COMPLEX SYSTEMS: AN INNOVATIVE APPROACH TO IMPROVE DRUG-RESISTANT TUBERCULOSIS TREATMENT ADHERENCE

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Health Policy and Management in the Gillings School of Global Public Health.

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ABSTRACT

Kei L. Alegria-Flores: Complex systems: An innovative approach to improve drug-resistant tuberculosis treatment adherence
(Under the direction of Bryan J. Weiner)

The burden of multidrug-resistant tuberculosis (MDR-TB) poses a serious challenge to global TB control and elimination; MDR-TB is far deadlier and more difficult and expensive to treat than drug-susceptible TB. Among the factors that influence MDR-TB treatment outcomes, adherence plays a very important role. Missing medication doses could result in poor treatment outcomes, further transmission of MDR-TB, and further resistance to drugs. The project investigated the key determinants of MDR-TB treatment adherence and develop specific recommendations to improve it in Lima, Peru. The project's main objective was to develop, test, and apply a model that describes how treatment adherence, and consequently, treatment outcomes, could be improved.

The specific aims of this dissertation were to 1) estimate the effects of the information-motivation-behavioral skills model on MDR-TB treatment adherence; 2) develop an integrated system dynamics (SD) model of the interactions most substantially affecting patient adherence to treatment over time, and based on a structured review of the literature as well as interviews and focused group discussions with key stakeholders; and 3) parameterize, calibrate, and test the SD model built in Aim 2 to simulate the effects of various intervention implementation scenarios on treatment outcomes. Implementation science and SD approaches were combined to inform the design of implementation strategies that improve treatment outcomes most effectively.

The analyses showed that adherence is a complex behavior and we need interventions that are designed to improve the patients' information, motivation, and behavioral skills with implementation strategies that are intentionally chosen and measured. Implementation strategies – *what, when, how, who* – must be evidence-based and have a long-term sustainability plan. Adherence, and LTFU, should be monitored during treatment, while interventions are finetuned to fit the context and maximize its impact prior to scaling-up. Though LTFU is an extension of adherence (LTFU is defined as zero adherence for a month of more), its determinants are not identical and we should consider interventions accordingly. The application of implementation science and SD methodology could facilitate and fast-track the process of improving these strategies, close the gap between knowledge and practice, and inform the allocation of resources to minimizing waste.

For my mom. Because through your sacrifices, you gifted me the freedom to be me.

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CLD	Causal loop diagram
CHW	Community health worker
CFI	Comparative Fit Index
DOT	Directly observed therapy
FGD	Focused group discussion
HIV	Human immunodeficiency virus
IMB	Information-motivation-behavioral skills
INEI	National Institute of Statistics and Informatics (abbreviation from its original name in Spanish)
LTFU	Lost-to-follow-up
MDR-TB	Multidrug-resistant tuberculosis
NIH	National Institutes of Health
NTP	National tuberculosis program
RMSEA	Root mean square error of approximation
STDSIM	Sexually transmitted disease stochastic microsimulation models
SEM	Structural equation modeling
SD	System dynamics
TB	Tuberculosis
TB MAC	Tuberculosis Modelling and Analysis Consortium
TLI	Tucker-Lewis Index
US	United States
UNC-CH	University of North Carolina at Chapel Hill

WHO	World Health Organization
XDR-TB	Extremely drug-resistant tuberculosis

CHAPTER I: INTRODUCTION

Background

In 2015, tuberculosis (TB) became the world's leading infectious disease killer again.[1] Peru accounts for 3.2% of the population of the Region of the Americas, but has 13.3% of the region's TB and 29% of the multidrug-resistant tuberculosis (MDR-TB) cases.[2] MDR-TB is defined as resistance to at least two of the most powerful TB drugs, isoniazid and rifampicin. It is far deadlier and more difficult and expensive to treat than drug-susceptible TB. It results from inconsistent or incorrect TB treatments, or from direct person-to-person transmission.[3] Directly observed therapy (DOT) –trained individuals observing patients take their medications– has been widely adopted as a method to deliver treatment.[4] DOT was adapted for MDR-TB patients for the first time in the late 1990s in Peru, with 83% treatment completion, 8% lost-to-follow-up (LTFU), and 8% death rates.[5] Twenty years later, Lima's MDR-TB treatment outcomes have worsened: completion rates have dropped to 60% and the rate of LTFU is at an alarming 30%.[6]

Global statistics are equally shocking. Less than half of the estimated cases of MDR-TB are diagnosed, and only 70% of the diagnosed cases initiated second-line medication treatment.[3] Furthermore, out of all the MDR-TB diagnosed patients in the 2011 cohort, only 48% completed treatment, 24% were LTFU or did not have a documented outcome, 16% died, and 12% were not cured despite treatment. Today, we are far from the 83% treatment completion observed in the 1990s study. The majority of the world population lives in urban areas where the risk of TB and MDR-TB is highest due to overcrowding, poverty, and migration.[7] In the capital of Peru, Lima,

as in many other cities around the world, MDR-TB treatment is free and accessible in public health facilities.[8] Several factors beyond cost and accessibility have amplified the gap between knowledge and practice, with devastating consequences for MDR-TB patients.

Among the factors that influence MDR-TB treatment outcomes, adherence plays a very important role. Missing medication doses could result in poor treatment outcomes, further transmission of MDR-TB, and further resistance to drugs.[9,10,11] Health complications, and additional treatment days to make up for missed doses, increase the workload for healthcare service providers and costs for the health system. Adherence is a complex behavior determined by numerous factors that needs to be repeated daily.[12] Unlike other treatment outcomes, the documentation of daily adherence can be found in patients' treatment logs. One of the pillars of DOT was ensuring patients' daily medication intake for the 18 months of MDR-TB treatment, and it was globally adopted in the 1990s.[4] However, DOT's advantage over self-administered treatment has no scientific basis.[13,14] Moreover, failure in its implementation may have contributed to the emergence of global drug resistance over the past two decades, which have resulted in MDR-TB, extremely drug-resistant TB, and totally drug-resistant TB.[15]

MDR-TB poses a serious challenge to TB control and elimination.[16] Nonetheless, investment in TB diagnostics, drugs, and technologies have not kept up with global needs. Recent innovations in MDR-TB are minimum, including two new drugs (bedaquiline and delamanid) and a shorter 'Bangladesh regimen'.[17,18] However, the new regimen is still long (9-12 months), includes the use of the new drugs and older ones at higher doses, has strict eligibility criteria, and does not exclude injectable drugs.[19] With the current levels of investment in research and development for MDR-TB, it is likely that short, patient-friendly treatment regimens are still many years away. In the meanwhile, a crucial step to TB elimination will include a shift to

strategies that help us replicate the 83% treatment completion and low LTFU and death rates that were possible 20 years ago.

Specific aims

This dissertation project applied innovative approaches to investigate the key determinants of MDR-TB treatment adherence and develop specific recommendations to improve it. Lima was chosen as the setting for this dissertation project due to its high burden of MDR-TB and because it was the site for the successful study in the 1990s. The project's long-term goal was to decrease the global burden of MDR-TB and its objective was to develop, test, and apply a model that describes how treatment adherence, and consequently, treatment outcomes, could be improved. The global hypothesis of this dissertation is that *how* we implement strategies that target adherence to improve MDR-TB treatment outcomes is the key to understanding and solving this complex public health problem.

