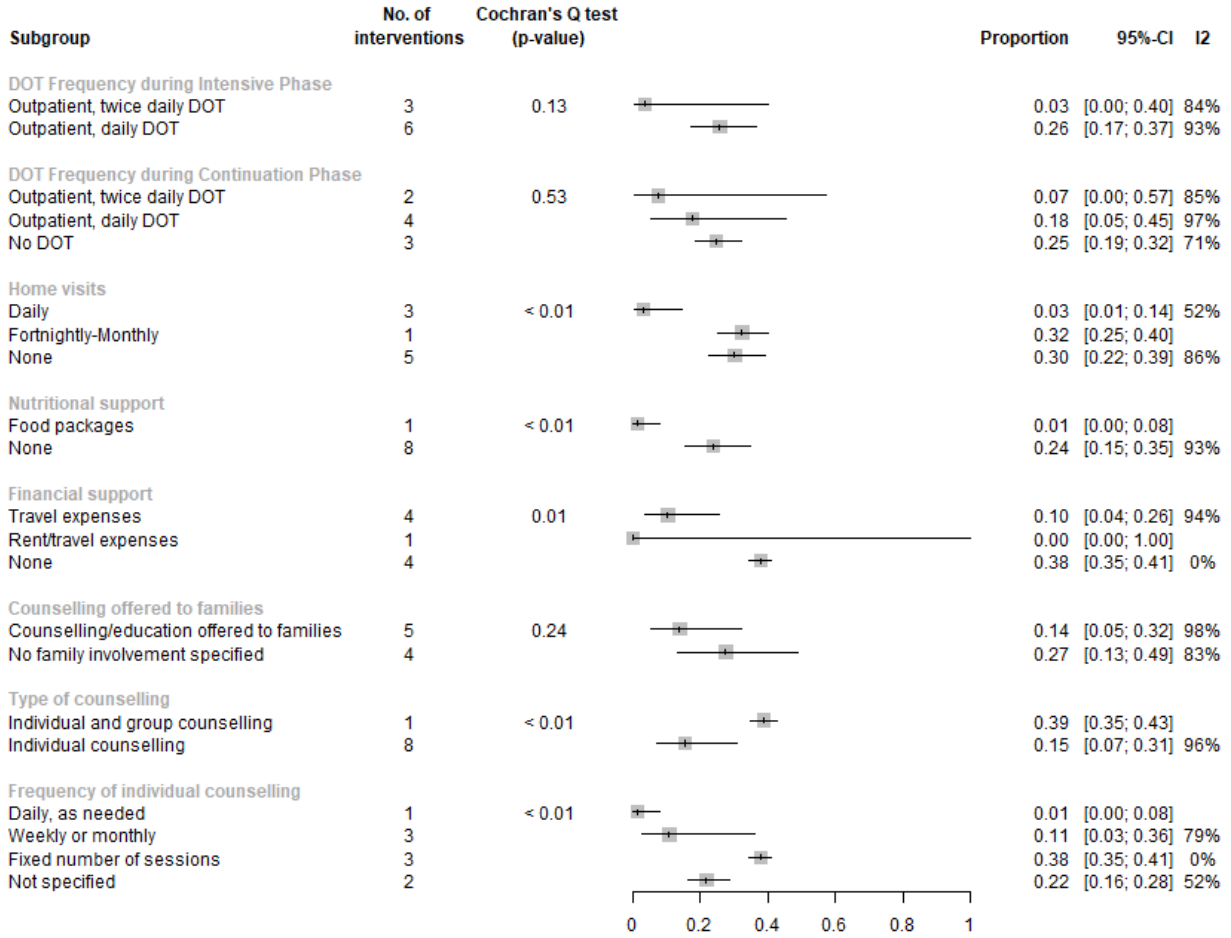


Figure 28. Forest plot of pooled proportions lost to follow-up among study cohorts with greater than 50% HIV prevalence, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

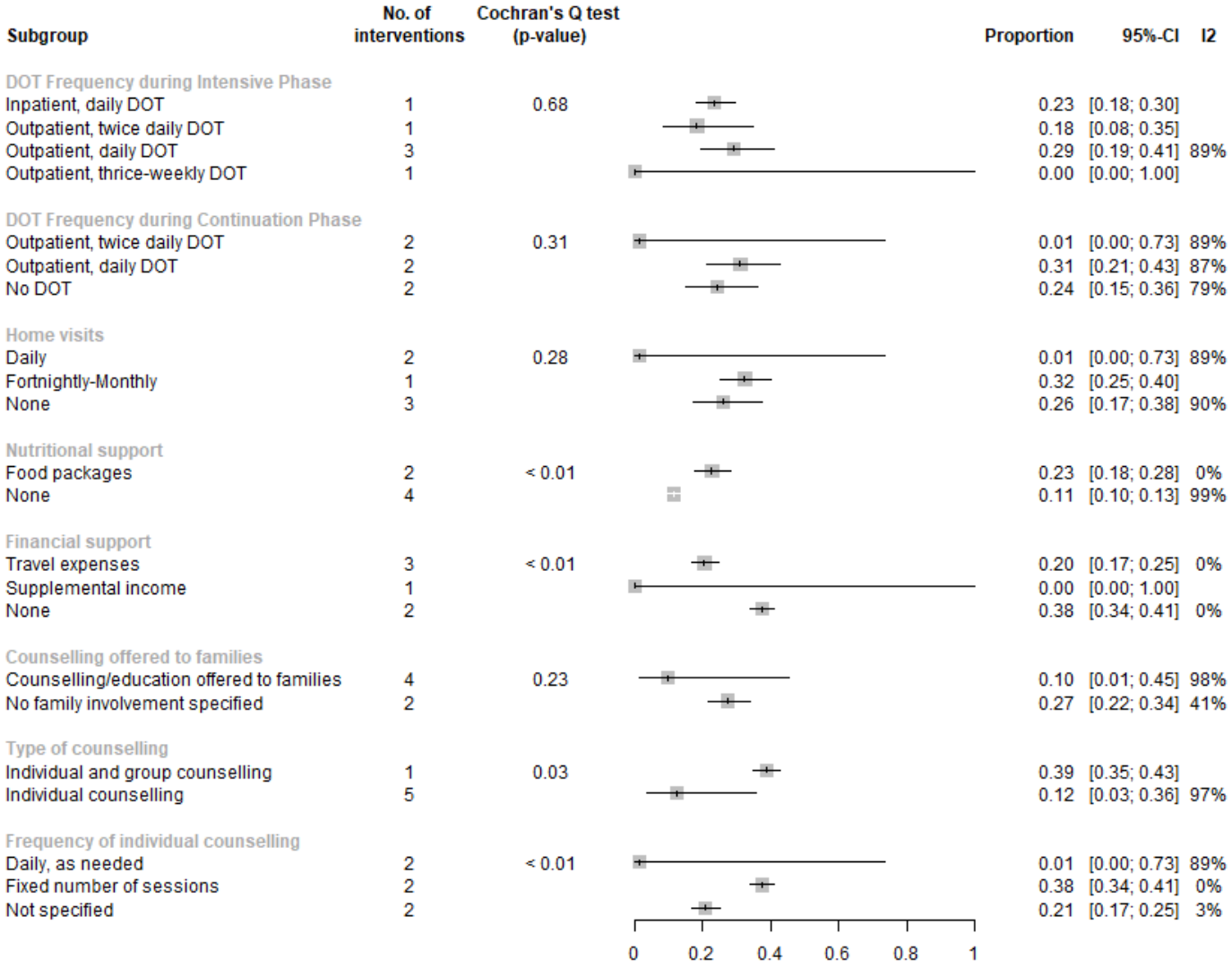


Figure 29. Forest plot of pooled proportions lost to follow-up among study cohorts with less than 70% previously treated patients, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

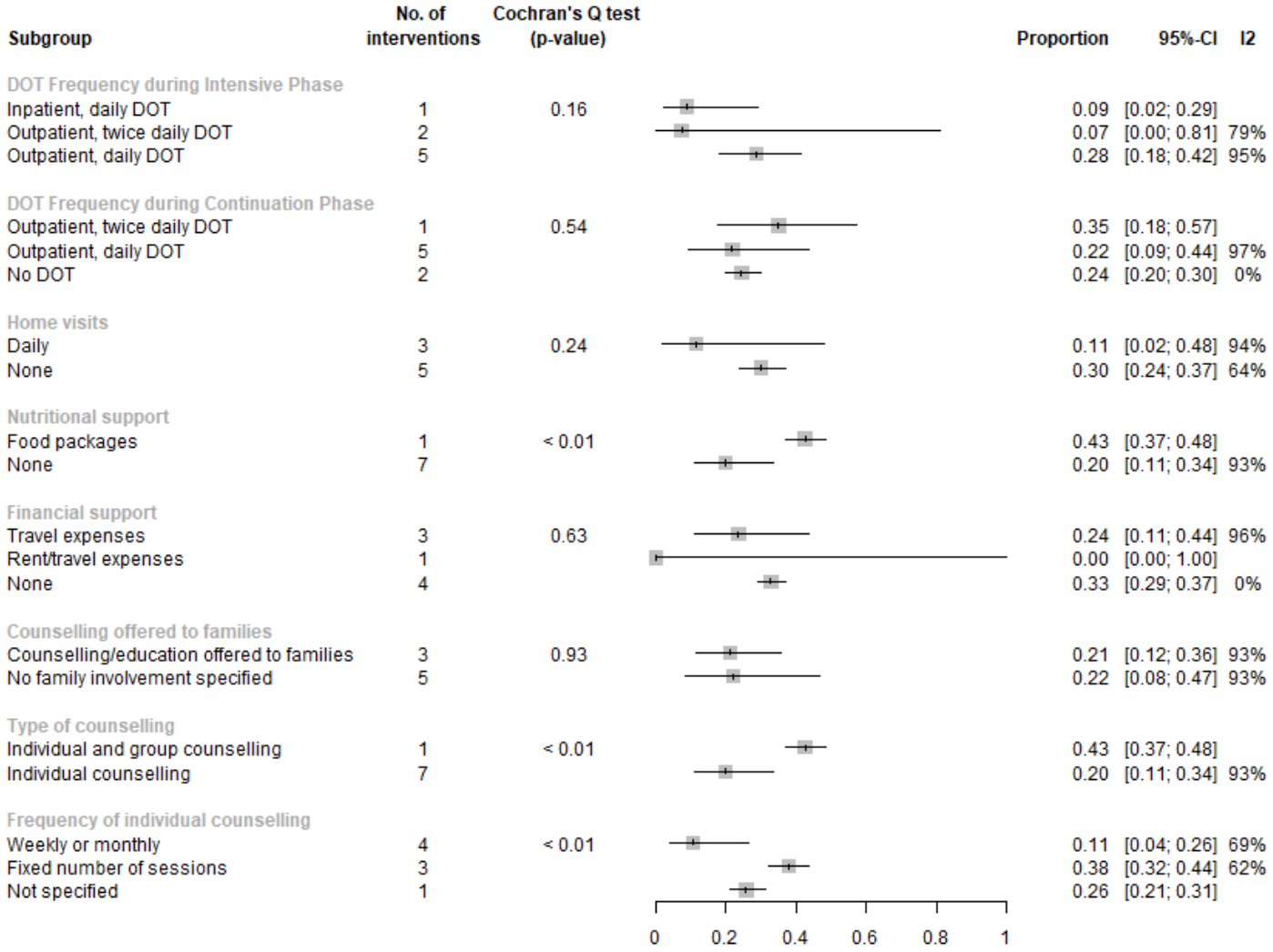


Figure 30. Forest plot of pooled proportions lost to follow-up among study cohorts with 70% to 90% previously treated patients, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

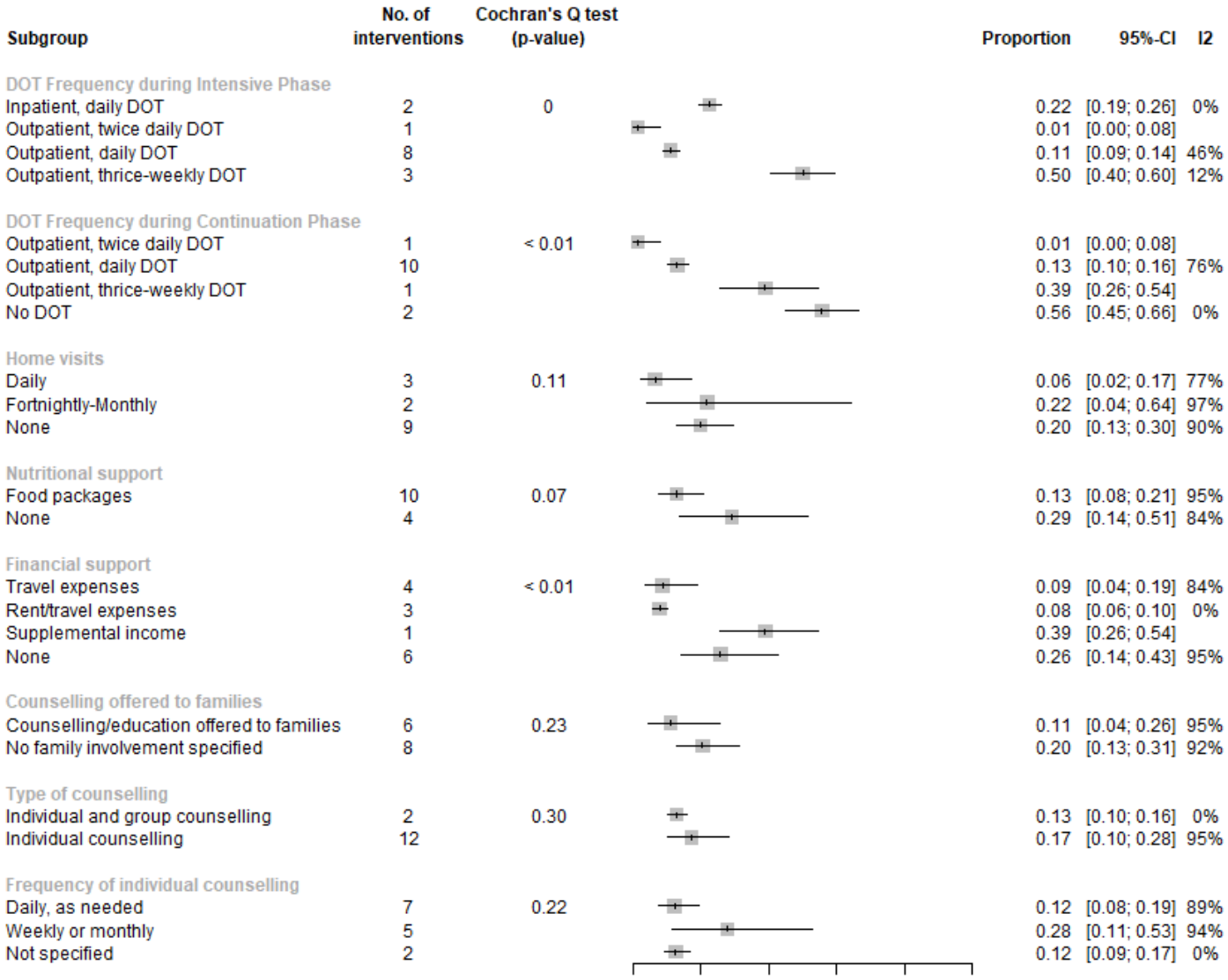


Figure 31. Forest plot of pooled proportions lost to follow-up among study cohorts with greater than 90% previously treated patients, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