To accomplish this dissertation's objective and test its global hypothesis, the project was grounded in theory and the published literature, and system dynamics (SD) methodology was applied as a tool to test implementation science principles. As will be explained in later chapters, SD is a modeling technique that uses feedback loops and stock-and-flow diagrams to illustrate and simulate complex systems.[20] Implementation science is an interdisciplinary study of the methods to promote the integration of research findings and evidence into healthcare policy and practice.[21] Three specific aims were designed to improve MDR-TB treatment adherence through the application of these innovative approaches:

Aim 1: Estimate the effects of the information-motivation-behavioral skills (IMB) model on MDR-TB treatment adherence and disentangle associations versus pathway mechanisms,

using structural equation modeling. Structured questionnaires were applied to collect cross-sectional quantitative and qualitative data between April and December, 2015, in Lima, Peru.

Aim 2: Develop an integrated SD model of the interactions most substantially affecting patient adherence to MDR-TB treatment over time. This diagram extends prior attempts to describe adherence, and was developed based on a structured review of the literature as well as interviews and focused group discussions (FGDs) with key stakeholders in Lima.

Aim 3: The SD model built in Aim 2 was parameterized, calibrated, and validated to simulate the effects of various intervention implementation scenarios on MDR-TB treatment outcomes. Implementation science and SD approaches were combined to inform the design of implementation strategies that improve treatment outcomes most effectively in the context of Lima.

Study setting

Peru's capital, Lima, and the adjacent constitutional province of Callao combined have 54% of the TB cases, 76% of the MDR-TB cases, and 89% of the extremely drug-resistant tuberculosis (XDR-TB) cases in the country.[6] Lima is also a site for continuous research in TB/MDR-TB for over 20 years. Its population has grown to 10 million, a third of the total population in Peru. The massive immigration from rural parts of the country into the capital of people looking for job opportunities, or escaping from terrorism, started in the 1950s with government-assisted shantytowns.[22] Today, these shantytowns cover the hills surrounding Lima and continue to grow along the peripheries of the city.

Each of the public health centers that provide treatment for MDR-TB patients have a TB unit and are administered by the Ministry of Health. As of 2012, there were 80 TB units in Lima,

covering approximately 80% of the MDR-TB population in need of services.[23] Generally, TB units are staffed by a small number of healthcare service providers including a specialized physician, nurses, and a lab technician. Occasionally, psychiatrists and nutritionists trained in TB care are available. Health centers' MDR-TB caseloads vary widely, usually in the range of 1-50, depending on their catchment areas. Most of the clinics are within walking, or a short bus ride distance away from patients' homes and located in Lima's shantytowns.

According to Peru's MDR-TB guidelines, treatment lasts for at least 18 calendar months at health centers ran by the Ministry of Health and following the World Health Organization's DOT strategy.[24,25] This means that a typical patient must go to the health center Monday-Saturday, excluding national holidays, to take their medications so they can be supervised as they swallow their pills. An MDR-TB patient is expected to be on injectable medications for approximately six months (or until obtaining four consecutive negative cultures, tested monthly) unless otherwise specified by their physician; and an LTFU case is defined as a patient who missed doses for 30 continuous days or more.

Sample size and power calculations

Sample size and power calculations guided the design, and data collection and analysis in Aim 1. The sample of health centers and adult MDR-TB patients was determined using cluster sampling given the restrictions in resources for data collection. I planned for data collection in 35 health centers with some of the highest MDR-TB prevalence in Lima. Then, I randomly sampled 7-10 patients from each of these health centers. High-prevalence health centers have anywhere between 5 and 50 patients. Based on 2013 data from Peru's Ministry of Health, 350 patients represent approximately 18% of the MDR-TB adult prevalence in Lima.[26]

For the sample size calculations, I assumed an intra-class correlation of 0.1 and a design effect size of 1.4, which is a constant that quantifies the extent to which the expected sampling error in a survey departs from the sampling error that can be expected under simple random sampling. I calculated the sample size based on a statistical significance = 0.05, power = 0.8, and an effect size of 0.5 using the one-sample Z-test formula. I calculated the sample size for the outcome variable measured as adherence rate, and then as a categorical variable.

Outcome as adherence rate: due to the lack of MDR-TB studies on adherence rate, I used data from a recent HIV systematic review with a pooled proportion of 70% (95% CI: 59-81),[27] and an approximated standard deviation of 25.[28] The calculated sample size to capture the desired effect size, adjusted by design effect, was 276 patients. The closest MDR-TB data available for the categorical outcome I proposed in this study was that of LTFU rates. For a hypothetical dichotomous outcome variable (LTFU vs. no LTFU), with a mean of 18% default,[29] the design effect adjusted sample size was 225 patients. Based on sample size calculations, I expected to have an adequate sample size (35 clinics, ~350 patients) for the purposes of this study, even with the limited resources that were available for data collection.

Institutional review board approvals

The study was approved by the institutional review boards of the University of North Carolina at Chapel Hill (US), Asociación Benéfica PRISMA (Peru), the Dirección Regional de Salud Callao, Dirección de Salud IV Lima Este, and Dirección de Salud II Lima Sur.

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Structure of the dissertation

This dissertation was written in five chapters: the introduction chapter (Chapter 1), the Aim 1 manuscript (Chapter 2), Aim 2 manuscript (Chapter 3), Aim 3 manuscript (Chapter 4), and the conclusion chapter (Chapter 5). References can be found at the end of each chapter.

REFERENCES

1. TB is now the World's Leading Infectious Killer | TB Alliance. Available from: https://www.tballiance.org/news/tb-now-worlds-leading-infectious-killer

2. Organización Panamericana de la Salud (2015). Tuberculosis in the Americas, Regional Report 2015, Epidemiology Control and Financing. Washington D.C., 2015. Available from: file:///C:/Users/Kei/Desktop/June%202016/Dissertation/PAHO%20TB%20Report%202015.pdf

3. World Health Organization (2014). Drug-resistant TB: surveillance and response. Supplement Global Tuberculosis Report 2014. Available from: http://www.who.int/tb/publications/global_report/gtbr14_supplement_web_v3.pdf

4. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2007;(4):CD003343.

5. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcantara F, et al. Community-Based Therapy for Multidrug-Resistant Tuberculosis in Lima, Peru. New England Journal of Medicine, 2003, 348:119.

6. Ministerio de Salud, Dirección General de Intervenciones Estratégicas en Salud Pública, Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis. 4ta Jornada Científica de la Tuberculosis. Lima, Perú, March 16-17, 2016. Presentación PowerPoint by Dr. Valentina Antonieta Alarcón Guizado (National Coordinator, ESNPCT/DGSP – MINSA)

7. Prasad A, Ross A, Rosenberg P, Dye C. A world of cities and the end of TB. Trans R Soc Trop Med Hyg. 2016 Mar;110(3):151–2.

8. Otero L, De Orbegoso A, Navarro AF, Ríos J, Párraga T, Gotuzzo E, et al. Time to initiation of multidrug-resistant tuberculosis treatment and its relation with outcome in a high incidence district in Lima, Peru. Trop Med Int Health. 2015 Mar;20(3):322–5.

9. Cadosch D, Abel Zur Wiesch P, Kouyos R, Bonhoeffer S. The Role of Adherence and Retreatment in De Novo Emergence of MDR-TB. PLoS Comput Biol. 2016 Mar;12(3):e1004749.

10. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. PLoS ONE. 2013;8(7):e70064.