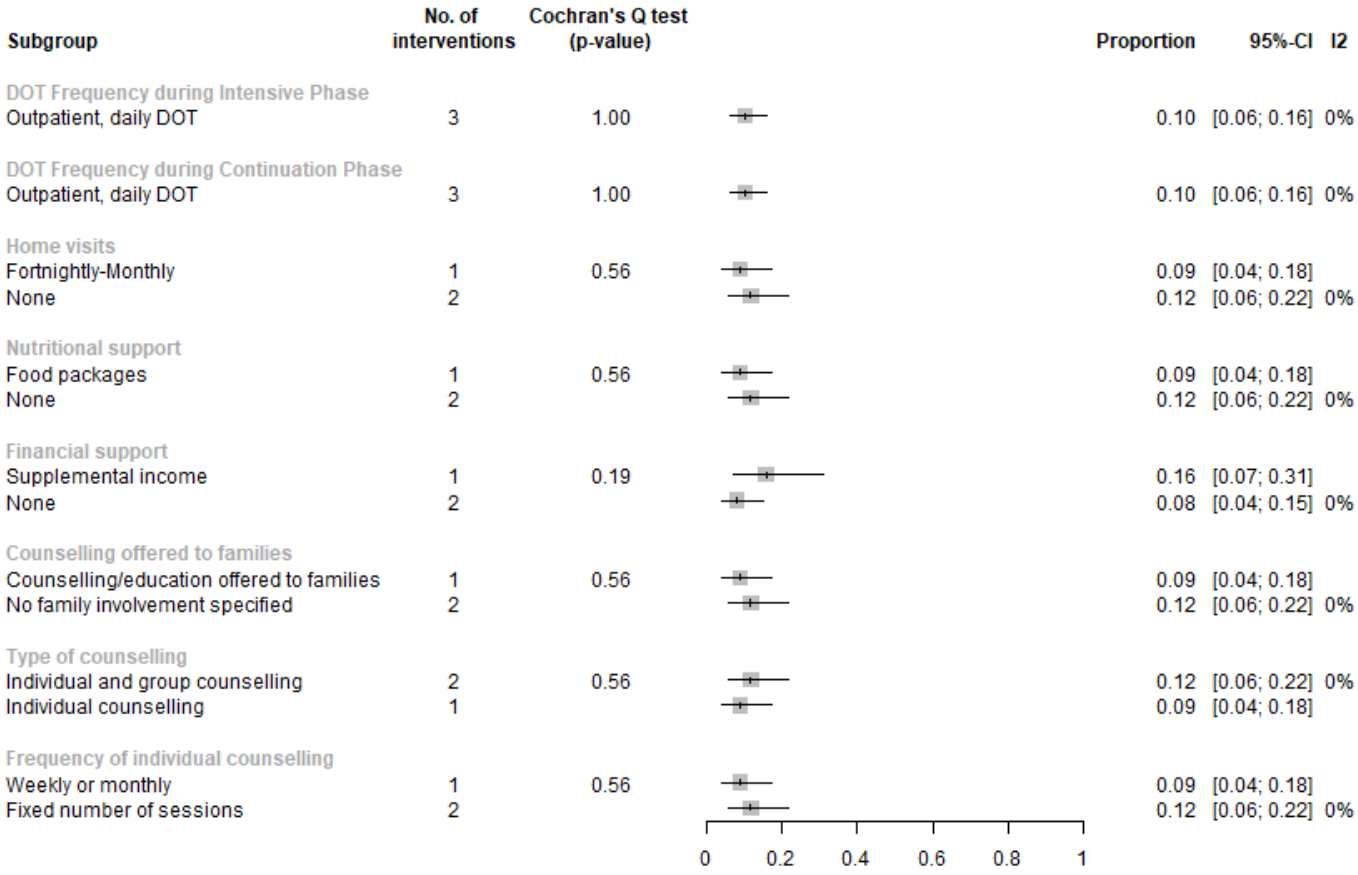


Figure 32. Forest plot of pooled proportions lost to follow-up among study cohorts that did not report the proportion of patients who were previously treated for TB, stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment.

Patients who died, failed treatment, transferred out or whose treatment outcome was not evaluated were excluded.

Table 6. Additional treatment adherence outcomes reported by study cohorts

Study (sample size, n)	Outcome	Result
Gelmanova 2011 (n= 38)	% Adherence (proportion of prescribed doses taken), mean (SD)	79.0 (16.9)
Bastard 2015 (n=323)	Overall duration of interruptions (days)	Median: 3 (IQR 2-7)
	Max duration of interruptions per patient (days)	Median: 18 (IQR 8-27)
	Time to first interruption, median (IQR), days	95 (42-205)
	Time to first interruption, No. (%)	
	≤ 3 months	155 (48.0)
	3 to <6 months	75 (22.2)
	6 to 12 months	50 (15.5)
	>12 months	43 (13.3)
	Incidence of interruptions due to patient, median (IQR)	1.03 (0.39-2.05)
	Incidence of interruptions due to adverse effects median (IQR)	0 (0-0.17)
	Duration of gaps between interruptions, median (IQR), days	13 (5-37)
	Interruptions of >2 days, No. (%) of patients	272 (84.2)
	Gaps between interruptions >10 days, No. (%)	194 (60.1)
	Adherence ≥ 80%, No. (%)	127 (39.3)
Shin 2006 (n=244)	% missed doses (of all prescribed doses), median (range)	5 (0-45)
	<2% missed doses	52 (21.3)
	≥2% and <5% missed doses	68 (27.9)
	≥5% and <11.0% missed doses	62 (25.4)
	≥11% missed doses	62 (25.4)

Table 7. Summary of feasibility and implementation issues reported by included studies

Study ID	Feasibility of intervention
Gelmanova 2011	The authors estimated an average per patient cost enrolled in the Sputnik program of approximately US$6.50/day, compared to the alternative of in-patient care for the duration of treatment, ranging from US$9.30/day to as high as US$35.00/day.
Loveday 2015	During the implementation and expansion of decentralized care, the four decentralized sites included in the study varied in number of days of hospitalization (from an average of 96 to 180 days), which suggested there were site differences in interpreting and implementing guidelines. The authors concluded that this highlighted "the importance of regular monitoring and support during service expansion, to ensure health systems are functional and new programmes implemented in accordance with guidelines." Many patients were hospitalized longer than the study planned (80 days vs. 2 weeks). Furthermore, the intensity and fidelity of the intervention delivery varied by site: at site 1 where there was more financial resources and ownership/support from the district leadership, there were 16 mobile injection teams – compared to 2 each at sites 2 and 3, and none at site 4 – as well as "additional staff at the out-patient clinic who established systems, implementation of a locally developed patient treatment literacy programme and home assessment by a multidisciplinary team before patient discharge. These programme components were partially implemented at other decentralised sites. Additionally, authors from an earlier study under the same intervention (Brust 2012) concluded, "This illustrates the difficulty in changing a long-standing practice in MDR-TB treatment, where the hospital staff was reluctant to discharge patients who were still culture positive due to concerns that they could transmit the disease to family and/or friends in the community." The authors estimated "the operational costs of the home-based treatment model are approximately 25% those of the centralized in-patient model (B Margot, personal communication), suggesting that the home-based program is both effective and less expensive."
Meressa 2015	The authors provided a gross estimate of program costs, exclusive of second-line drugs, at approximately $2000 per patient over the 2-year treatment period. These costs included: ancillary medications, laboratory monitoring (e.g. cultures, DST and other routine labs), food supplementation, transportation and accommodation for patients, home visits, capacity building, programme management, personnel training, salaries for dedicated staff, salary supplementation of national staff and some infrastructure improvements. These estimates do not include the overhead costs associated with hospital-based care.
Mitnick 2003	The therapy costs per patient ranged from $504 to $32,383 (mean of $15,681 per patient), which were approximately 10 percent of those for hospitalized patients. In a qualitative study (Acha 2007) exploring the social support groups provided under this intervention, the authors found participation varied widely: average of 6 sessions per patient. There were undocumented activities related to participation (spillover effects, such as: "mutual home visits, weekend socialization, and significant friendships among group members", which could contribute to overall treatment adherence. There were logistical challenges to organizing the support groups, including: "finding adequate and low-cost meeting places, ensuring attendance, tardiness and delays (in large part due to Peruvian custom), finding willing facilitators, securing the resources to finance the sessions and excursions, and subsidising transportation costs in necessary cases." Also difficult to find willing facilitators due to TB-related stigma, and lack of prior experience.
Mohr 2017	There was initial reluctance from some care providers to endorse the pilot intervention, as such, some eligible patients in pilot clinics were never offered SAT.
Suarez 2002	The study showed second-line treatment for TB was feasible and cost-effective: "The total programme cost was affordable in the context of the National Tuberculosis Programme's budget, and the mean cost per DALY gained was around US$150-200."
Thomas 2007	Finding DOT providers who could give intramuscular injection to the patients in rural areas was difficult. As such, rural patients received their injections from the village health worker when possible, otherwise either from a private provider by paying a fee or from the primary health center. The authors concluded, "all efforts should be taken before starting treatment to identify a DOT provider nearer to the patient's residence, who could administer injections, possibly by involving network of private providers available in most villages."

Table 8. Summary of Included Studies.

INCLUDED COHORTS	
Author, Year:	Alene 2017
Study period:	Jan 2011 to Dec 2014
Study setting:	The study was conducted in Hunan Province, in central-south China. Hunan Chest Hospital in Changsha, is the province's only chest hospital. The hospital has 610 beds, and treats and diagnoses patients with chest and lung diseases including TB, MDR-TB, and XDR-TB, referred from throughout the province. The MDR-TB treatment centre was established at the hospital in 2011 and serves as a referral hospital for all HIV-negative persons with presumptive drug resistant TB in the province. The national treatment success rates for people with MDR-TB and XDR-TB in 2013 were 55% and 22%, respectively.
Description of Intervention:	Patients were initially hospitalized for 1 to 2 months during the intensive phase and received DOT by trained medical staff, as well as free nutritional meals, and psychological support and counselling from nurses. After discharge, patients received daily DOT and psychosocial support from trained family members or trained community-based supervisors, and returned to the hospital monthly to collect medication. Education and counselling was routinely provided to patients and families.
Patient eligibility:	All bacteriologically-confirmed MDR-TB patients registered at the treatment centre during the study period were included. Exclusion criteria included: patients who were diagnosed with MDR-TB but did not start treatment (n=8); patients who were transferred out (n=8); and patients co-infected with HIV.
Sample size:	481 (471 MDR-TB; 10 XDR-TB)
Treatment regimen:	Individualized regimen containing four drugs based on DST results and previous TB treatment, usually includes: an injectable agent (kanamycin, amikacin or capreomycin), a fluoroquinolone (i.e. levofloxacin, ofloxacin or moxifloxacin), PAS, prothionamide, pyrazinamide, clarithromycin, ethambutol, or cycloserine).
Treatment duration:	24 months for MDR-TB; 30 months for XDR-TB
Duration of injectable:	6+ months for MDR-TB; 12+ months for XDR-TB
Hospitalization period:	1 to 2 months
Funding source:	Reported no specific funding from public, commercial or not-for-profit organizations
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Bastard 2015
Study period:	Jun 2002 to Jul 2010
Study setting:	Drug-resistant TB programs supported by MSF in Yerevan, Armenia and Abkhazia, Georgia. The programs covered the entire city of Yerevan in Armenia and the autonomous region of Abkhazia in Georgia.
Description of Intervention:	Patients were hospitalized initially and discharged after 2 smear-negative sputum samples. After discharge, DOT 6 days a week at closest health facility, or at home from health personnel or trained community member. Psychological support was

	provided, individually and in group sessions, together with socioeconomic support (financial and nutrition support and transport reimbursement).
Patient eligibility:	All DST-confirmed MDR-TB patients who started treatment during the study period and who had a treatment outcome (24+ months follow-up) by 31 July 2010. Patients who were transferred out or still on treatment at the end of study were excluded from analysis.
Sample size:	393
Treatment regimen:	Individualized regimens based on DST results, including at least 4 effective drugs, including 2nd-line drugs (ofloxacin, levofloxacin and moxifloxacin, kanamycin and capreomycin, para-aminosalicylic acid, ethionamide, cycloserine).
Treatment duration:	18 to 24 months
Duration of injectable:	6+ months (4+ months past culture conversion)
Hospitalization period:	Until 2 smear-negative sputum samples
Funding source:	Funding support from MSF.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Cox 2007
Study period:	Oct 2003 to Jan 2005
Study setting:	Nukus City and Chimbay in Karakalpakstan, a semiautonomous region in western Uzbekistan, with high levels of poverty, environmental degradation and slow reform of health services.
Description of Intervention:	The pilot program is a collaborative effort between MSF, the Ministries of Health in Karakalpakstan and Uzbekistan and the National Reference Centre for Mycobacteria in Germany. Patients received counselling, reimbursement for treatment-related transport costs during outpatient care, four meals daily during hospitalization, and monthly food parcels.
Patient eligibility:	Inclusion criteria were: residents of Nukus City and Chimbay; culture positive pulmonary TB; previously been treated in the DOTS program; and no concomitant medical conditions that precluded anti-TB treatment, which included cirrhosis, uncontrolled seizure disorder, significant psychiatric disease and known allergies to second-line anti-TB drugs.
Sample size:	87
Treatment regimen:	A standardized empiric regimen of pyrazinamide, ofloxacin, ethionamide, p-aminosalicylic acid (PAS), cycloserine and either capreomycin or kanamycin, was provided until DST results become available, after which the regimen is adjusted accordingly.
Treatment duration:	Minimum 18 months after culture conversion
Duration of injectable:	6 months
Hospitalization period:	Patients were generally hospitalized for the first six months. The total duration depended on the use of an injectable, availability of family support, and clinical condition.