11. Bastard M, Sanchez-Padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, et al. Effects of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia. J Infect Dis. 2015 May 15;211(10):1607–15.

12. Alegria-Flores K, Hassmiller Lich KL, Van Rie A, Weiner BJ, Becerra Herrera N: Complex systems: Visualizing multidrug-resistant tuberculosis treatment adherence in a causal loop diagram. In the 21st Annual Conference of The Union-North American Region. Vancouver: The Union-NAR; 2017: 11.

13. 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:e0150511.

14. Pasipanodya JG, Gumbo T. A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients. Clin Infect Dis. 2013;57:21–31.

15. Keshavjee S, Farmer PE. Tuberculosis, Drug Resistance, and the History of Modern Medicine. New England Journal of Medicine. 2012 Sep 6;367(10):931–6.

16. Sotgiu G, D'Ambrosio L, Centis R, Mura I, Castiglia P, Spanevello A, et al. The multidrug-resistant tuberculosis threat: old problems and new solutions. J Thorac Dis. 2015 Sep;7(9):E354–60.

17. Bonnet M, Bastard M, du Cros P, Khamraev A, Kimenye K, Khurkhumal S, et al. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study. Int J Tuberc Lung Dis. 2016;20:177–86.

18. Sotgiu G, Tiberi S, Centis R, D'Ambrosio L, Fuentes Z, Zumla A, et al. Applicability of the shorter "Bangladesh regimen" in high multidrug-resistant tuberculosis settings. Int J Infect Dis. 2017;56:190–3.

19. Khan F: Meta-analysis of Short-Course MDR-TB Treatment Regimens. 21st Annual Conference The Union-North America Region; Vancouver, 2017.

20. Meadows DH. Thinking in Systems: A Primer. White River Junction, Vt: Chelsea Green Publishing; 2008.

21. Eccles MP, Armstrong D, Baker R, Cleary K, Davies H, Davies S, et al. An implementation research agenda. Implementation Science. 2009 Apr 7;4(1):18.

22. Fernandez Maldonado, A.M., TU Delft. Las barriadas de Lima como estímulo a la reflexión urbana sobre la vivienda. Revisitando a Turner y de Soto. Available from: http://resolver.tudelft.nl/uuid:53578ab9-d734-4d1c-b257-cbc81248cc4c

23. Ministerio de Salud (2013). Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis. Available from: http://www.tuberculosis.minsa.gob.pe/

24. Ministerio de Salud, Perú. Norma Técnica de Salud para la Atención Integral de las Personas afectadas por Tuberculosis. 2013. Available from: http://www.minsa.gob.pe/dgsp/observatorio/documentos/infecciones/RM715-2013_MINSA_TB.pdf

25. WHO | Pursue high-quality DOTS expansion and enhancement. WHO. Available from: http://www.who.int/tb/dots/en/

26. Casos de tuberculosis disminuyeron en el Perú en el 2013. EL COMERCIO. 2014. Available from: http://elcomercio.pe/lima/ciudad/casos-tuberculosis-disminuyeron-peru-2013-noticia-1718107

27. Kumar A, Alandikar V, Mhaskar R, Emmanuel P, Djulbegovic B, Patel S, et al. Adherence to antiretroviral therapy in India: A systematic review and meta-analysis. Indian Journal of Community Medicine. 2013;38(2):74.

28. Wagner GJ, Ryan GW. Relationship between routinization of daily behaviors and medication adherence in HIV-positive drug users. AIDS Patient Care STDS. 2004 Jul;18(7):385–93.

29. World Health Organization. Global tuberculosis report 2013. Geneva: World Health Organization; 2013. Available from: http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf?ua=1

CHAPTER II: AN INNOVATIVE APPROACH TO DESIGN AND EVALUATE DRUG-RESISTANT TUBERCULOSIS TREATMENT ADHERENCE INTERVENTIONS (AIM 1)

OVERVIEW

Objective. Multidrug-resistant tuberculosis (MDR-TB) treatment is expensive, lengthy, and can cause severe side effects. Patients face socio-economic, psychosocial, and systemic barriers to adherence; poor adherence results in poor treatment outcomes. This study estimates the effects of the Information-Motivation-Behavioral skills model components on MDR-TB treatment adherence.

Design. We interviewed 326 adults receiving MDR-TB treatment and 86 of their healthcare service providers from 40 health centers in Lima, Peru. The main outcome was adherence – the proportion of prescribed dosages taken by a patient. Exposure measures were adherence information, motivation, and behavioral skills; lost-to-follow-up during previous TB treatment(s); providers' work engagement; and patient-perceived support from his/her social network.

Results. Structural equation modeling revealed that adherence information and motivation had positive effects on adherence, but only when mediated through behavioral skills ($\beta=0.02$, $p<0.01$ and $\beta=0.07$, $p<0.001$, respectively). Behavioral skills had a direct positive effect on adherence ($\beta=0.27$, $p<0.001$). Lost-to-follow-up during previous treatment had a direct

negative effect, providers' work engagement had a direct positive effect, and perceived support had indirect positive effects on adherence. The model's overall R-squared was 0.76.

Conclusion. The Information-Motivation-Behavioral skills model components were associated with adherence and could be used to design, monitor, and evaluate interventions targeting MDR-TB treatment adherence.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) threatens TB control worldwide; it results from inconsistent or incorrect TB treatment or direct person-to-person transmission.[1] Compared to drug-susceptible TB, MDR-TB is far deadlier and current treatments are expensive, lengthy, and often cause severe side-effects.[2] Many patients face biological, financial, psychosocial, and systemic barriers to treatment adherence, which often lead to poor outcomes and amplification of drug-resistance.[3,4,5] Directly observed therapy (DOT) –where trained individuals observe patients taking their medication– has been widely adopted as a method to deliver treatment;[6,7] however, its effectiveness has been disputed.[8,9] Effective and supportive interventions are thus needed to improve MDR-TB treatment adherence.[4,10]

In recent years, there has been a surge in publications about interventions that target adherence.[11,12,13] While some studies show promising results, there is a lack of theoretical frameworks to guide intervention design, implementation, and evaluation. Implementation processes and strategies (such as the duration, content, and provider of an intervention) are also poorly documented.[14,15] These limitations make it difficult to evaluate their effectiveness at improving adherence and applicability in different settings.

The main aim of our study was to estimate the effects of the information-motivation-behavioral skills (IMB) model components on MDR-TB treatment adherence.[16] The IMB model

was first developed for the field of HIV to conceptually and empirically link adherence to personal and socioeconomic factors. The IMB model has also been used as the theoretical basis to design behavioral interventions across a variety of clinical applications.[17,18] We adapted the IMB model to the context of MDR-TB and evaluated whether it could inform the design, monitoring, and evaluation of interventions that target treatment adherence.

STUDY POPULATION AND METHODS

Our study population resided in Peru's capital, Lima, where approximately 80% of the MDR-TB population in need of services access treatment.[19] In the late 1990s, Lima was the first place to adopt DOT for MDR-TB patients in a few clinics, a project which also included psychosocial support and resulted in 83% cure and 8% loss to follow-up (LTFU) rates.[20,21] After that project ended, interventions that target adherence were never widely implemented. In 2015, the rate of MDR-TB LTFU in Lima reached 30%.[22]

Participants and procedures

Participants (patients and their health care providers) were recruited at 40 of the 80 TB-units at public health centers with the highest number of MDR-TB cases. Most of the health centers were in shantytowns, within walking distance or a short bus ride away from patients' homes. At each health center's TB-unit, 1-3 providers were recruited. Providers were defined as nurses, nurse technicians, and physicians who had daily contact with MDR-TB patients. All adult (ages 18-65) TB patients registered in 2013-2014 who had been on treatment for ≥ 12 days, had microbiological evidence of any drug resistance, and/or were prescribed a treatment scheme for drug-resistant TB at the 40 TB-units were identified.