Funding source:	Funding support from Médecins Sans Frontières, and contributions in kind from the Ministry of Health in Karakalpakstan and the National Reference Center for Mycobacteria in German.y
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/ab
Author, Year:	Cox 2014 (*Note: Patients in the pilot program were excluded from main analyses because they formed part of the larger, and more up-to-date, sample in Mohr 2015. However, this study was retained for the analysis of comparative studies.)*
Study period:	Jan 2005 to Dec 2011 (treatment outcomes not available for patients initiating treatment in 2011)
Study setting:	Khayelitsha, a township near Cape Town, South Africa, with high rates of HIV, TB and DR-TB. There are approximately 200 cases of DR-TB diagnosed in Khayelitsha each year, with a HIV infection rate of 72%. Eleven health facilities in Khayelitsha provide integrated HIV and TB services for patients. HIV-infected TB patients are started on antiretroviral therapy shortly after initiating TB treatment. In early 2007, MSF and the City of Cape Town Health Department conducted a review of DR-TB diagnosis and treatment in Khayelitsha, of the 181 patients identified up to the end of 2006, 30% of patients were successfully treated and 70% suffered a poor treatment outcome (including LTFU, failure or death).
Description of Intervention:	A pilot program to provide community-based DR-TB diagnosis and treatment was introduced in late-2007. *Before pilot program (hospital-based):* Hospitalization during intensive phase (6 months) followed by clinic-based DOT without additional support. *Pilot program (community-based):* After diagnosis at a primary care clinic, patients are counselled by a dedicated DR-TB counsellor and treatment is started by the clinic TB medical officer. Patients who are severely ill and requiring hospitalisation, or who have XDR-TB, are referred directly to the tertiary TB hospital for admission. Also includes social assistance and support groups, routine home visit at start of treatment by trained community health worker, and daily DOT at local clinic.
Patient eligibility:	Rifampicin-resistant TB adult patients who resided in Khayelitsha or were diagnosed in one of 10 primary care facilities in the subdistrict. Excluded patients transferred to Khayelitsha after starting treatment elsewhere and those restarted on treatment after previous default or treatment failure.
Sample size:	970 started treatment between 2005 to 2011. Excluding those initiating treatment in 2011: 787 with treatment outcomes available (216 before pilot program; 571 after pilot program).
Treatment regimen:	*Before pilot program*: Standardized treatment regimen. Intensive phase: 5 drugs for 4 months (kanamycin, ethionamide, ofloxacin, ethambutol and pyrazinamide) Continuation phase: 3 drugs (ethionamide, ofloxacin and ethambutol) for 12 to 18 months. Pyrazinamide was continued for extensive cavitary disease. If ethambutol resistance was diagnosed, then ethambutol was replaced with terizidone. *Pilot program*: Standardized regimen adapted based on DST results. Intensive phase: five drugs (kanamycin, ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine) Continuation phase: four drugs (ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine).

Treatment duration:	*Before pilot program*: 16 to 24 months. *Pilot program*: 24+ months
Duration of injectable:	6 months, and at least 4 months after culture conversion.
Hospitalization period:	*Before pilot program*: Minimum 6 months [183/216 (84.7%)] *Pilot program*: Patients were hospitalized only if they were clinically unstable and unable to attend their clinic daily [145/571 (25.4%)]
Funding source:	Program implementation was funded by Medecins Sans Frontieres (MSF Belgium). Programme evaluation was supported by MSF and the University of Cape Town.
Potential conflicts of interest:	The funders were involved in study design, data collection and analysis. However, final preparation of the manuscript and the decision to publish rests with the first author.
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Escudero 2006
Study period:	Jun 1998 to Dec 2000
Study setting:	Hospital La Fuenfría, Madrid.
Description of Intervention:	Psychological support and counselling was provided by repeated clinical interviews during hospitalization and during out-patient follow-up. The clinician and a psychologist focused on the need for optimal treatment adherence and explored the main difficulties patients found in achieving these goals. Patients could be contacted by phone by the medical team after discharge.
Patient eligibility:	Confirmed adult MDR-TB patients without HIV enrolled for treatment at the hospital.
Sample size:	25
Treatment regimen:	Individualized regimen containing one injectable drug plus at least three oral drugs, adjusted based on prior anti-tuberculosis treatment and DST results.
Treatment duration:	18 months or 12 months after first two negative cultures
Duration of injectable:	6 months (5 days/week for months 1-2, 3 days/week for months 3-4, and 2 days/week for months 5-6)
Hospitalization period:	Until first negative sputum culture. Mean 65 days (range 9–483 days).
Funding source:	Not stated
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Gelmanova 2011
Study period:	Dec 2006 to Nov 2008
Study setting:	Tomsk City metropolitan area (population: 526 000) has a high burden of MDR-TB. The area's DOTS TB program expanded to include MDR-TB treatment in 2000.

Description of Intervention:	The 'Sputnik' program was implemented in Dec 2006 jointly by the Tomsk Oblast Tuberculosis Services (TOTBS) and Partners In Health (PIH). The program goal is to improve treatment adherence among patients with adherence problems in the standard ambulatory care TB program. Most smear-positive patients initiate treatment in hospitals. After discharge, patients are provided with transportation passes, daily food sets and monthly hygiene sets. The program is staffed by a team of two nurses who visit patients at their convenience and provide twice-daily DOT. A physician joins the team every 10 days for home visits and clinical follow-up. Patients also receive clothing and assistance through state social services. Sputnik has a high nurse-to-patient ratio, and includes provision of cellphones to nursing staff, patient access to specialists and social/psychological support (a psychologist visited patients at home and also worked with family members), and provides additional training to program nurses for addressing patients' biosocial challenges.
Patient eligibility:	MDR-TB patients treated under the Sputnik program. Patients who were referred to the Sputnik program from standard care by a clinical committee included: those who refused to start treatment or stopped taking medications; those missing more than 25% of prescribed doses; those with a history of loss to follow-up in the previous 6 months; and those considered to be at high risk for loss to follow-up for other medical, social or economic reasons. Due to limited program capacity, patients are only referred to the Sputnik program after all standard options are exhausted.
Sample size:	38
Treatment regimen:	Standardized regimen. Intensive phase (6-9 months): 6 drugs- kanamycin, ofloxacin (levofloxacin), ethionamide, pyrazinamide, ethambutol and cycloserine Continuation phase (18 months): 4 drugs- ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine. p-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Ofl, Z and Eto) or 2 bacteriostatic (E and Cs) drugs are not tolerated.
Treatment duration:	24+ months
Duration of injectable:	6 to 9 months
Hospitalization period:	Initial hospitalization until smear-negative
Funding source:	Not reported
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	The Sputnik program cost per patient was approximately US$6.50/day. This is compared to average in-patient care of US$9.30/day to US$35.00/day.
Author, Year:	Huerga 2017
Study period:	May 2006 to May 2012
Study setting:	The study took place at three sites in Kenya: Mathare Green House Clinic, which provides free outpatient HIV/TB care to people living in the Mathare slum (population of 340,000); Homa Bay County Hospital, serving a rural area of Western Kenya (population of 360,000); and Kenyatta National Hospital in Nairobi, the largest referral facility in East Africa.
Description of Intervention:	All patients received DOT 6 days a week. Patients at the Mathare and Nairobi sites received clinic-based outpatient care throughout treatment. In Homa Bay, the majority of patients received twice-daily DOT: at the nearest health facility in the morning and by CHWs at patient homes in the evening during the intensive phase, and DOT was provided by CHWs at patient homes during continuous phase.

	TB education and psychosocial counselling were provided at all sites. At the Mathare and Homa Bay sites, counselling sessions were provided by a counsellor following a standardized guide, weekly during the first month of intensive phase, bi-weekly thereafter, followed by monthly during continuation phase. At the Nairobi site, counselling was provided by nurses on request by the doctor available [from email correspondence with H Huerga]. A multi-disciplinary team provided medical, psychological and social care to the MDR-TB patients. The team is composed of a medical doctor, a clinical officer, a nurse, and a counsellor. In addition, there was a full-time social worker available in Mathare due to the magnitude of the social problems in a slum context. Furthermore, in Homa Bay, for each patient treated at home, two community health workers were identified and trained. Financial support was provided to all patients to cover income losses due to treatment and transport fees to attend the clinic. Patients at the Mathare site also received a daily hot meal at the day-care unit, and a monthly food basket.
Patient eligibility:	All patients who started MDR-TB treatment at the study sites.
Sample size:	169 (70 in Mathare; 28 in Homa Bay; 71 in Nairobi)
Treatment regimen:	Standardized regimen, individualized based on DST results once available. The intensive phase (minimum 6 months) consisted of an injectable agent (kanamycin or capreomycin) and 3 or 4 oral drugs (levofloxacin, prothionamide, cycloserine, or para-aminosalicylic acid). Patients at the Nairobi site were treated with ethambutol or PZA instead of PAS, and until 2009 ofloxacin (OFX) was used instead of LVX. The continuation phase (18 months) included the same drugs as in the intensive phase minus the injectable agent.
Treatment duration:	24+ months
Duration of injectable:	6+ months
Hospitalization period:	None required
Funding source:	Not stated
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Isaakidis 2011
Study period:	May 2007 to May 2011
Study setting:	An urban, overpopulated slum setting in Mumbai, India. MSF started treating MDR-TB among HIV-infected individuals in May 2007. MDR-TB treatment became available in Mumbai's public sector in late 2010, prior to which it was only available in the private sector.
Description of Intervention:	Patients in stable clinical conditions started treatment on an ambulatory basis, otherwise they were hospitalized under the supervision of the MSF clinical team. Twice-daily DOT by trained DOT provider at a facility no more than 10 minutes walking distance from patients' home, including public health posts, private practitioners and local NGOs. Patients attended the MSF clinic monthly for medical and psychosocial follow-up.
Patient eligibility:	All HIV-infected patients treated for MDR-TB (bacteriologically confirmed or suspected based on clinical findings and treatment history) at the clinic during the study period.
Sample size:	58

Treatment regimen:	Standardized regimen modified based on DST results, included six drugs: pyrazinamide, capreomycin, moxifloxacin, ethionamide, cycloserine and PAS.
Treatment duration:	18+ months
Duration of injectable:	6+ months
Hospitalization period:	Only if patient was clinically unstable for outpatient care.
Funding source:	No external funding sources.
Potential conflicts of interest:	This is an MSF study.
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Joseph 2011
Study period:	Jun 2006 to Sep 2007
Study setting:	Tiruvallur district and the Chennai Corporation area (with a combined population of almost 7.5 million) in southern India, in Chennai, Tamil Nadu. Previous reports from the TB Research Centre (TRC) in Chennai have shown MDR-TB treatment success rates of 37% to 50%.
Description of Intervention:	Hospitalization was recommended for the first two to four weeks of treatment. After discharge, patients attended the nearest health centre of their choice for DOT by trained DOT providers, which included government health care providers, private medical practitioners, and friends and relatives staying close by. DOT providers received one-on-one training from the TRC to administer drugs, counsel patients for drug regularity, identify and refer patients to the medical officer in case of any adverse drug reactions, and send patients to the TRC for monthly follow-ups. Patients were given emergency contact details for the medical officer and TRC field workers.
Patient eligibility:	Patients with DST-confirmed MDR-TB in the study district were traced and enrolled into the study. Exclusion criteria were: under 18 years of age; pregnancy; concurrent major psychiatric illness or serious medical illness; previous treatment (>1 month) with any second line anti-TB drugs; and HIV infection.
Sample size:	38
Treatment regimen:	The standardized regimen consisted of: an intensive phase (6 to 9 months) with 6 drugs (Km, Ofx, Eto, Z, E abd Cs); followed by a continuation phase (18 months) with 4 drugs (Ofx, Eto, E and Cs).
Treatment duration:	24+ months
Duration of injectable:	6 months, or 9 months if culture conversion occurred after the 4th month.
Hospitalization period:	2 to 4 weeks recommended
Funding source:	WHO and the United States Agency for International Development (Model DOTS Project)
Potential conflicts of interest:	Not stated
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Keshavjee 2008

Study period:	Sep 2000 to Nov 2004
Study setting:	Tomsk Oblast in western Siberia, Russia, which has about 1·1 million inhabitants, approximately half of whom live in remote villages.
Description of Intervention:	Patients are routinely hospitalized during intensive phase, and discharged for the continuation phase, unless there is an underlying condition that precludes discharge (such as a psychiatric disorder, alcoholism or homelessness). TB physicians routinely assessed all patients initiating treatment for possible alcohol or substance use disorders. Daily DOT was provided by feldshers, who are often nurses at very rural outposts, to supervise the TB and Naltrexone medications, or at TB clinics, TB hospital or day hospital. Supplementary nutritional support is provided to prisoners and in-patients, and monthly food packages and/or free meals are given to fully adherent out-patients.
Patient eligibility:	Patients who started MDR-TB treatment and had documented MDR-TB during the study period.
Sample size:	608
Treatment regimen:	The individualized treatment containing at least 5 drugs, based on DST or drugs thought to be sensitive, including: any first-line oral agent to which isolate is sensitive; an injectable to which an isolate is sensitive; a quinolone; other second-line drug (usually ethionamide or cycloserine or PAS).
Treatment duration:	18 months after culture conversion
Duration of injectable:	6+ months after culture conversion
Hospitalization period:	Routinely hospitalized for the duration of injectable use, between 6 to 9 months.
Funding source:	Financial and travel support from Bill & Melinda Gates Foundation and Eli Lilly Foundation, the Frank Hatch Fellowships in Global Health Equity at the Brigham & Women's Hospital, Infectious Disease Society of America, the Heiser Foundation, and the US National Institutes of Health, and the John D and Catherine T MacArthur Foundation.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Kliiman 2009
Study period:	Jan 2003 to Dec 2005
Study setting:	Estonia, a republic of the former Soviet Union, which has a high burden of MDR-TB and XDR-TB.
Description of Intervention:	Daily DOT at clinics after discharge. Patients received nutritional support and transportation reimbursement for clinic visits.
Patient eligibility:	MDR-TB patients with culture-confirmed pulmonary TB with a recorded treatment outcome.
Sample size:	235 MDR-TB and 54 XDR-TB patients
Treatment regimen:	Individualized regimen based on DST results, containing at least four oral drugs used daily and an injectable daily until culture conversion, and three to five times weekly for another 2 to 3 months after.
Treatment duration:	12 to 18 months after culture conversion
Duration of injectable:	Two to three months after culture conversion

Hospitalization period:	Until culture conversion
Funding source:	None stated
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Loveday 2015
Study period:	Jul 2008 to Jun 2010
Study setting:	A community-based model of MDR-TB treatment was piloted in 2008 at four community-based sites attached to purposively selected rural hospitals in areas with high reported incidence of MDR-TB, in Kwazulu-Natal, South Africa. Treatment outcomes at the four sites are compared to those at a centralized hospital. Approximately 76% of MDR-TB patients in KwaZulu-Natal are HIV-infected.
Description of Intervention:	Directly observed therapy (DOT) was not consistently implemented and most patients self-administered oral treatment with limited adherence monitoring. *Hospital site*: Patients were initially hospitalized at a centralized, specialist TB hospital, followed by monthly outpatient visits to the same hospital. Patients were often discharged before the completion of the injectable phase and were not provided intensive education (as done at the community-based sites). *Community-based sites 1-4*: Patients were initially hospitalized at rural hospitals attached to community-based sites. Monthly outpatient visits to community-based sites after discharge. Home-based care was available for patients discharged from the community-based sites during the intensive phase of treatment, where injections were administered daily at the local clinic or by mobile injection teams (at sites 1 to 3 only). Education was provided to patients and their families about MDR-TB and HIV. There was some variability in delivery of intervention at the four sites (see Table 4 for details). Additionally at Site 1 (only): Weekly education sessions were held, led by a clinic assistant and a nurse, on MDR-TB and HIV treatment with patients and their treatment supporters (family or friend). After the intensive phase, CHWs replaced nurses in making home visits and providing DOT. Travel expenses incurred by patients and their treatment supporters for clinic visits were reimbursed.
Patient eligibility:	Adult patients (>18 years) with laboratory-confirmed MDR-TB were enrolled. Patients with resistance to any second-line drug, or who received care at both the hospital and a community-based site, or who were participating in an MDR-TB clinical trial, were excluded. *Hospital site*: All eligible MDR-TB patients, excluding those from the catchment areas of the community-based sites. *Community-based sites*: All eligible MDR-TB patients in the catchment areas of the sites.
Sample size:	1549 (813 from hospital; 736 from community-based sites)
Treatment regimen:	Standardized regimen Intensive phase: kanamycin (KM), PZA (Z), EMB (E),ethionamide (ETH), ofloxacin (OFX) and cycloserine (CS) Continuation phase: Z, E, ETH, OFX and CS.
Treatment duration:	22+ months
Duration of injectable:	4 to 6 months
Hospitalization period:	Median 144 days (IQR 83 to 185)

Funding source:	Funding support from the Medical Research Council of South Africa (Cape Town, South Africa), Izumi Foundation (Boston, MA, USA) and a United Way Worldwide grant from the Lilly Foundation/Lilly MDR-TB Partnership (Indianapolis, IN, USA). Additional funding from the Columbia University- Southern African Fogarty AIDS International Training and Research Program (AITRP), Implementation Science Traineeship Program funded by the United States President's Emergency Plan for AIDS Relief (PEPFAR) through the Fogarty International Center, National Institutes of Health (grant # D43TW00231), Bethesda, MD, the National Institute of Allergy and Infectious Diseases (K23AI083088), Bethesda, MD, USA.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	Treatment success rates across community-based sites varied widely. This could be due to different interpretation and implementation of guidelines. For instance, the hospitalization period varied from 96 to 180 days.
Economic information (if reported):	n/a
Author, Year:	Meressa 2015
Study period:	Feb 2009 to Dec 2014
Study setting:	St. Peter's Hospital in Addis Ababa, Ethiopia and the University of Gondar Hospital (UoG) in Gondar, northwestern Ethiopia. Ethiopia is a high MDRTB-burdened country. The national MDR-TB treatment program was established in 2009, and is based on a multidisciplinary HIV/TB care model developed in Cambodia. This study reports the treatment outcomes from the first four years of the program.
Description of Intervention:	As outpatients, monthly visits to hospital outpatient clinic and daily DOT at local health centres by health staff or at home by family DOT supporter. Family treatment supporters trained on adherence monitoring. Monthly home visits by outpatient team in Addis Ababa and Gondar. Monthly food basket provided to all patients. Economic assistance, if needed, for transportation and housing. Patients who were initiated on therapy as outpatients were followed by the GHC (Global Health Committee) outpatient team, including roving nurses who provided them with daily injections of the injectable agent (5–6 days per week).
Patient eligibility:	All MDR-TB patients who initiated treatment before December 2012 (with at least 24 months of follow-up by December 2014) at two hospital-based study sites. MDR-TB was presumed for 61 (10.0%) patients, who had documented unsuccessful cure by first-line treatment, but without microbiological confirmation.
Sample size:	612
Treatment regimen:	Standardized second-line drug regimen: (1) at least three oral agents to which the patient was presumed to have susceptibility (eg, levofloxacin, ethionamide, cycloserine or para-aminosalicyclic acid (PAS)), (2) pyrazinamide and (3) an aminoglycoside (amikacin or kanamycin) or polypeptide (capreomycin) injectable agent.
Treatment duration:	18 months after bacteriological conversion
Duration of injectable:	Minimum 8 months. Median 9.6 months (IQR 8.1-11.0 months).
Hospitalization period:	Until smear conversion or clinically stable. A subset of healthier patients was initiated on therapy as outpatients beginning in 2010.
Funding source:	Funding support from the Jolie-Pitt Foundation, the Annenberg Foundation, Lilly MDR Partnership, and Lilly Foundation, the Ethiopian Federal Ministry of Health, The Stanford Center for Innovation in Global Health, the National Institutes of Health (K01 AI104411) and Children's Hospital Boston.
Potential conflicts of interest:	None declared

Issues with implementation (if reported):	n/a
Economic information (if reported):	Gross estimate of programme costs, exclusive of second-line drugs, is approximately $2000 per patient over the 2-year period of treatment. Costs include: ancillary medications, laboratory monitoring, food supplementation, transportation and accommodation for patients, home visits, capacity building, programme management, personnel training, salaries for dedicated staff and salary supplementation of national staff and some infrastructure improvements. Excludes overhead costs for infrastructure and personnel associated with hospital-based care.
Author, Year:	Mitnick 2003
Study period:	Aug 1996 to Feb 1999
Study setting:	Resource-poor setting, Northern Lima (Carabayllo, Comas, and Independencia districts), Peru.
Description of Intervention:	Patients received limited nutritional, financial, and social support through Socios En Salud. A team of specially trained community health workers, nurses, and physicians provided treatment on an outpatient bases. Daily DOT at homes or local health centres.
Patient eligibility:	Patients who initiated supervised, individualized treatment for MDR-TB before 1 Feb 1999 under a community-based treatment program (joint initiative of an NGO (Socios En Salud) and the Peruvian Ministry of Health). Inclusion criteria were: residence in the government-approved catchment area in northern Lima (Carabayllo, Comas, and Independencia districts); referral to the program by a collaborating health center after the failure of at least one course of directly observed, standardized short-course chemotherapy; laboratory-documented multidrug-resistant tuberculosis; survival until the results of drug-susceptibility testing became available; and provision of written informed consent.
Sample size:	75
Treatment regimen:	Individualized regimens containing a minimum of 5 first and second-line drugs based on DST results. First-line drugs were preferred if susceptible. An injectable was given for at least six months after culture conversion.
Treatment duration:	18+ months (12 consecutive negative cultures)
Duration of injectable:	6+ months after culture conversion
Hospitalization period:	None
Funding source:	Supported by Thomas J. White, the Massachusetts State Laboratory Institute, the National Institute of Allergy and Infectious Diseases, Eli Lilly, and the Bill and Melinda Gates Foundation.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	Cost of therapy ranged from US$504 to $32,383 per patient. Mean of $15,681 was approximately 10% of costs for hospitalized patients.
Author, Year:	Mitnick 2008
Study period:	Feb 1999 to Jul 2002
Study setting:	Metropolitan Lima, Peru. A comprehensive individualized MDR-TB treatment program was introduced in 1996.
Description of Intervention:	Comprehensive supervised outpatient treatment, free of charge to patients. All patients received DOT through local hospitals, health clinics, and daily home visits by community health workers. Patients with emotional and psychosocial difficulties,

	who had weak social support, or with adherence problems were invited to participate in a social support group that included weekly, and later bi-monthly support groups/group therapy, recreational excursions, symbolic celebrations and family workshops (Acha 2008). Limited nutritional and financial support and opportunities for income generation were provided, as needed. Hospitalization was available, if medically indicated.
Patient eligibility:	All MDR-TB patients who initiated individualized treatment under the program, with baseline DST results for at least four drugs: isoniazid, rifampicin, one fluoroquinolone, and one second-line injectable (kanamycin, capreomycin, or amikacin).
Sample size:	651 (48 XDR-TB patients; 603 MDR-TB patients)
Treatment regimen:	Individualized treatment based on DST results, containing at least five drugs likely to be effective, including a fluoroquinolone and an injectable agent.
Treatment duration:	18+ months
Duration of injectable:	8+ months after culture conversion
Hospitalization period:	Only if medically indicated. Overall, 29 (4.5%; 3/48 XDR-TB patients and 26/603 MDR-TB patients) initiated treatment in hospital. Duration depended on when the patient became clinically stable and ready for discharge.
Funding source:	Supported by grants from the Bill and Melinda Gates Foundation, Thomas J. White, Partners in Health, the Peruvian Ministry of Health, the David Rockefeller Center for Latin American Studies at Harvard University, the Francis Family Foundation, the Pittsfield Anti-tuberculosis Association, the Eli Lilly Foundation, and the Hatch Family Foundation and by career development awards from the National Institute of Allergy and Infectious Diseases (5 K01 A1065836, to Dr. Mitnick) and the National Heart, Lung, and Blood Institute (5 K01 HL080939, to Dr. Becerra).
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Mohr 2015
Study period:	Aug 2008 to Jan 2012
Study setting:	Khayelitsha, a township near Cape Town, South Africa, with high rates of HIV, TB and DR-TB. There are approximately 200 cases of DR-TB diagnosed in Khayelitsha each year, with a HIV infection rate of 72%. Eleven health facilities in Khayelitsha provide integrated HIV and TB services for patients. HIV-infected TB patients are started on antiretroviral therapy shortly after initiating TB treatment.
Description of Intervention:	Individual-specific DR-TB counselling (four sessions throughout treatment – three in the first month of treatment, including a home visit with counselling and education for families by the DR-TB counsellor and a social worker/peer educator/nurse, and one during the continuation phase). Patients are invited to attend weekly peer support groups conducted at the clinics, moderated by a DR-TB counsellor or peer educator. Daily DOT at local clinic. A dedicated social assistant is available in Khayelitsha to assist patients in accessing disability/social grants, and refer patients to other support services. Hospitalization only if patients were clinically unstable and unable to attend their clinic daily.
Patient eligibility:	All DR-TB (resistance to at least Rifampicin) patients registered in Khayelitsha during the study period with known HIV status, and without previous treatment with second line drugs. Patients who transferred from facilities outside the sub-district

	and those with bacteriologically unconfirmed DR-TB (mostly children aged ≤5 years) were excluded.
Sample size:	853
Treatment regimen:	Standardized regimen adapted to DST results. Intensive phase: 5 drugs (kanamycin, ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine) Continuation phase: 4 drugs (ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine).
Treatment duration:	24+ months
Duration of injectable:	6 months
Hospitalization period:	No mandatory hospitalization
Funding source:	Funding support from MSF and Wellcome Trust.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Mohr 2017
Study period:	Jan 2010 to Dec 2014
Study setting:	Khayelitsha is a peri-urban township outside of Cape Town, South Africa, most of the 450,000 residents in informal settlements. There are approximately 200 newly diagnosed RR-TB patients each year, with a case notification rate of 55/100,000 and an HIV co-infection rate of 70%. Progressive implementation of SAT took place from 2012 to 2015 at 5 of 10 primary care clinics in Khayelitsha. These initial pilot clinics were chosen based on available resources, functionality, and willingness of staff to participate. The national LTFU rate among RR-TB patients ranges from 20% to 31%.
Description of Intervention:	*Standard of care (SOC) cohort*: Patients attended the clinic 5 days per week for DOT for the entire treatment. Patients received four standardized counseling sessions provided by trained RR-TB counselors: upon diagnosis; at treatment initiation; during the intensive phase; and upon completion of intensive phase. Patients lost to follow-up were traced telephonically or via home visits from local community health workers or counselors. *Self-administered therapy (SAT) cohort*: The same care is received during the intensive phase. After completion of the intensive phase, patients received tailored counselling from an RR-TB counsellor, which includes discussing the option of SAT. Prior to enrollment into SAT, local community health workers conduced home visits to assess the social situation, identify a treatment supporter, and determine adherence barriers. After enrollment patients received an adherence counseling session by a dedicated MSF counselor, where medications were reviewed, a pillbox was issued and adherence barriers were addressed. Patients received weekly or monthly supply of medications, depending on clinic and patient preference. Community health workers visited weekly initially and monthly as soon as patients were deemed to be doing well in the programme, during which they provided support and addressed adherence barriers.
Patient eligibility:	All RR-TB patients who initiated treatment during the study period, and who had a final treatment outcome before 1 Jan 2017, at the 5 pilot clinics were considered for