Based on power analysis, the sampling goal was eight patients per health center. When more than eight eligible patients were identified, we used stratified and simple random sampling

without replacement to select patients within each category of provider-reported adherence (90-100%, 70-89%, 50-69%, 1-49%, LTFU) over the past two months. Among those selected, 10 patients were excluded because they were not found at the health center, home, or workplace; and one was unable to participate due to cognitive impairments. Three patients and two providers declined to participate.

We used structured questionnaires to collect cross-sectional data between April and December, 2015. Questionnaires were administered in Spanish using iPads and Magpi software (www.magpi.com) by two trained research assistants from Peru. The interviews lasted 30-60 minutes including the time to obtain informed consent. All data collection tools were piloted and adjusted for contextual fit.

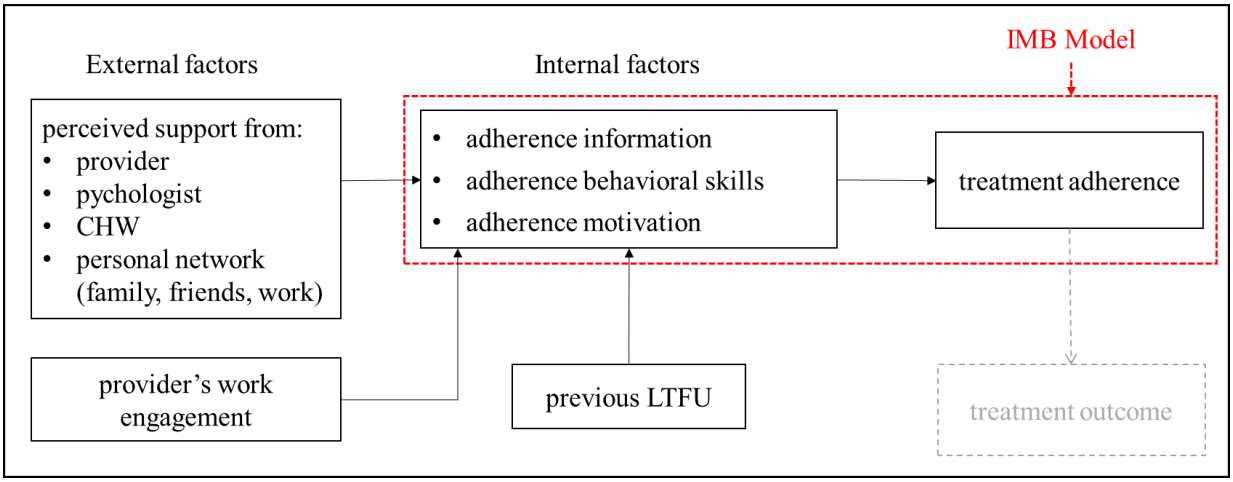
Measures

We adapted the IMB model to identify the key determinants of MDR-TB treatment adherence and their corresponding relationships (Figure 2.1). The main outcome was *treatment adherence*, measured as the proportion (rate) of prescribed dosages taken by a patient during the two calendar months prior to data collection. In Peru, patients take doses Monday-Saturday. One dose was considered taken if all medications prescribed for that day were marked by their providers as taken in the patient treatment attendance logs.

Our main exposure measures were the three core constructs in the IMB model: *adherence information, adherence motivation, and adherence behavioral skills*.[16] *Adherence information* measures whether the patient's knowledge regarding the disease, medications, potential side effects, and the consequences of treatment interruption or LTFU is correct. *Adherence motivation* includes the personal and social motivation to adhere to treatment. *Behavioral skills* refer to a patient's objective abilities as well as his or her perceived self-efficacy concerning the execution

of the sequence of behaviors that result in adherence. IMB model constructs were measured using a validated questionnaire consisting of 30 questions on a 5-point scale ("strongly disagree" to "strongly agree") to react to statements such as "skipping a few of my medications from time to time would not really hurt my health".[23]

Figure 2.1 Model of MDR-TB treatment adherence, adapted from the IMB model by Fisher et al. (2016)



We also measured *provider's work engagement* because under DOT, providers interact daily with patients. In the field of organizational behavior, *provider's work engagement* is defined as an active, positive work-related state that is characterized by vigor, dedication, and absorption.[24] *Providers' work engagement* was measured using the Utrecht Work Engagement Scale, which has 17 questions on a 7-point scale ranging from "never" to "always/every day" for questions such as "I am proud of the work that I do".[25] Because patients can be treated by different providers on different days, the average providers' score per health center was used in the analysis.

The analytic model also included measures for *previous LTFU* (as a continuous variable), and patient-perceived financial and/or emotional support from specific members of their social networks. Response options for perceived support by family, friends, work, and providers were "yes", "no", "they do not know I have TB", or "not applicable". A latent variable was used to

measure the construct of *personal support network* with support from family, friends, and at work, as indicator variables. Support from the psychologist was measured with responses to the statement "talking with the psychologist helped me feel better about having MDR-TB" on a 3-point scale. Support from community health workers (CHWs) was measured with responses to the statement "when I see my CHW, s/he motivates me to adhere to treatment" on a 5-point scale. For all scales, a higher score was preferred.

Data analysis

We used structural equation modeling (SEM) with maximum likelihood estimation to understand the strength of association of hypothesized determinants with treatment adherence.[26] SEM is a statistical technique composed of multivariable regression models for building and testing statistical models and their structural assumptions.[27] With confirmatory SEM, we tested the fit between our model and the data collected.

The model fit was evaluated using the Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI), the root mean square error of approximation (RMSEA), and the coefficient of determination. CFI and TLI values range from 0 to 1, with values ≥ 0.90 representing adequate fit. RMSEA values < 0.06 and an upper bound of the confidence interval < 0.1 are considered acceptable. The coefficient of determination – overall model R-squared – ranges from 0 to 1, with higher values representing more variance accounted for.[26] In SEM, fit is improved through an iterative process of re-specification by using theory and modification indices either to adjust pathways between variables or to allow them to co-vary. We evaluated the correlations and significance levels of the standardized estimates after a well-fitting SEM model was attained.

All analyses were conducted in Stata® version 13.0 statistical software.[28] The study was approved by the institutional review boards of the University of North Carolina at Chapel Hill

(US), Asociación Benéfica PRISMA (Peru), the Dirección Regional de Salud Callao, Dirección de Salud IV Lima Este, and Dirección de Salud II Lima Sur.

RESULTS

Of the 326 patients interviewed, 215 (66%) had laboratory-confirmed MDR-TB, 204 (63%) were male, and 34 (11%) had been LTFU during treatment (Table 2.1). The mean treatment adherence rate was 76%. Means scores for adherence information, motivation, and behavioral skills were 3.8, 3, and 3.1, respectively. Over 90% of patients reported feeling supported by family members, and 25% said that visiting the psychologist was helpful. Most (85%) healthcare service providers were women (Table 2.2). Their average work engagement score was 5.3. TB services were available for ≤6 hours per day in 55% of the health centers. Less than half (45%) of the health centers counted with CHWs. Fidelity to DOT was low; 58% of patients were never or almost never observed when they took their medications.