	study enrollment. Patients were excluded if they had a treatment outcome within 6 months of treatment initiation (42 in SOC cohort; 67 in SAT cohort). *SOC cohort*: Eligible RR-TB patients who initiated treatment at least 6 months prior to SAT implementation at their respective clinics. Treatment initiation times for inclusion in the SOC cohort ranged from January 2010 to July 2013. *SAT cohort*: Eligible RR-TB patients who initiated treatment at least 6 months after SAT implementation at their respective clinics were considered for SAT. Treatment initiation times for patients included in the SAT cohort ranged from Jan 2012 to Dec 2014. Patient eligibility for SAT was assessed based on: treatment adherence history (for RR-TB and concomitant diseases); and clinical status and any adverse events requiring ongoing monitoring. Enrollment decisions were made at weekly clinic meetings attended by community health workers, doctors, RR-TB professional nurses and MSF counsellors. Eligible patients, who gave verbal consent, and who were no longer receiving an injectable agent (including those who were already in the continuation phase) were enrolled.
Sample size:	295 RR-TB patients who completed at least 6 months of treatment (118 in SOC cohort; 177 in SAT cohort); of which 292 had final treatment outcomes by 1 Jan 2017 (118 in SOC cohort; 174 in SAT cohort)
Treatment regimen:	Patients from both cohorts received a standard RR-TB treatment regimen provided to patients contained all or most of the following drugs: kanamycin, moxifloxacin, pyrazinamide, ethambutol, terizidone, ethionamide and high dose isoniazid. The initial phase (6 months, and at least 4 months after culture conversion) consisted of kanamycin, ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine. The continuation phase (at least 18 months) consisted of ethionamide, pyrazinamide, ofloxacin, and either terizidone or cycloserine.
Treatment duration:	24+ months
Duration of injectable:	6+ months, at least 4 months after culture conversion
Hospitalization period:	None
Funding source:	The pilot SAT program was funded by MSF and Cape Town City Health, and the study was funded by MSF.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	Among patients enrolled in the SOC cohort (n=118), 17 (14.4%) were later considered for and received SAT (due to the phased implementation of SAT at the clinics), with a median time to SAT-enrollment of 14.8 months (IQR 12.8-20.3). In addition to these patients, other patients in the SOC cohort might have received an informal version of SAT as facilities occasionally provided a supply of medications for self-administration to relieve pressure on the clinic. These patients however did not receive the specialized counseling and community support integral to the SAT pilot programme. Some eligible patients were never offered SAT due to the slow, phased implementation of the pilot program, reluctance from some providers to provide SAT, and limited resources.
Economic information (if reported):	n/a
Author, Year:	Satti 2012
Study period:	Jan 2008 to Sep 2009
Study setting:	All 10 districts in Lesotho under the national MDR-TB program.
Description of Intervention:	A team of community nurses assessed the home situation, educated families, and arranged for a community health worker to provide twice-daily DOT in the patient's

	home, who also accompanied the patients for monthly clinic visits. Community health workers received regular training on HIV and MDR-TB, and in psychological support. They were reimbursed for all costs incurred and compensated with performance-based payment. Treatment was provided free-of-charge. All patients received a food package and reimbursement for travel expenses incurred during treatment.
Patient eligibility:	All adult patients (15 years or older) with DST-confirmed MDR-TB, who received second-line TB treatment between Jan. 1, 2008 and Sep. 29, 2009 in the national MDR-TB program.
Sample size:	134
Treatment regimen:	Patients were initiated on a standardized regimen of six drugs –pyrazinamide, kanamycin, levofloxacin, prothionamide (or ethionamide), cycloserine, and para-aminosalicylic acid – until DST results are available, after which it is adjusted accordingly.
Treatment duration:	Median duration of 22.9 months (IQR, 21.6–24.0)
Duration of injectable:	6 months
Hospitalization period:	Not mandatory; patients who were critically ill or who had severe adverse events were hospitalized.
Funding source:	Support received from the Department of Global Health and Social Medicine Research Core at Harvard Medical School
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Shin 2006
Study period:	Jun 1998 to Dec 2000
Study setting:	The Tomsk Oblast in western Siberia, where there is a very high burden of MDR-TB. Half of the population lives Tomsk, the capital city, and the remainder lives in remote rural villages, which are often inaccessible for parts of the year.
Description of Intervention:	Patients are routinely hospitalized during intensive phase, and discharged for the continuation phase, unless there is an underlying condition that precludes discharge (such as a psychiatric disorder, alcoholism or homelessness). TB physicians routinely assessed all patients initiating treatment for possible alcohol or substance use disorders. Daily DOT was provided by feldshers, who are often nurses at very rural outposts, to supervise the TB and Naltrexone medications, or at TB clinics, TB hospital or day hospital. Supplementary nutritional support is provided to prisoners and in-patients, and monthly food packages and/or free meals are given to fully adherent out-patients.
Patient eligibility:	Confirmed or suspected MDR-TB (based on history of previous treatment failures) who were receiving DOTS-Plus treatment from the civilian sector (n=134, 54.9%) and prison sector (n=110, 45.1%)
Sample size:	244
Treatment regimen:	The individualized treatment containing at least 5 drugs, based on DST or drugs thought to be sensitive, including: any first-line oral agent to which isolate is sensitive; an injectable to which an isolate is sensitive; a quinolone; other second-line drug (usually ethionamide or cycloserine or PAS).
Treatment duration:	18+ months

Duration of injectable:	6+ months after culture conversion
Hospitalization period:	Routine hospitalization in the civilian sector during the intensive phase (i.e. duration of injectable). Among civilian patients, 98 (73.1%) started treatment in the hospital (median duration of 7.9 months), the remainder started as outpatients in the day hospital.
Funding source:	Funding for medications and patient care was provided by the Bill & Melinda Gates Foundation and the Open Society Institute. Funding for physician and health care worker training was provided by the Eli Lilly foundation.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Suarez 2002
Study period:	Oct 1997 to Mar 1999
Study setting:	Peru, a middle-income country where TB treatment is provided free of charge.
Description of Intervention:	Daily DOT by nurses and monthly medical check-up by doctors. Patients were provided appointment cards and weekly food parcels.
Patient eligibility:	Patients with confirmed MDR-TB who were enrolled in the second-line treatment programme in Peru.
Sample size:	298
Treatment regimen:	Standardized regimen consisting of kanamycin (1 g injectable), ciprofloxacin (1 g orally), ethionamide (750 mg orally), pyrazinamide (1500 mg orally), and ethambutol (1200 mg orally). Kanamycin was administered for the first 3 months.
Treatment duration:	18 months
Duration of injectable:	3 months
Hospitalization period:	None
Funding source:	Not declared
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	The average cost per patient for those who completed the full course of treatment was US$2381, with the second-line drugs, at US$824 per patient, being the most expensive item.
Author, Year:	Thomas 2007
Study period:	Jan 1999 to Dec 2003
Study setting:	Predominantly rural sub-district of Tiruvallur district, in south India, and nearby Chennai Sity. The Revised National TB Control Programme (RNTCP) was implemented in Triuvallur district in 1999, the area has 17 governmental health care facilities, including 7 designated microscopy centers.
Description of Intervention:	After discharge, patients attend primary health centres or NGO for thrice-weekly DOT. Monthly clinical assessment and sociological counselling. Reminders were sent one week prior to monthly check up. Financial assistance was provided at the monthly visits for all patients to compensate for loss of wages and travel expenses.

Patient eligibility:	All culture-confirmed MDR-TB patients who were referred to the Tuberculosis Research Centre during the study period from the study area in Tiruvallur district, and from an NGO working in nearby Chennai city.
Sample size:	66
Treatment regimen:	Individualized regimen based on DST results. The regimens used were: Group I: $6Sm_3(Km_3)$OfxEtoZE daily followed by 12OfxEtoZE daily Group II: Other combinations. E.g.: $6Sm_3(Km_3)$OfxEtoZ$H_{high\ dose}$ daily followed by 12OfxEtoZH daily; or $6Sm_3(Km_3)$OfxZE with Cs/PAS/High dose INH daily followed by 12 months of oral drugs; etc.
Treatment duration:	18+ months
Duration of injectable:	6 months
Hospitalization period:	Recommendation of 1 month. 30 (45%) were not hospitalized, and 10 (15%) hospitalized for <10 days.
Funding source:	Funding support from the World Health Organization and the United States Agency for International Development under the Model DOTS Project.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Vaghela 2015
Study period:	Aug 2009 to Mar 2010
Study setting:	Northeast, East, Central and West districts of Delhi, India – large metropolitan area with a high burden of TB and MDR-TB.
Description of Intervention:	Daily DOT by a DOT Provider at a DOTS-plus centre or hospital. Mobile multi-disciplinary teams, consisting of one male and one female trained community health workers, made home visits every 15 days during intensive phase and every 45 days in continuation phase. The home visits included psychosocial support and counselling for patients and their families, hygiene and nutrition counselling, and nursing care. Patients from very poor socioeconomic backgrounds were provided free multigrain biscuits and an egg per day. Patients were given the mobile numbers for the team members such that in case of an adverse drug reaction or early warning symptoms, they can get immediate attention. Teams assisted patients in registering for financial support under the government TB scheme.
Patient eligibility:	All new MDR-TB patients registered at clinics in the selected districts
Sample size:	101
Treatment regimen:	Standardized regimen. Intensive phase: kanamycin, ofloxacin (levofloxacin), ethionamide, pyrazinamide, ethambutol and cycloserine Continuation phase: ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine P-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Ofl, Z and Eto) or 2 bacteriostatic (E and Cs) drugs are not tolerated.
Treatment duration:	24 to 29 months

Duration of injectable:	6 to 9 months
Hospitalization period:	Not reported
Funding source:	Funded by Eli Lilly and Company (India) Pvt. Ltd.
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Yu 2015
Study period:	Jan 2007 to Jun 2008 [updated to 2012 using unpublished data (Yu 2018, accepted manuscript: https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciy066/4831095?redirectedFrom=fulltext)]
Study setting:	Northern Taiwan, where the government established a new patient-centred MDR-TB treatment program in May 2007 to standardize MDR-TB care, named Taiwan MDR-TB Consortiums (TMTC). Prior to its establishment, MDR-TB patients had to visit either prescribed hospitals or a contracted out-patient clinic for daily injections, and public health nurses were not familiar with the complicated regimens for MDR-TB or the related adverse effects. Between 1992 and 1996, the national lost to follow-up rate among MDR-TB patients was approximately 30%.
Description of Intervention:	Hospitalization was encouraged at treatment initiation. Designated observers and nurses provided DOT and injections to patients, typically at their home. Taiwan CDC also provided NTD 1 million for every patient (a maximum of NTD 2 million for the 2-year treatment period, excluding the cost of medicine) to be used flexibly by the medical team for incentives and enablers to improve adherence. Education and counselling provided by the medical team during home visits to patients and their families. When patients attended out-patient clinics for refills or check-ups, they were accompanied by team members from the TMTC to address hospital affairs and have examinations done in regards of infection control.
Patient eligibility:	All pulmonary, bacteriologically confirmed MDR-TB cases who received treatment with second-line drugs, during the study period. MDR-TB patients with positive culture results after January 2007 were informed and consented to participate in the Consortium program.
Sample size:	126
Treatment regimen:	Individualized regimens based on DST results. Four susceptible drug, including EMB, PZA, a fluoroquinolone, an injectable, and other oral 2nd-line drugs.
Treatment duration:	18 to 24 months (18 months after sputum conversion)
Duration of injectable:	6 months
Hospitalization period:	2 weeks to 2 months
Funding source:	Centers for Disease Control, Taiwan
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
INCLUDED TRIALS	
Author, Year:	Baral 2014 (mixed methods)

Study period:	Jan 2008 to Dec 2008
Study setting:	Nepal, a mid-TB burden country where TB is highly stigmatised. MDR TB treatment is provided from 10 treatment centres and 34 sub-centers throughout the country. There is a well-functioning national TB programme but management is complicated by the country's terrain. A national DOTS-Plus program for MDR-TB was piloted in November 2005. The reported non-completion rates under the program were 22%, 15% and 18% in 2005, 2006 and 2007 respectively. This study was conducted at the 7 DOTS-Plus centres in the Kathmandu Valley.
Randomization:	The seven DOTS-Plus centres were randomized to 3 types of care by randomly selecting from the numbers 1 to 7 (representing each centre): 2 to standard care (controls); 2 to standard care plus counselling; and 3 to standard care plus counselling and financial support. Individual randomization could not be done due to the certainty of contamination among patients within a centre.
Trial arms:	Control arm (standard care): Each patient nominated someone (usually a family member) as a treatment supporter. Daily DOT at the clinic. Intervention arm 1: Standard care plus individual (2 to 5 sessions) and small-group counselling (every 2-3 weeks) by trained Public Health Nurse. Counselling sessions were between 15 to 30 minutes, and were tailored to issues identified in previous sessions. The general content was information about disease, drugs and treatment, curability, treatment continuation, social barriers such as stigma, support from health workers, community and family members, financial hardship due to MDR TB etc. Intervention arm 2: Standard care plus counselling sessions (as in Intervention arm 1), and additionally, patients received financial support (2000 Nepali Rupees (~28USD) per month).
Patient eligibility:	All MDR-TB patients starting treatment at the DOTS-plus centres in 2008 were eligible for study inclusion.
Sample size:	156 (control: 81; intervention 1: 33; intervention 2: 42)
Treatment regimen:	Standardized regimen. Intensive phase: five drugs (pyrazinamide, kanamycin, ofloxacin, ethionamide, and cycloserine) for eight months, but is extended to twelve months if the patient is smear- or culture-positive at six months (8Z-Km-Ofx-Eto-Cs/16Z-Ofx-Eto-Cs). Continuation phase: same as intensive phase, but without kanamycin.
Treatment duration:	16 months, extended by up to 8 months if culture conversion occurred between 12 and 18 months of treatment
Duration of injectable:	8 to 12 months
Hospitalization period:	Hospitalization only for severe side effects.
Funding source:	Funded by UK Aid from the UK Department for International Development (DFID).
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a
Author, Year:	Taneja 2017
Study period:	Apr 2014 to May 2014

Study setting:	This pilot study was conducted at two sites (Malviya Nagar Government Hospital and Nehru Nagar Chest Clinic, both in New Delhi) randomly selected from a list of 20 hospitals in Delhi, India, at which a cluster trial was being plan.
Randomization:	Cluster randomization by hospital site
Trial arms:	Control arm (Nehru Nagar site): The control arm received regular treatment and investigations as per RNTCP guidelines. During the intensive phase, patients visited the DOTS centre thrice weekly for DOT provided by health workers. During the continuation phase, patients received weekly supplies of drugs from the DOTS centre to be consumed at home. Health education and counselling was given at each visit to the DOTS centre. DOTS health workers were given incentives from program funding for every patient that successfully completed treatment. Intervention arm (Malviya Nagar site): In addition to standard care (as in control arm), a team of two trained homecare providers provided comprehensive home-based care to MDR-TB patients and their family members, which included counselling on the importance of treatment adherence, on their emotional needs, as well as health education on coughing etiquettes, avoiding risk to family members, etc. Additional support included: nursing care and referral to other higher centres in case of illness or mental health issues; physical, mental and vocational rehabilitation; assistance in obtaining Government financial support; support for obtaining or returning to work and school; and nutritional support (eggs and nutritious multigrain provisions) and counselling. The homecare team visited patients fortnightly during the intensive phase and every 45 days during the continuation phase. In addition to providing counselling and education, the team also recorded body weight, side-effects of medicines and complications of the disease. The team also motivated the patients to go for routine sputum microscopy, X-Ray, sputum culture and other relevant investigations.
Patient eligibility:	MDR-TB patients who received treatment for more than 6 months. Exclusion criteria were: any form of disability and comorbidities; and pregnancy.
Sample size:	100 (50 in each arm)
Treatment regimen:	Standardized regimen, adjusted based on DST results, consisting 6 drugs (Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol and Cycloserine) during the intensive phase (6 to 9 months), and 4 drug (sLevofloxacin, Ethionamide, Ethambutol and Cycloserine) during continuation phase (18 months).
Treatment duration:	24 to 27 months
Duration of injectable:	6 to 9 months
Hospitalization period:	None
Funding source:	None stated
Potential conflicts of interest:	None declared
Issues with implementation (if reported):	n/a
Economic information (if reported):	n/a

Table 9. Detailed quality assessment of non-randomized studies (based on Robins-I Tool)

Author, Year	Alene 2017
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information – unclear on whether counselling continued after hospital discharge
Overall risk due to deviations from interventions	No information
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	8/489 (1.6%) patients were not included because their outcomes were not available (i.e. transferred out or not assessed)
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – treatment outcomes were obtained from an internet-based TB Management Information System in the Tuberculosis Control Institute of Hunan Province, and from MDR-TB medical records and the DST registration book at Hunan Chest Hospital.
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low

OVERALL BIAS	No information
Author, Year	Bastard 2015
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information – unclear how frequent or for how long were individual and group counselling provided for, and whether this was routinely provided to all patients
Overall risk due to deviations from interventions	No information
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	No – 22/415 (5.3%) were excluded from analysis because they did not have an outcome at the administrative censoring date (12 were still receiving treatment and 10 had transferred out).
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Moderate
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – treatment outcomes obtained from routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	No information
Author, Year	Cox 2007
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No

Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No, this was a pilot program with a small sample that appeared to adhere to the protocol.
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – treatment outcomes obtained from routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Escudero 2006
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No

Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – provided clear details of intervention implementation and delivery.
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Most – 2/25 (8%) patients transferred to other hospitals
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Moderate
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – used routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	Low
Overall Risk of reporting bias	Low
OVERALL BIAS	Moderate
Author, Year	Gelmanova 2011
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes

Overall Risk of selection bias	Low
Bias due to deviations from intended interventions	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No - clear details of intervention implementation and delivery.
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes, except 1/38 (2.6%) patient who was transferred out
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Isaakidis 2011
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – clear details of intervention implementation and delivery.
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	No – 23/58 (39.7%) were still on treatment at the end of the observational period, all initiated treatment <24 months before end date. Thus, although they were censored, their exclusion does not affect results.
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Joseph 2011
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information – the intervention required a network of trained DOT providers to deliver treatment, and also weekly delivery of the TB drugs to the DOT providers by research staff, it was not reported whether this was done successfully and that treatment was consistently delivered without interruptions.
Overall risk due to deviations from interventions	No information
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	No information
Author, Year	Joseph 2011
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes

Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
Overall risk due to deviations from interventions	Low
Bias due to missing data	Low
Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Meressa 2015
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – detailed description of intervention delivery
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Mitnick 2003
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low

Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data. However, this study used a non-standard definition for lost to follow-up: "Withdrawal from therapy was defined by one or more months of missed therapy during the first year, and two or more months missed during the second year." Of the 5 patients lost to follow-up, it is not clear how many were lost during the first year. If many were lost in the first year, *and* interrupted treatment for less than 2 months, then the lost to follow-up rate would be overestimated in this study compared to other studies. However, this seems unlikely to be true.
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Mitnick 2008
Bias in selection of participants into the study	

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – unlikely given the type of intervention provided was flexible.
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes, except 5/651 (0.8%) who were transferred out (n=4) or still on treatment at end of study (n=1).
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – however, the definition for lost to follow-up was not done according to the same WHO standard as other studies: "Treatment default was a physician-defined end point assigned upon the failure of attempts to return to therapy those patients who had not been adhering to their treatment regimen." Therefore, there is a possibility that among 18/651(2.8%) patients who failed, there could be a proportion who in fact would have been classified as lost to follow-up if they had interrupted therapy for 2 or more consecutive months. However, this would be a small proportion and have little influence on the results.
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low

Author, Year	Mohr 2015
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not beyond what would be expected: "In the earlier years of the programme, DR-TB counselling was less structured and focused primarily on treatment initiation."
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	No – 96/853 (11.3%) were transferred out of the study clinics, therefore their outcomes were not recorded.
Were participants excluded due to missing data on other variables needed for the analysis?	Yes – 14 patients were included due to unknown HIV status. However, unlikely to affect results.
Overall risk of bias due to missingness	Moderate
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Moderate

Author, Year	Satti 2012
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – very clear description of intervention development and implementation
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Most – 3/134 (2.2%) of patients were transferred out.
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – used routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Shin 2006

Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – detailed description of intervention implementation and delivery
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Shin 2006
Bias in selection of participants into the study	

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – detailed description of intervention implementation and delivery
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Thomas 2007
Bias in selection of participants into the study	

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	Yes – the study reported difficulties identifying DOT providers near patients (as planned in the intervention), therefore patients often travelled further than expected for treatment, or had to pay a fee to receive treatment from a private provider.
Overall risk due to deviations from interventions	Moderate
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Moderate
Author, Year	Vaghela 2015
Bias in selection of participants into the study	

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – clear implementation and delivery description
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes – 1/101 (1%) patients transferred out
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Author, Year	Yu 2015
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No

Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No – the study intervention had a flexible adherence support component.
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes – 2/126 (1.6%) patients transferred out
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No – routinely collected data
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Low
Cohort studies with 2 or more interventions	
Author, Year	Mohr 2017
Bias due to baseline confounding	
Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No – one important potential confounder that was unbalanced at baseline between the SOC and SAT cohorts was history of previous TB treatment. A smaller proportion of patients in the SAT cohort had a TB treatment history (59.8% in SAT cohort vs 76.3% in SOC cohort) – this could confound the relationship between the intervention and the outcome of lost to follow-up, likely biasing the effect of intervention away from the null.
Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N/A
Did the authors control for any post-intervention variables that could have been affected by the intervention?	No
Overall risk of confounding bias	Serious
Bias in selection of participants into the study	

Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No – patients were selected to receive self-administered therapy (SAT) based on an assessment by the care team made after the intensive phase of treatment, however, the authors did an intention-to-treat analysis where cohort group assignment depended on time of treatment initiation relative to implementation of intervention, and not on whether the patient actually received SAT or not.
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall Risk of selection bias	Low
Bias in classification of interventions	
Were intervention groups clearly defined?	Yes
Was the information used to define intervention groups recorded at the start of the intervention?	Yes
Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
Overall risk due to intervention classification	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	Yes – Due to the staggered recruitment of patients based on the timing of implementation of the intervention (SAT – self-administered therapy), there were some patients in the control (SOC- standard of care) cohort who received the intervention (n=17). However, they tended to only be placed out for SAT late in treatment (median time to SAT-enrollment was 14.8-months (IQR 12.8±20.3)), thus the bias would be minimal and towards the null. Additionally, patients in the SOC-cohort might have received an informal version of SAT as facilities occasionally provided a supply of medications for self-administration to relieve pressure on the clinic, despite clinic DOT being the SOC. This would so slightly bias the estimated effect of SAT towards the null. These patients however, did not receive the specialized counseling and ongoing community support integral to the intervention. Similarly, the
If yes, were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Yes – the estimated effect was likely biased towards the null due to contamination and slight deviations in the SOC group.

Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	No – 42/244 (17.2%) and 24/160 (15.0%) in the SAT and SOC cohorts were transferred out/not evaluated for final treatment outcomes. The proportions were similar across two groups.
Were participants excluded due to missing data on intervention status?	No
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No
Were outcome assessors aware of the intervention received by study participants?	Yes
Were the methods of outcome assessment comparable across intervention groups?	Yes
Were any systematic errors in measurement of the outcome related to intervention received?	No
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall Risk of reporting bias	Low
OVERALL BIAS	Serious
Author, Year	Loveday 2015
Bias due to baseline confounding	

Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No - there was no multivariate adjusted analysis for confounders. Some important confounders that were unbalanced at baseline between the two groups included: previous TB treatment (96% among patients at the centralized hospital vs. 60% among patients at the decentralized sites); and sputum smear-positivity (54% among patients at centralized hospital vs. 73% among patients at the decentralized sites). Unclear what direction this would bias the effect estimates.
Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N/A
Did the authors control for any post-intervention variables that could have been affected by the intervention?	No
Overall risk of confounding bias	Serious
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall risk of selection bias	Low
Bias in classification of interventions	
Were intervention groups clearly defined?	Yes
Was the information used to define intervention groups recorded at the start of the intervention?	Yes
Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
Overall risk due to intervention classification	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
If yes, were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	N/A
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	Yes – 2.7% among those at the decentralized sites and 0.2% of those at the centralized site were transferred out or were not evaluated for final treatment outcomes.
Were participants excluded due to missing data on intervention status?	No
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Low
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No
Were outcome assessors aware of the intervention received by study participants?	Yes
Were the methods of outcome assessment comparable across intervention groups?	Yes
Were any systematic errors in measurement of the outcome related to intervention received?	No
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No

Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall risk of reporting bias	Low
OVERALL BIAS	Serious
Author, Year	Cox 2014
Bias due to baseline confounding	
Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No - the paper had a multivariate adjusted model for estimating the effect of intervention on 'time to death', but not for lost to follow-up (our primary outcome of interest). The final treatment outcomes were available as stratified by HIV-status in the intervention (community-based model) group, but not for the control (hospital-based model) group. Limited data available on important potential confounders such as additional resistance to second-line drugs, and severity of disease.
Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N/A
Did the authors control for any post-intervention variables that could have been affected by the intervention?	N/A
Overall risk of confounding bias	Serious
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	Yes
Overall risk of selection bias	Low
Bias in classification of interventions	
Were intervention groups clearly defined?	Yes
Was the information used to define intervention groups recorded at the start of the intervention?	Yes
Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
Overall risk due to intervention classification	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	

Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
If yes, were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	N/A
Overall risk due to deviations from interventions	Low
Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	No – 10.3% and 4.6% of the community-based and hospital-based cohorts were transferred out or not evaluated for final treatment outcomes.
Were participants excluded due to missing data on intervention status?	No
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Moderate
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No
Were outcome assessors aware of the intervention received by study participants?	No
Were the methods of outcome assessment comparable across intervention groups?	Yes
Were any systematic errors in measurement of the outcome related to intervention received?	No
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall risk of reporting bias	Low
OVERALL BIAS	Serious
Author, Year	Huerga 2017

Bias due to baseline confounding	
Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No –there was a multivariate analysis for the "unfavourable outcomes", not for lost to follow-up. Did not report on many potential confounders, however, among those reported, proportions infected with HIV were not balanced at baseline across the three groups (21.4% in Mathare; 60.7% in Homa Bay; and 15.7% in Nairobi), and was associated with unfavourable outcomes in both univariate and multivariate analyses.
Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N/A
Did the authors control for any post-intervention variables that could have been affected by the intervention?	No
Overall risk of confounding bias	Serious
Bias in selection of participants into the study	
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No
Do start of follow-up and start of intervention coincide for most participants?	N/A
Overall risk of selection bias	Low
Bias in classification of interventions	
Were intervention groups clearly defined?	Yes
Was the information used to define intervention groups recorded at the start of the intervention?	No
Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No
Overall risk due to intervention classification	Low
Bias due to deviations from intended interventions (assessing effect of assignment to intervention)	
Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
If yes, were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	N/A
Overall risk due to deviations from interventions	Low

Bias due to missing data	
Were outcome data available for all, or nearly all, participants?	No – 25.0% in Homa Bay, 11.4% in Mathare and 12.7% in Nairobi sites were transferred out or not evaluated for final treatment outcomes. This is likely associated with both the intervention and lost to follow-up.
Were participants excluded due to missing data on intervention status?	No
Were participants excluded due to missing data on other variables needed for the analysis?	No
Overall risk of bias due to missingness	Moderate
Bias in measurement of outcomes	
Could the outcome measure have been influenced by knowledge of the intervention received?	No information
Were outcome assessors aware of the intervention received by study participants?	Yes
Were the methods of outcome assessment comparable across intervention groups?	N/A
Were any systematic errors in measurement of the outcome related to intervention received?	N/A
Overall risk of outcome measurement bias	Low
Bias in selection of the reported result	
Multiple outcome measurements within the outcome domain?	No
Multiple analyses of the intervention-outcome relationship?	No
Bias in selection of the reported result [different subgroups?]	No
Overall risk of reporting bias	Low
OVERALL BIAS	Serious

Table 10. Detailed quality assessment of cluster randomized trials

Author, year	Baral 2014
Random sequence generation (selection bias)	Low
Support for judgement	"Prior to the start of the formative study, we randomly allocated the DOTS-plus centres to 3 types of care – 2 to counselling, 3 to combined support, and 2 to usual care – by selecting randomly from the numbers 1 to 7"
Allocation concealment (selection bias)	Low
Support for judgement	Cluster randomized trials – all patients at each randomized site received the same treatment. There is low risk of selection bias (of sites) due to lack of allocation concealment.
Blinding of participants and personnel (performance bias)	High
Support for judgement	Site staff likely knew they were randomized to an intervention site or not due to changes in treatment delivery practices. This could have caused better performance in non-intervention duties as well, which could lead to bias.
Blinding of outcome assessment (detection bias)	Low
Support for judgement	Assessment of final treatment outcomes are objective and unlikely to vary based on intervention status.
Incomplete outcome data (attrition bias)	Low
Support for judgement	Final treatment outcomes were reported for all enrolled patients.
Selective outcome reporting? (reporting bias)	Low
Support for judgement	All treatment outcomes were reported.
Other bias	Not enough clusters for randomization to eliminate confounding bias. Likely residual confounding, especially given some baseline imbalances. There was multivariate analysis for loss to follow-up outcome to adjust for age or sex, separately, but not for other important confounders, such as severity of disease.
Author, Year	Taneja 2017
Random sequence generation (selection bias)	Low
Support for judgement	"Cluster trial was being planned in twenty hospitals in Delhi, therefore this pilot study was planned to be conducted with two hospitals. Among the hospitals two

	hospitals- Malviya Nagar Government Hospital and Nehru Nagar Chest Clinic were selected by simple random sampling using lottery method."
Allocation concealment (selection bias)	Low
Support for judgement	Use of simple random sampling to assign sites to cluster trial, unlikely to induce bias due to lack of concealment
Blinding of participants and personnel (performance bias)	High
Support for judgement	Site staff likely knew they were randomized to an intervention site or not due to changes in treatment delivery practices. This could have caused better performance in non-intervention duties as well, which could lead to bias.
Blinding of outcome assessment (detection bias)	Low
Support for judgement	Assessment of final treatment outcomes are objective and unlikely to vary based on intervention status.
Incomplete outcome data (attrition bias)	Low
Support for judgement	Final treatment outcomes were reported for all enrolled patients.
Selective outcome reporting? (reporting bias)	Low
Support for judgement	All treatment outcomes were reported.
Other bias	There were only two sites included in the study, which is a small sample size and susceptible to confounding. Also cluster design means site-specific characteristics could introduce confounding. There were baseline difference in important covariates such as religion, death of family member due to TB, family members with TB, that could have confounded results. However, there was no multivariate analyses done.