Modifications made to the original model (Figure 2.1) to improve fit were repositioning *provider's work engagement* and *previous LTFU* as factors directly affecting treatment adherence; and allowing a co-variance between patient-perceived support from their provider and the health center's psychologist. Figure 2.2 displays the final model of MDR-TB treatment adherence. Model fit was excellent with CFI=0.947, TLI=0.926, RMSEA=0.035 (90% CI, 0.005-0.055), and coefficient of determination=0.76.

SEM analysis revealed that adherence information (β=0.02, $p<0.01$) and motivation (β=0.07, $p<0.001$) had a positive effect on treatment adherence, but only through behavioral skills (Figure 2.3). The indirect effects of adherence information and motivation on treatment adherence were β=0.02 ($p<0.01$) and β=0.07 ($p<0.001$), respectively. Behavioral skills had a direct and positive effect on treatment adherence (β=0.27, $p<0.001$). The number of previous

LTFU had a direct negative effect (β=-0.23, p<0.001), whereas providers' work engagement had a direct positive effect (β=0.15, p<0.01) on adherence.

Table 2.1 Description of patient participants

Variable	Female (n=122)	Male (n=204)	Total (n=326)
Age ($\bar{x}$)	32	32.1	32.1
Treatment duration, in days, at data collection (median) [range]	253 [12-899]	214 [13-1135]	235 [12-1135]
TB type, laboratory confirmation in medical history			
MDR-TB	80	135	215
Other or incomplete drug-resistance profile	35	52	87
No results available	7	17	24
New TB cases (%)	64.1	49.2	54.9
HIV co-infection (%)	2.5	10.8	7.7
Diabetes mellitus co-morbidity (%)	9	9.8	9.5
LTFU cases (%)	6.6	12.8	10.5
LTFU during previous TB treatments[ǂ] (%)	12.8	31.3	24.3
Treatment adherence, last 2 months (%)	82.1	72.7	76.2
Adherence information score ($\bar{x}$) [range] in a 5-point scale	3.9 [1.9-5]	3.7 [2.2-4.9]	3.8 [1.9-5]
Adherence motivation score ($\bar{x}$) [range] in a 5-point scale	3 [1.4-5]	3 [1.4-4.7]	3 [1.4-5]
Adherence behavioral skills score ($\bar{x}$) [range] in a 5-point scale	3.2 [1.2-5]	3.1 [1.3-4.4]	3.1 [1.2-5]
I feel financially and/or emotionally supported* (%)			
by my family	93.4	90.6	91.7
by my friends	56.2	61.9	59.9
at work	58.3	51	52.9
Perceived emotional support from provider* (%)	93.4	86.1	88.9
Seeing the psychologist helped me feel better about having MDR-TB** (%)	25.9	25	25.3
When I see my CHW, s/he often or always motivates me to adhere to treatment*** (%)	84.6	83.3	83.8

[ǂ] The total number of times a patient was LTFU during previous treatments ranged from 0 to 4; LTFU once=15%, LTFU twice=5%, LTFU three times or more=5%. *Answer options were yes/no. **Answer options were "not at all", "somewhat better", and "a lot better". ***Answer options were "never", "rarely", "sometimes", "often", "always".

Perceived financial/emotional support from patients' social networks, and providers had indirect positive effects on treatment adherence. Patient-perceived support from their providers had positive direct effects on adherence information (β=0.18, p<0.001) and motivation (β=0.3, p<0.001), and treatment adherence indirectly. Patient-perceived support from their social

networks also affected adherence information (β=0.2, p<0.01) and motivation (β=0.33, p<0.001) directly, which in turn affected adherence. Perceived support from the psychologist or CHW had no effect on adherence motivation.

Table 2.2 Description of healthcare service providers and health centers

HEALTHCARE SERVICE PROVIDERS

Variable	Total (n=86)
Age ($\bar{x}$) [range]	42.8 [25-65]
Female (%)	84.9
Work engagement score ($\bar{x}$) [range] in a 7-point scale	5.3 [3.2-6]
>12 months of experience with TB (%)	73.2
Nurse	36.1
Nurse Technician	51.2
Physician	11.6
TB training in the last 12 months (%)	
0 times	62.4
≥1 times	37.6

HEALTH CENTERS

Variable	Total (n=40)
Hours of operation with TB providers: ≤ 6 per day (%)	54.6
≤ 4 providers in TB team (%)	87.5
Nutritionist available* (%)	80.0
Nutritionist TB trained in the past 12 months (%)	15.6
Psychologist available* (%)	87.5
Psychologist TB trained in the past 12 months (%)	37.1
Social worker available* (%)	92.5
Social worker TB trained in the past 12 months (%)	21.6
CHWs working with DR-TB patients available* (%)	45.0
DOT is implemented as intended** (%)	
Never or almost never	58.3
Sometimes	21.5
Always or nearly always	20.2

*Availability of staff members did not guarantee patients have access to these services at the health centers. ** Observed data at each health center over the course of 1-2 weeks.

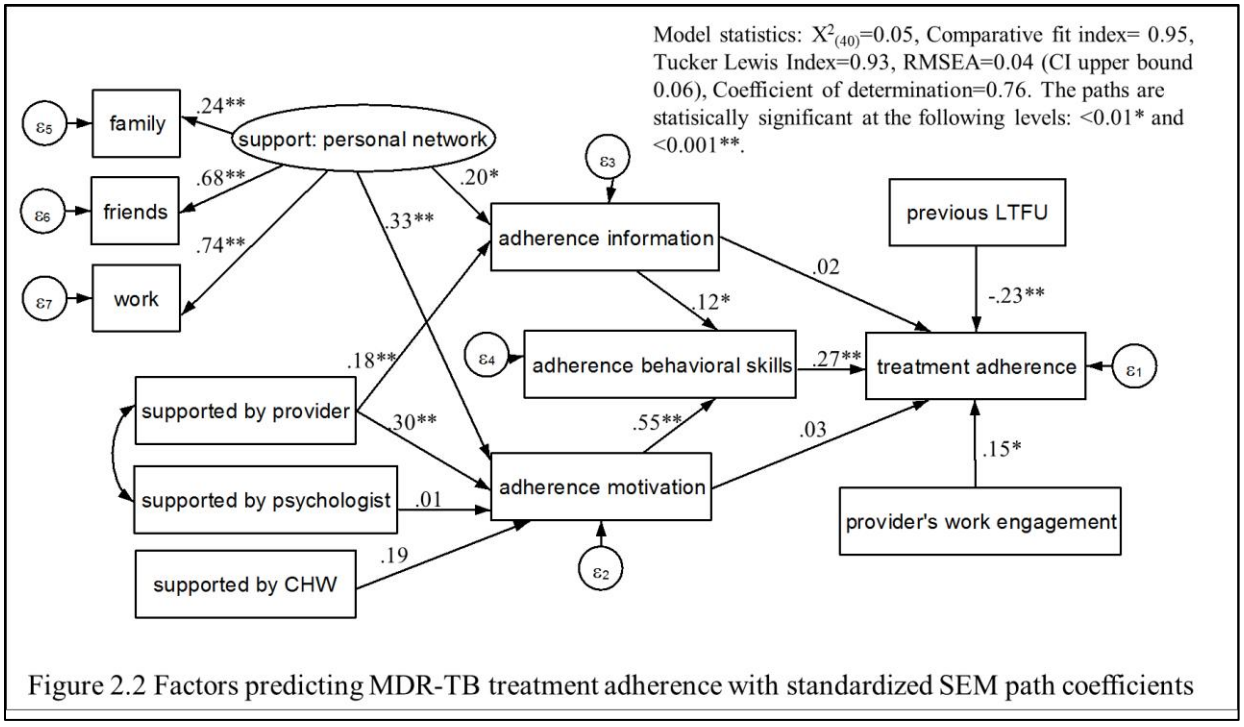


Figure 2.2 Factors predicting MDR-TB treatment adherence with standardized SEM path coefficients