STUDY 4: STRENGTHENING THE TUBERCULOSIS CASCADE OF CARE TO REDUCE TUBERCULOSIS MORTALITY AND DRUG RESISTANCE: A DYNAMIC MODELLING STUDY

The following is a duplicate of the online supplement to the manuscript prepared for submission to Lancet Global Health. Law S, Oxlade O, Menzies D. Strengthening the tuberculosis cascade of care to reduce tuberculosis mortality and drug resistance: A dynamic modelling study. [Prepared for submission]

Model calibration against WHO-estimated TB mortality

The model was calibrated to predict a TB epidemic that matched the WHO-estimated TB incidence, as well as the prevalence of INH and RR/MDR resistance, between 2007 and 2016.[1] However, it was only calibrated against the WHO-estimated TB mortality rate in 2016, and not to the WHO-estimated TB mortality rates during the same period. This was because our model assumed that the decrease in HIV incidence, and increase in access to antiretroviral therapy (ART), during that period would lead to reductions in mortality among TB/HIV co-infected individuals, but the WHO estimates do not reflect this downward trend.

To calibrate the model, we first ran the model without any risk of acquiring drug resistance over 500 years, such that the drug-susceptible TB epidemic reached an equilibrium. Then, we introduced probabilities of acquiring resistance to isoniazid and ran the model over another 50 years, with risk of acquiring resistance to rifampicin being added only over the last 40 years. This was done to approximate the number of years the two drugs became widely available in South Africa before 2007. Between 2007 and 2016, changes to drug susceptibility testing (DST) were introduced (described in main text). Other annual changes to model parameters during the calibration period included (appendix): gradual decline in non-TB/HIV-related mortality rate; increase in ART and IPT coverage among people living with HIV; decrease in HIV incidence; and variations in TB treatment lost to follow-up rates to reflect changes to the quality of TB care.

Table 1. TB-related parameters

	Value	Range	Source
TB transmission per active untreated TB case, no.			
Smear+	*11.3**	1-22	Styblo, Meijer, & Sutherland, 1969[2]; Vynnycky & Fine, 1997[3]
Smear-	*2**	0.2-4.4	Behr et al·, 1999;[4] Van Geuns, Meijer, & Styblo, 1975[5]
Early reactivation rate (first 2 years), %/year	*4.7**	2-5	Sutherland, 1976[6]
Late reactivation rate, HIV- (after 2 years), %/year	*0.22**	0.1-0.3	Comstock, Edwards & Livesay, 1974[7]; Nolan & Elarth, 1988[8]
Protection against disease after re-infection, HIV- (RR)	0.59	0.57-0.62	Vynnycky & Fine, 1997[3]
Annual mortality - untreated TB, HIV-, %			
Smear+ (first 10 years)	19	12.6-27.3	Grzybowski, 1993[9]; Tiemersma, et al, 2011[10]**
Smear+ (after 10 years)	4.1	2.1-19.3	*Ibid.*
Smear- (first 10 years)	5.6	3.2-7.4	*Ibid.*
Smear- (after 10 years)	1.3	1.2-1.5	*Ibid.*
Spontaneous cure rate - untreated TB, HIV-, %			
Smear+	18	7-33	*Ibid.****
Smear-	51	46-57	*Ibid.*
Relapse after spontaneous cure, %	1.3		Law, 2017[11]
Reduced transmissibility of drug-resistant strains, RR			
INH-R	1		Cohen, 2004[12]; Haas, 1997[13]; Kiepiela, 2000[14]
RR/MDR	0.8*	0.53-1	Knight et al, 2015[15]

*Adjusted during model calibration (see methods in text)

** Fixed annual mortality rates for the first 10 years are estimated in order to match sample size-weighted average of 10-year survival rates, stratified by smear status (Grzybowski 1993). Fixed annual mortality rates for after 10 years are estimated such that the total mortality rate between years 11 and 20 is 3·4% (out of total TB population), regardless of smear status.

*** One-time spontaneous cure rates were estimated by multiplying sample size-weighted average of 10-year survival rates, stratified by smear status (Grzybowski 1993), by 65%, which is the estimated proportion of survivors of untreated TB who become bacteriologically negative.

Table 2. HIV-related parameters

	Value	Range	Source
HIV incidence, %	Varied annually	n/a	UNAIDS, 2018[16]
Annual AIDS-related mortality rate, %	4.9*	3.6-5.3	UNAIDS, 2018[16]
Effect of untreated HIV on TB parameters			
Increased reactivation rate, RR	16.2*	15.4-27.5	WHO, 2009[17]
Increased annual mortality, untreated TB, RR	assume same as initial TB treatment		Assumed
Increased mortality during initial TB treatment, RR	5.78	1.82-18.3	Murray, 1999[18]; Malkin, 1997[19]; Wilkinson, 1996[20]; Perriëns, 1995[21]; Ackah, 1995[22]**
Increased mortality during retreatment, RR	assume same as initial treatment	n/a	Assumed
Increased mortality during MDR treatment, RR	2.52	95% CI 2.04–3.13	Farley, 2011[23]
Relapse after LTFU, %	100%	n/a	Assumed
Increased failure rate during TB treatment	none	n/a	Assumed based on lack of association found in: Murray, 1999[24]; Malkin, 1997[25]; Wilkinson, 1996[26]; Perriëns, 1995[27]; Ackah, 1995[28]; Brust et al, 2010.[29]
Increased LTFU rate during TB treatment	none	n/a	Assumed based on lack of association found in: Farley, 2011[23]; and Kigozi et al, 2017[30]
Increased relapse rate after treatment success	none	n/a	Assumed based on lack of association found in: Chiasson et al, 2010[31]; Houben et al, 2011[32].
Increased risk of acquired drug resistance	none	n/a	Assumed based on lack of association found in: Shenoi et al, 2009[33]; Suchindran et al, 2009.[34]
Protection against disease after re-infection (RR)	1	n/a	Assumed no protection if HIV-positive.
Effectiveness of ART			

Reduction in reactivation rate, RR	0.35	0.28- 0.44	Suthar et al, 2012[35]
Protection against disease after re-infection, RR	Same as HIV-negative	n/a	Assumed
Relapse after LTFU, %	Same as HIV-negative	n/a	Assumed
Reduction in TB mortality rate, RR	0.42	95%CI: 0.29–0.56	Odone et al, 2014[36]
Reduction in AIDS-related deaths, RR	0	n/a	Assumed
Effectiveness of IPT for HIV+ patients			
Reduction in reactivation rate, RR	0.68	0.54-0.85	Akolo et al, 2010[37]
Joint effectiveness of IPT & ART			
Reduction in reactivation rate, RR	same as HIV-negative	0.02-0.78	Assumed if on both IPT and ART, then the risk of reactivation is equal to HIV-negative, based on findings in: Golub et al, 2009[38].
ART coverage, non-TB-co-infected %	Varied annually	n/a	UNAIDS, 2018[16]
ART coverage, TB co-infected, %	Varied annually	n/a	WHO, 2018[1]
ART retention, %	72.3	67.4% - 76.9%	Assumed the 36-month retention rate in Fox et al, 2011[39].
IPT coverage, %	Varied annually	n/a	WHO, 2018[1]
IPT Retention, %	59%		Golub, 2009[38]
Spontaneous cure rate, HIV+			
Smear+/HIV+ no ART, %	0	n/a	Assumed as in: Sharma et al, 2017[40]; and Azman et al, 2014[41].
Smear-/HIV+ no ART, %	0	n/a	*Ibid.*

Smear+/HIV+ on ART, %	18	7-33	Assumed same as HIV-negative
Smear-/HIV+ on ART, %	51	46-57	Assumed same as HIV-negative

*Adjusted during model calibration

**Random effects pooled estimates (inverse variance method, maximum-likelihood estimator for tau^2 of all studies reporting 6-month RIF-containing regimens included in Mukadi et al, 2001.[42]

Table 3. TB Treatment outcomes in South Africa

	Value	Range	Source
INITIAL TREATMENT OUTCOMES			
Death, % of all treated			
DS-TB, HIV-	*1.8**	1.8 - 2.5	WHO, 2018[1]
INHR, HIV-	Assume same as DS-TB		Assumed
RR/MDR, HIV-	Assume same as untreated TB		Assumed
LTFU, % of all survived			
any TB, HIV-	Varied annually		WHO, 2018[1]
Failure, % of all completed			
DS-TB, HIV-	2	1-3	Menzies et al, 2009[43]
INHR, HIV-	11	6-17	Gegia et al, 2017[44]
RR/MDR, HIV-	#		Remainder after assuming spontaneous cure if untreated.
Relapse, % of all completed**			
DS-TB, HIV-	5	2-7	Gegia et al, 2017[44]
INHR, HIV-	10	5-15	*Ibid.*
RR/MDR, HIV-	19.7	5.6-50.1	Updated data used in Law, 2017[11]
RETREATMENT OUTCOMES			

Death, % of all treated	8.3		WHO, 2018[1]
DS-TB, HIV-	2.3*	2.3-3.2	WHO, 2018[1]
INHR, HIV-	Assume same as DS-TB		
RR/MDR, HIV-	Assume same as untreated TB		
LTFU, % of all survived			
any TB, HIV-	Varied annually		WHO, 2018[1]
Failure, % of all completed			
DS-TB, HIV-	1	0-2	Gegia et al, 2017[44]
INHR, HIV-	6	2-10	*Ibid.*
RR/MDR, HIV-	#		Remainder after assuming spontaneous cure
Relapse, % of all completed			
DS-TB, HIV-	5	4-7	Gegia et al, 2017[44]
INHR, HIV-	5	2-8	*Ibid.*
RR/MDR, HIV-	Assume same as initial treatment		
ACQUIRE DRUG RESISTANCE AFTER INITIAL/RETREATMENT			
Acquire INHR after failure/LTFU/relapse, %			
CAT I/IIregimen, DS-TB, HIV-	3.44	1.38-8.35	Updated data used in Law, 2017[11]
Acquire RR/MDR after failure/LTFU/relapse, %			
CAT I regimen, DS-TB, HIV-	1	0-2	Gegia et al, 2017[44]
CAT II regimen, DS-TB, HIV-	0.3	0-0.6	*Ibid.*
CAT I regimen, INHR-TB, HIV-	8	3-13	*Ibid.*
CAT II regimen, INHR-TB, HIV-	3%	0-6	*Ibid.*
MDR TREATMENT OUTCOMES (HIV-)			
Death, % of treated	16.2	13.0-19.9	Farley et al, 2011[23]

LTFU, % of survived	28	n/a	WHO, 2018[1]
Failure, % of completed	17.5	14.1-21.6	Farley et al, 2011[23]
Relapse, % of completed	3.8	3.1- 4.7	Ahuja et al, 2012[45]
RELAPSE AFTER LTFU, ANY TB, %			
HIV-	20.8	18.3-23.5	Parthasarathy et al, 1986[46]; East African and British Medical Research Councils, 1978[47]; Balasubramanian et al, 1990[48]; Eule et al, 1986[49].***

* Overall mortality among new TB patients and retreatment patients was 6.5% and 8.3%, respectively (WHO, 2018[1]). The mortality rate was calibrated within a range from: if we assumed HIV contributes to 61% (HIV has no effect on mortality, and is equal to proportion of notified cases with HIV), to 72% (i.e. the estimated proportion of overall TB mortality attributable to TB-HIV cases based on WHO data).

** We assumed all relapses happened in the first year after treatment. This is consistent with literature which shows majority of recurrences happen in the first year after treatment cure[50,51]

*** Pooled estimate from random effects model using an exact binomial likelihood approach.

Table 4. Model-estimated TB burden in South Africa between 2007 to 2016

Year	Proportion with drug resistance		TB Incidence			TB Mortality		
	INH	RR/MDR	TB only	TB-HIV	Total	TB-only	TB-HIV	Total
2007	0.0959	0.0413	350.77	915.26	1266.03	43.9396	388.4702	432.4098
2008	0.0984	0.0442	351.76	897	1248.76	44.39	387.6863	432.0763
2009	0.1014	0.0478	350.88	870.42	1221.3	44.7021	379.8267	424.5288
2010	0.1043	0.052	346.7	818.49	1165.19	44.7964	356.38	401.1764
2011	0.1076	0.057	338.98	713.14	1052.12	44.777	316.0773	360.8543
2012	0.1109	0.0633	323.5	609.91	933.41	43.7785	265.6863	309.4648
2013	0.1135	0.0697	304.19	514.55	818.74	43.7409	222.5607	266.3016
2014	0.1155	0.0756	281.54	420.41	701.95	40.2505	176.8907	217.1412
2015	0.1167	0.0783	261.13	348.35	609.48	37.2008	141.5129	178.7137
2016	0.1168	0.0793	246.17	336.93	583.1	34.9054	126.1259	161.0313

Table 5. WHO-estimated TB burden in South Africa between 2007 and 2016

	% with drug resistance		TB incidence							TB mortality								
Year	INH-R*	RR/MDR**	WHO Total	WHO Total - LE	WHO Total - UE	WHO TB only	WHO TB-HIV	HIV - LE	HIV - UE	WHO TB-only	TB only - LE	TB only - UE	WHO TB-HIV	TB-HIV - LE	TB-HIV - UE	WHO Total	WHO Total LE	WHO TOTAL UE
2007	n/a	4.1	977	632	1390	385	592	375	859	55	42	69	196	125	282	251	167	351
2008	n/a	4.2	977	717	1280	384	593	423	790	53	40	68	172	120	233	225	160	301
2009	n/a	4.3	967	728	1240	381	586	429	768	50	37	64	159	113	213	209	150	277
2010	n/a	4.4	948	710	1220	373	575	418	756	46	34	59	157	111	210	203	145	269
2011	n/a	4.5	922	712	1160	326	596	454	757	44	33	56	151	111	196	195	144	252
2012	9.3	4.6	892	639	1190	322	570	404	765	46	35	58	170	119	230	216	154	288
2013	9.3	4.6	860	612	1150	330	530	373	713	45	34	56	160	111	217	205	145	273
2014	9.3	6.1%	834	593	1110	326	508	358	684	43	33	54	153	105	208	196	138	262
2015	n/a	6.8%	807	568	1090	338	469	326	636	42	32	53	150	103	207	192	135	260
2016	n/a	8.0%	781	543	1060	320	461	315	635	41	31	52	181	120	254	222	151	306

Abbreviations: LE = lower estimate; UE = upper estimate.

*National Drug Resistance Survey, 2012-2014.

**Years 2007-2013 interpolated based on National Drug Resistance Surveys in 2001-2002 and 2012-2015; years 2014-2016 based on notified cases in WHO database.

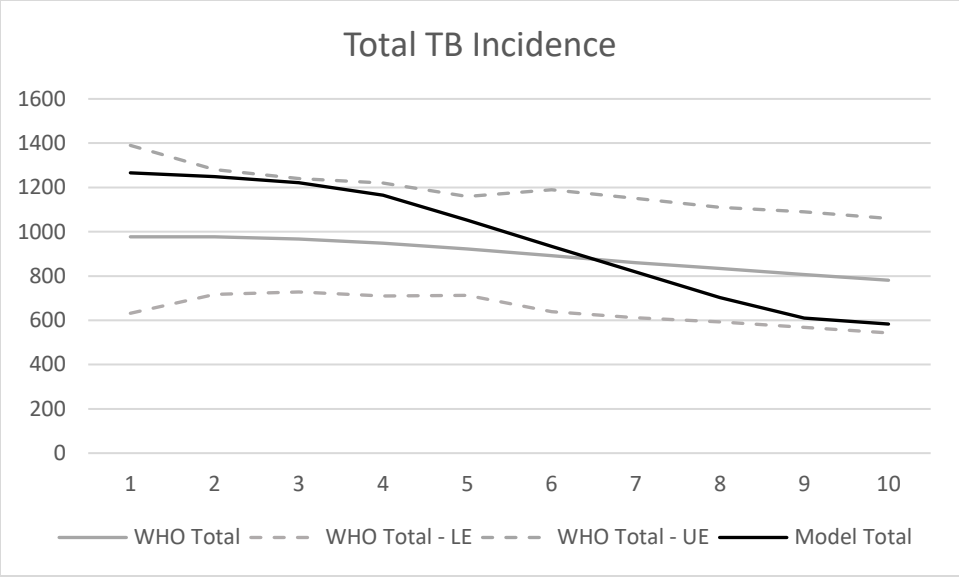


Figure 33 Model-estimated compared to WHO-estimated total TB incidence between 2007-2016. Abbreviations: LE = lower estimate; UE = upper estimate

References

[1] World Health Organization [WHO]. WHO TB burden estimates. Geneva, Switzerland: WHO; 2018. Downloaded from http://www.who.int/tb/country/data/download/en/ on February 2, 2018.
[2] Styblo K, Meijer J, Sutherland I. Tuberculosis Surveillance Research Unit Report No. 1: the transmission of tubercle bacilli; its trend in a human population. Bull Int Union Tuberc Lung Dis, 1969; 42: 1-104.
[3] Vynnycky E, Fine PE. The annual risk of infection with Mycobaterium tuberculosis in England and Wales since 1901. Int J Tuberc Lung Dis, 1997; 1(5): 389-96.
[4] Behr MA, Warren SA, Salamon H, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacill. Lancet 1999; 353(9151): 444-9.
[5] Van Geuns HA, Meijer J, Styblo K. Results of contact examination in Rotterdam, 1967-1969. Bull Int Union Tuberc Lung Dis 1975; 50: 107-21.

[6] Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. Adv Tuberc Res 1976; 19: 1-63.

[7] Comstock GW, Edwards LB, Livesay VT. Tubercuosis morbidity in the US Navy: its distribution and decline. Am Rev Respir Dis,1974; 110: 572-80.

[8] Nolan CM, Elarth AM. Tuberculosis in a cohort of Southeast Asian refugees: a five-year surveillance study. Am Rev Respir Dis, 1988; 137: 805-9.

[9] Grzybowski S. Drugs are not enough. Failure of short-course chemotherapy in a district in India. Tuberc Lung Dis, 1993; 74(3): 145-6.

[10] Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural History of Tuberculosis Duration and Fatality of Untreated Pulmonary Tuberculosis in HIV Negative Patients: A Systematic Review. PloS one, 2011; 6(4): e17601.

[11] Law S, Piatek AS, Vincent C, Oxlade O, Menzies D. Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study. Lancet Public Health, 2017;2(1):e47-e55.

[12] Cohen T, Becerra MC, Murray MB. Isoniazid Resistance and the Future of Drug-Resistant Tuberculosis. Microb Drug Resist, Microb Drug Resist, 2004; 10(4): 280–285.

[13] Haas WH, Schilke K, Brand J, Amthor B, Weyer K, Fourie PB, Bretzel G, Sticht-Groh V, Bremer HJ. Molecular analysis of katG gene mutations in strains of *Mycobacterium tuberculosis* complex from Africa. Antimicrob Agents Chemother,1997;41:1601–1603.

[14] Kiepiela P, Bishop KS, Smith AN, Roux L, York DF. Genomic mutations in the katG, inhA and aphC genes are useful for the prediction of isoniazid resistance in *Mycobacterium tuberculosis* isolates from Kwazulu Natal, South Africa. Tuberc Lung Dis, 2000;80:47–56.

[15] Knight GW, Colijn C, Shrestha S, Fofana M, Cobelens F, White RG, et al. The Distribution of Fitness Costs of Resistance-Conferring Mutations Is a Key Determinant for the Future Burden of Drug-Resistant Tuberculosis: A Model-Based Analysis. Clin Infect Dis, 2015; 61(Suppl 3): S147–S154.

[16] UNAIDS. UNAIDS 2018 estimates. Geneva, Switzerland: UNAIDS; 2018. Downloaded from http://aidsinfo.unaids.org/ on February 2, 2018.

[17] WHO. Global tuberculosis control: a short update to the 2009 report. Geneva, Switzerland: WHO; 2009.

[18] Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P. Human Immunodeficiency Virus and the Outcome of Treatment for New and Recurrent Pulmonary Tuberculosis in African Patients. Am J Resp Crit Care Med, 1999; 159(3): 733-40.

[19] Malkin JE, Prazuck T, Simonnet F, Yameogo M, Rochereau A, Ayeroue J, et al. Tuberculosis and human immunodeficiency virus infection in West Burkina Faso: clinical presentation and clinical evolution. Int J Tuberc Lung Dis, 1997; 1(1): 68-74.

[20] Wilkinson D, Moore DAJ. HIV-related tuberculosis in South Africa – clinical features and outcome. S Afr Med J, 1996; 86: 64-7.

[21] Perriëns JH, St. Louis ME, Mukadi YB, Brown C, Prignot J, Pouthier F, et al. Pulmonary tuberculosis in HIV-infected patients in Zaire: a controlled trial of treatment of either 6 or 12 months. N Engl J Med, 1995;332:779-84.

[22] Ackah AN, Digbeu H, Daillo K, Greenberg AE, Coulibaly D, Coulibaly M, et al. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abijdan, Côte d'Ivoire. Lancet, 1995; 345(8950): 607-10.

[23] Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, Weyer K, Lancaster J, van der Walt M. Outcomes of Multi-Drug Resistant Tuberculosis (MDR-TB) among a Cohort of South African Patients with High HIV Prevalence. PLoS ONE, 2011; 6(7): e20436.

[24] Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P. Human Immunodeficiency Virus and the Outcome of Treatment for New and Recurrent Pulmonary Tuberculosis in African Patients. Am J Resp Crit Care Med, 1999; 159(3): 733-40.
[25] Malkin JE, Prazuck T, Simonnet F, Yameogo M, Rochereau A, Ayeroue J, et al. Tuberculosis and human immunodeficiency virus infection in West Burkina Faso: clinical presentation and clinical evolution. Int J Tuberc Lung Dis, 1997; 1(1): 68-74.
[26] Wilkinson D, Moore DAJ. HIV-related tuberculosis in South Africa – clinical features and outcome. S Afr Med J, 1996; 86: 64-7.
[27] Perriëns JH, St. Louis ME, Mukadi YB, Brown C, Prignot J, Pouthier F, et al. Pulmonary tuberculosis in HIV-infected patients in Zaire: a controlled trial of treatment of either 6 or 12 months. N Engl J Med, 1995;332:779-84.
[28] Ackah AN, Digbeu H, Daillo K, Greenberg AE, Coulibaly D, Coulibaly M, et al. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abijdan, Côte d'Ivoire. Lancet, 1995; 345(8950): 607-10.
[29] Brust JC, Gandhi NR, Carrara H, Osburn G, Padayatchi N. High treatment failure and default rates for patients with multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa, 2000-2003. Int J Tuberc Lung Dis, 2010;14(4):413-9.
[30] Kigozi G, Heunis C, Chikobvu P, Botha S, van Rensburg D. Factors influencing treatment default among tuberculosis patients in a high burden province of South Africa. International Journal of Infectious Diseases, 2017; 54:95-102.
[31] Chiasson RE, Churchyard GJ. Recurrent Tuberculosis – Relapse, Re-infection and HIV. J Infect Dis, 2010 Mar; 201(5): 653–655.
[32] Houben RMGJ, Crampin AC, Ndlovu R, Sonnenberg P, Godfrey-Faussett P, Haas WH, et al. HIV increases the risk of TB due to recent infection more than that due to reactivation of latent infection. Int J Tuberc Lung Dis, 2011; 15:24–31.
[33] Shenoi S, Heysell S, Moll A, Friedland G. Multidrug-resistant and extensively drug-resistant tuberculosis: consequences for the global HIV community. Curr Opin Infect Dis, 2009 Feb; 22(1): 11–17.
[34] Suchindran S, Brouwer ES, Van Rie A. Is HIV Infection a Risk Factor for Multi-Drug Resistant Tuberculosis? A Systematic Review. PLoS One, 2009; 4(5): e5561.
[35] Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, et al. (2012) Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. PLoS Med, 9(7): e1001270.
[36] Odone A, Amadasi S, White RG, Cohen T, Grant AD, Houben RM. The Impact of Antiretroviral Therapy on Mortality in HIV Positive People during Tuberculosis Treatment: A Systematic Review and Meta-Analysis. PLoS One, 2014; 9(11): e112017.
[37] Akolo C, Adetifa I, Shepperd S, Volmink J (2010). Treatment of latent tuberculosis infection in HIV infected persons (Review). Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD000171
[38] Golub JE, Pronyk P, Mohapi L, Thsabangu N, Moshabela M, Struthers H. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS, 2009; 23(5): 631-6
[39] Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Trop Med Int Health, 2011; 15(s1):1-15.
[40] Sharma A, Hill A, Kurbatova E, van der Walt M, Kvasnovsky C, Tupasi TE, Caoili JC. Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study. Lancet Infect Dis, 2017; 17(7): 707-15.

[41] Azman AS, Golub JE, Dowdy DW. How much is tuberculosis screening worth? Estimating the value of active case finding for tuberculosis in South Africa, China, and India. BMC Med. 2014;12:216.
[42] Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. AIDS, 2001; 15(2): 143-52.
[43] Menzies D, Benedetti A, Paydar A, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med, 2009; 6(9): e1000146.
[44] Gegia M, WInters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. Lancet Infectious Disease, 2017; 17(2): 223–34.
[45] Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients. PLoS Med, 2012 Aug; 9(8): e1001300.
[46] Parthasarathy R, Prabhakar R, Somasundaram PR. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. Tuberculosis Research Centre, Madras, and National Tuberculosis Institute, Bangalore. Am Rev Respir Dis, 1986 Jul;134(1):27-33.
[47] East African and British Medical Research Councils. Controlled clinical trial of five short-course (4-month) chemotherapy regimens in pulmonary tuberculosis: First report of 4th study. Lancet, 1978; 312(8085):334-8.
[48] R Balasubramanian, Madras.; S Sivasubramanian; VK Vijayan; R Ramachandran; MS Jawahar. Five year results of a 3-month and two 5-month regimens for the treatment of sputum-positive pulmonary tuberculosis in south India. Tubercle, 1990 Dec; 71(4): 253-8
[49] Eule H, Beck H, Evers H, Fischer P, Kwiatkowski H, Merkel S, et al. [Daily ultrashort chemotherapy and intermittent short-term chemotherapy with 4 drugs of communicable pulmonary tuberculosis treated for the first time. Results of a cooperative multicenter study] .Z Erkr Atmungsorgane, 1986;167(1-2):29-41.
[50] Lee H, Kim J. A Study on the Relapse Rate of Tuberculosis and Related Factors in Korea Using Nationwide Tuberculosis Notification Data. Osong Pub Health Res Perspect, 2014;5:S8-17.
[51] Narayanan S, Swaminathan S, Supply P, Shanmugam S, Narendran G, Hari L, et al. Impact of HIV infection on the recurrence of tuberculosis in South India. J Infect Dis, 2010; 201(5):691-703.