Figure 2.3 Mediation analyses: Standardized regression coefficients for the mediated pathways from the model of drug-resistant tuberculosis treatment adherence

Outcome: treatment adherence

Adherence information → adherence behavioral skills → treatment adherence: $\beta = 0.02$, $p < 0.01$
Adherence motivation → adherence behavioral skills → treatment adherence: $\beta = 0.07$, $p < 0.001$

Outcome: adherence behavioral skills, through adherence information

Support: personal network → adherence information → adherence behavioral skills: $\beta = 0.03$, $p < 0.01$
Supported by provider → adherence information → adherence behavioral skills: $\beta = 0.02$, $p < 0.01$

Outcome: adherence behavioral skills, through adherence motivation

Support: personal network → adherence motivation → adherence behavioral skills: $\beta = 0.18$. $p < 0.001$
Supported by provider → adherence motivation → adherence behavioral skills: $\beta = 0.16$, $p < 0.001$

We compared the relative effects of varying scores to their lower and upper 95th percentiles (Table 2.3). The estimated treatment adherence rate was 89% for a patient with a behavioral skills score of 4 and 62% for someone with a score of 2.2 (diff=27%). This 27% difference in treatment adherence rate due to behavioral skills was larger than the 18% estimated difference due to providers' work engagement scores: 83% with high (5.9) vs. 65% with low (4.3) work engagement. Greater positive differences in behavioral skills were observed in higher motivation scores (diff=1.03 or a 21% increase), than in higher information scores (diff=0.25 or a 5% increase). When motivation and information scores were both high, behavioral skills scores were 1.28 (26%) higher than when the two scores were low.

Table 2.3 Relative effects on treatment adherence and behavioral skills when patients' adherence information, motivation, and provider's work engagement are varied

SEM equations:	
treatment adherence: [rate: 0-1]	$Y_{\text{treatment adherence}} = \beta_0 + \beta_1$*(previous LTFU) + β_2*(provider's work engagement) + β_3*(adherence information) + β_4*(adherence motivation) + β_5*(adherence behavioral skills)
adherence behavioral skills: [scale: 1-5]	$Y_{\text{behavioral skills}} = \beta_6 + \beta_7$*(adherence information) + β_8*(adherence motivation)

Outcomes	**Variables compared**[l]	**Constants ($\bar{x}$)**	**Y'' – Y'**
$Y''_{\text{treatment adherence}} = 0.83$	high work engagement[ǂ] = 5.9	previous LTFU, information, motivation, behavioral skills	0.18*
$Y'_{\text{treatment adherence}} = 0.65$	low work engagement = 4.3		
$Y''_{\text{treatment adherence}} = 0.89$	high behavioral skills = 4	previous LTFU, work engagement, information, motivation	0.27**
$Y'_{\text{treatment adherence}} = 0.62$	low behavioral skills = 2.2		
$Y''_{\text{behavioral skills}} = 3.26$	high information = 4.6	information	0.25*
$Y'_{\text{behavioral skills}} = 3.01$	low information = 2.9		
$Y''_{\text{behavioral skills}} = 3.64$	high motivation = 4	motivation	1.03**
$Y'_{\text{behavioral skills}} = 2.61$	low motivation = 1.9		
$Y''_{\text{behavioral skills}} = 3.77$	high information = 4.6, high motivation = 4		1.28**
$Y'_{\text{behavioral skills}} = 2.49$	low information = 2.9, low motivation = 1.9		

*p-value<0.01, **p-value<0.001, [l]95th percentile data values were used for variables compared, [ǂ]provider's work engagement score range is 0 and 6.

DISCUSSION

The IMB model produced a well-fit model describing adherence to MDR-TB treatment and its key determinants. Adherence information and motivation were found to be predictors of adherence through behavioral skills. Furthermore, patients' perceived support from their social network and providers improved adherence through information and motivation. Providers' work engagement also improved adherence directly, emphasizing the importance of patient-provider interactions. Finally, the model showed that patients with prior LTFU to TB treatment were less likely to adhere.

Most prior research on adherence to TB treatment has focused on drug-sensitive TB and found that social support, previous LTFU, and knowledge about TB are associated with adherence.[4,29,30] Research on the determinants of adherence to MDR-TB patients (e.g. side effects, financial difficulties) has mainly consisted of qualitative studies.[15] Our findings of the value of the IMB model were similar to adherence studies in the fields of human immunodeficiency virus (HIV), reproductive health, diabetes, and heart disease.[17,18]

For patient-centered interventions the IMB model could be used to measure the progress, and evaluate the effectiveness of interventions aimed at improving adherence. Adherence information, motivation, and behavioral skills could be the intermediate targets for intervention activities, which would have the goal to improve one, or a combination of these targets. Checking the progress of interventions over time using these targets also allows practitioners to finetune activities in real-time. The common approach to interventions is to implement at time zero and then report results at the end of the study. Therefore, practitioners would have the opportunity to maintain intervention activities on target during implementation and improve the chances of a successful intervention.

Our study also suggests examples for intervention activities. We observed an additive effect from patient-perceived support by providers and social networks. Greater improvement in adherence information and motivation were observed if the support was perceived to come just from both rather than one or the other. This may be a reflection of the psychosocial barriers patients face, which have been documented in the literature.[4,21] The direct positive effect of providers' work engagement, on the other hand, highlights the importance of addressing provider-level barriers to improve adherence. Some of these include high-risk work environments, understaffing, and difficulties coordinating care with supporting services (e.g. psychologists).[31,32]

We did not find an association between patient-perceived support by psychologists or CHWs in our model. This may be because patients only had an average of two psychology appointments throughout treatment and most of the few CHWs were involved in MDR-TB care as former TB-CHWs had either retired or were supporting other public health campaigns (e.g. dengue and chikungunya).

Limitations

Our study was a cross-sectional observational study, limiting any causal interpretation. It is possible that some of our participants responded to questions even when they did not remember the answers well. We reduced potential recall biases limiting adherence data to 2 months prior to data collection. To focus on the IMB model and social networks, we did not include covariates such as sex and income. Such omission could have affected model parameter estimates, standard errors, and broader inferences about structure.

CONCLUSIONS

While there is a growing consensus that patient-centered care is essential for optimal adherence, a complex human behavior, global and national treatment guidelines are based on limited evidence on *how* to implement patient-centered care.[33,34] Our results suggest that comprehensive interventions should include adherence information, motivation, and behavioral skills. The IMB model could be used to design adherence interventions and measure their effectiveness. Future studies should follow patients over time to understand how adherence barriers change, and which interventions are most effective at different stages of treatment.

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REFERENCES

1. World Health Organization. Global tuberculosis report 2015. 2015. Available from: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1

2. Abubakar I, Zignol M, Falzon D, Raviglione M, Ditiu L, Masham S, et al. Drug-resistant tuberculosis: time for visionary political leadership. Lancet Infect Dis. 2013 Jun;13(6):529–39.

3. Bastard M, Sanchez-Padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, et al. Effects of Treatment Interruption Patterns on Treatment Success Among Patients With Multidrug-Resistant Tuberculosis in Armenia and Abkhazia. J Infect Dis. 2015 May 15;211(10):1607–15.

4. Thomas BE, Shanmugam P, Malaisamy M, Ovung S, Suresh C, Subbaraman R, et al. Psycho-Socio-Economic Issues Challenging Multidrug Resistant Tuberculosis Patients: A Systematic Review. PLoS ONE. 2016;11(1):e0147397.

5. Deshmukh RD, Dhande DJ, Sachdeva KS, Sreenivas A, Kumar AMV, Satyanarayana S, et al. Patient and Provider Reported Reasons for Lost to Follow Up in MDRTB Treatment: A Qualitative Study from a Drug Resistant TB Centre in India. PLoS ONE. 2015;10(8):e0135802.

6. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2007;(4):CD003343.

7. JN Newell, SC Baral, SB Pande, DS Bam, P Malla. Family-member DOTS and community DOTS for tuberculosis control in Nepal: cluster-randomised controlled trial. Lancet, 2006; 367: 903-9.

8. 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.

9. Pasipanodya JG, Gumbo T. A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients. Clin Infect Dis. 2013 Jul;57(1):21–31.

10. Frick M, Zhang A. Patient-Centered TB Treatment Will Require Modernizing Directly-Observed Therapy. Speaking of Medicine. Available from: http://blogs.plos.org/speakingofmedicine/2013/10/30/patient-centered-tb-treatment-will-require-modernizing-directly-observed-therapy/

11. Khachadourian V, Truzyan N, Harutyunyan A, Thompson ME, Harutyunyan T, Petrosyan V. People-centered tuberculosis care versus standard directly observed therapy: study protocol

for a cluster randomized controlled trial. Trials. 2015 Jun 22;16. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4479352/

12. Sripad A, Castedo J, Danford N, Zaha R, Freile C. Effects of Ecuador's national monetary incentive program on adherence to treatment for drug-resistant tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2014 Jan 1;18(1):44–8.

13. 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. The International Journal of Tuberculosis and Lung Disease. 2011 Oct 1;15(10):1373–9.

14. Munro S, Lewin S, Swart T, Volmink J. A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS? BMC Public Health. 2007 Jun 11;7:104.

15. 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. The International Journal of Tuberculosis and Lung Disease. 2013 Mar 1;17(3):299–307.

16. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. Health Psychol. 2006 Jul;25(4):462–73.

17. Chang SJ, Choi S, Kim S-A, Song M. Intervention Strategies Based on Information-Motivation-Behavioral Skills Model for Health Behavior Change: A Systematic Review. Asian Nursing Research. 2014 Sep 1;8(3):172–81.

18. Mayberry LS, Osborn CY. Empirical validation of the information-motivation-behavioral skills model of diabetes medication adherence: a framework for intervention. Diabetes Care. 2014;37(5):1246–53.

19. Ministerio de Salud (2013). Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis. Available from: http://www.tuberculosis.minsa.gob.pe/

20. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcantara F, et al. Community-Based Therapy for Multidrug-Resistant Tuberculosis in Lima, Peru. New England Journal of Medicine, 2003, 348:119.

21. 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. Global Public Health. 2007 Oct 1;2(4):404–17.

22. Ministerio de Salud, Dirección General de Intervenciones Estratégicas en Salud Pública, Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis. 4ta Jornada Científica de la Tuberculosis. Lima, Perú, March 16-17, 2016. Presentación PowerPoint by Dr. Valentina Antonieta Alarcón Guizado (National Coordinator, ESNPCT/DGSP – MINSA)

23. The LifeWindows Project Team. The LifeWindows Information Motivation Behavioral Skills ART Adherence Questionnaire (LW-IMB-AAQ). 2006. Center for Health, Intervention, and Prevention. University of Connecticut.

24. Bakker AB. An Evidence-Based Model of Work Engagement. Current Directions in Psychological Science. 2011 Aug 1;20(4):265–9.

25. Schaufeli WB, Bakker AB, Salanova M. The Measurement of Work Engagement With a Short Questionnaire A Cross-National Study. Educational and Psychological Measurement. 2006 Aug 1;66(4):701–16.

26. Kline RB. Principles and Practice of Structural Equation Modeling. 3rd ed. New York, NY: The Guidlford Press; 2011.

27. Bollen KA. Structural Equations with Latent Variables. United States of America: John Wiley & Sons, Inc.; 1989.

28. StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

29. Volmink J, Garner P. Systematic review of randomised controlled trials of strategies to promote adherence to tuberculosis treatment. BMJ. 1997 Nov 29;315(7120):1403–6.

30. Tola HH, Tol A, Shojaeizadeh D, Garmaroudi G. Tuberculosis Treatment Non-Adherence and Lost to Follow Up among TB Patients with or without HIV in Developing Countries: A Systematic Review. Iran J Public Health. 2015 Jan;44(1):1–11.

31. Nansera D, Bajunirwe F, Kabakyenga J, Asiimwe PKJ, Mayanja-Kizza H. Opportunities and barriers for implementation of integrated TB and HIV care in lower level health units: experiences from a rural western Ugandan district. Afr Health Sci. 2010 Dec;10(4):312–9.

32. Wannheden C, Westling K, Savage C, Sandahl C, Ellenius J. HIV and tuberculosis coinfection: a qualitative study of treatment challenges faced by care providers. Int J Tuberc Lung Dis. 2013 Aug;17(8):1029–35.

33. Ministerio de Salud, Perú. Norma Técnica de Salud para la Atención Integral de las Personas afectadas por Tuberculosis. 2013. Available from: http://www.minsa.gob.pe/dgsp/observatorio/documentos/infecciones/RM715-2013_MINSA_TB.pdf

34. WHO | Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. WHO. Available from: http://www.who.int/tb/publications/pmdt_companionhandbook/en/

CHAPTER III: COMPLEX SYSTEMS: VISUALIZING MULTIDRUG-RESISTANT TUBERCULOSIS TREATMENT ADHERENCE WITH CAUSAL LOOP DIAGRAMS (AIM 2)

OVERVIEW

Background. Multidrug-resistant tuberculosis (MDR-TB) treatment adherence poses a complex public health challenge, due to the many important facilitators and barriers at multiple levels affecting each other over time. Interventions designed based on an incomplete understanding of this complexity are likely to fail. This paper extends prior attempts to describe adherence behaviors by presenting a broad, integrated systems diagram depicting the interactions most substantially affecting patient adherence to MDR-TB treatment.

Methods. We engaged mixed stakeholder groups in urban Peru using system dynamics qualitative methods to diagram the most important cause-and-effect connections determining MDR-TB treatment adherence over time. These causal loop diagrams were then validated and expanded based on a review of the scientific literature. Finally, expanded diagrams were reviewed with local stakeholders to ensure final versions continued to reflect local reality.

Results. Adherence was affected by adverse reactions to medications, psychosocial factors, and health care system barriers, among others. These factors vary in importance across three phases of treatment – intensive, continuation, and maintenance – as defined by patients. In many cases, the ripple effects triggered by treatment adherence (or nonadherence) circled back to both reinforce and undermine adherence over time ("feedback loops"). All stakeholder-

diagrammed relationships were substantiated in the scientific literature. Additional relationships were added based on the literature, including financial difficulties, substance abuse, and gender effects. The final diagram had high face validity with stakeholders.

Conclusion and recommendations. Future research is needed to validate and expand upon our initial model. However, the many feedback loops are important in shaping outcomes, and should be considered when designing intervention.

INTRODUCTION

In 2014, Tuberculosis (TB) surpassed human immunodeficiency virus (HIV) as the leading cause of death from infectious disease worldwide.[1] Multidrug-resistant TB (MDR-TB) is defined as resistance to at least two of the most powerful TB drugs, isoniazid and rifampicin. Compared to drug-sensitive TB, MDR-TB treatment is longer (≥18 months) and side effects are often more severe.[2] Missing doses could result in poor treatment outcomes, further transmission of MDR-TB, and amplified resistance to drugs.[3–5] Barriers and facilitators at multiple levels (e.g. patient, healthcare provider, health system) affect patient adherence and loss-to-follow-up (LTFU) during treatment.[6,7]

Barriers and facilitators to MDR-TB treatment adherence are part of a system that includes biomedical,[8] cognitive,[6] socioeconomic,[9] and operational factors.[10] Relationships among these barriers and facilitators are complex because they likely differ in direction and magnitude over the period of treatment.[7,11] Interventions designed based on an incomplete understanding of this complexity may not have the desired impact or cause negative unintended consequences. Recent efforts to study similar complex systems include sexually transmitted disease stochastic microsimulation models (STDSIM), which evaluate behavioral interventions, treatments, and programmatic strategies;[12] and the TB Modelling and Analysis

Consortium (TB MAC), which has been modelling the natural history and epidemiology of TB.[13]

A simulation platform like the STDSIM could accelerate our ability to evaluate and scale-up interventions in the field of TB. System dynamics (SD) is a modeling technique that uses feedback loops and stock-and-flow diagrams to illustrate and simulate complex systems.[14] In this paper, we present an integrated system dynamics diagram of the interactions most substantially affecting patient adherence to MDR-TB treatment over time. This diagram extends prior attempts to describe adherence, and was developed based on a structured review of the literature as well as interviews and focused group discussions (FGDs) with key stakeholders. This diagram is the first step to a simulation platform that decision-makers could use to evaluate the effects of different interventions on MDR-TB treatment outcomes for their specific contexts.

METHODS

Utility of system dynamics using feedback loops and stock variables

SD is a methodology and mathematical modeling technique for mapping and modeling the forces of change in complex systems to identify critical points for change.[15] SD models are composed of stocks, flows, internal feedback loops, and time delays, put together through a participatory approach to model-building. Simulations using SD can be used to model and compare complex interventions over time to aid in policy decision-making.[16] SD has been used extensively in the fields of business, engineering, economics, environmental science, and most recently in public health (operations, diabetes care, substance abuse, heart disease).[17]

In the United States (US), the Centers of Disease Control and Prevention has sponsored the development of SD models for diabetes, obesity, and non-communicable diseases broadly. These efforts have aided in public health planning in the US and most recently, the

Caribbean.[18] In our study we used SD methodology – including the engagement of mixed stakeholder groups in urban Peru – to diagram the disease trajectory of MDR-TB, and the most important cause-and-effect connections determining treatment adherence over time. Analyses were conducted in Microsoft Excel (2010) and Vensim DSS (2016) software.[18,19]

Study setting

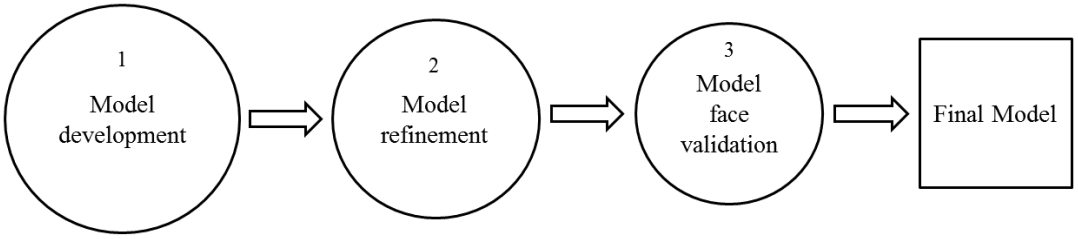
We used data from a previous study in Lima, Peru,[20] to aid us in setting the model's boundary between MDR-TB treatment initiation and treatment completion or LTFU during treatment. Peru accounts for 3.1% of the population of Latin America and the Caribbean region, but has 11.6% of the region's TB and 35.3% of the MDR-TB cases.[21] Peru's capital, Lima, and the constitutional province of Callao combined have 54% of the TB cases, 76% of the MDR-TB cases, and 89% of the extremely drug-resistant tuberculosis (XDR-TB) cases in the country. The model we developed illustrates the disease trajectory in the context of Peru's national guidelines for MDR-TB treatment.[22]

Under Peru's TB guidelines, treatment is provided Monday-Saturday for at least 18 months at health centers ran by the Ministry of Health and following the World Health Organization's Directly Observed Therapy (DOT) strategy.[22,23] An MDR-TB patient is expected to be on injectable medications a maximum of six to eight months (or after four consecutive negative cultures, tested monthly) unless otherwise specified by their physician; second-line drugs should be administered in one daily dose except for ethionamide, PAS, and cycloserine, which should be administered in two doses each day, eight hours apart, to avoid adverse reactions; and a LTFU case is defined as a patient who missed doses for 30 continuous days or more.

Developing a qualitative model of MDR-TB treatment adherence

The development of our model was an iterative process grounded on an extensive literature review, structured interviews, and FGDs with patients, healthcare service providers, decision-makers, and community health workers (CHWs) in Lima, Peru. These findings were incorporated in three stages – model development, refinement, and face validation – to develop a model that represented the MDR-TB disease trajectory and determinants of treatment adherence (Figure 3.1).

Figure 3.1 Model building process



The model building process consisted of 3 stages. Stage 1: data collection through structured interviews and FGDs; Stage 2: literature review based on the results from the first stage; Stage 3: face validation of the model with a final round of interviews and FGDs.

Model development

In the model development stage, we used structured questionnaires to conduct structured interviews with 212 patients and 86 of their providers, and conducted two FGDs with patients (n=8), one with CHWs (n=4) and one with providers (n=3). Participants were recruited from the 40 health centers with the highest 2013-2014 MDR-TB prevalence in Lima, Peru. We included adults (ages 18-65) diagnosed with MDR-TB who had been in treatment for at least 12 days. In each health center seven to 10 patients and up to three of their providers (physicians, nurses, nurse technicians) were recruited. Health centers were mostly from shantytowns in the outskirts

of Lima, and patients lived or worked less than 20 min away walking or using public transportation.

The patient questionnaire included questions about demographics, medical history, socio-economic and psychosocial states, and patient-perceived barriers and facilitators for treatment adherence. The provider questionnaire focused on provider-perceived operational and programmatic barriers and facilitators to treatment adherence, as well as their own capacity to facilitate adherent behavior among patients. We also accessed patients' medical histories and daily patient treatment logs. A detailed description of the data can be found elsewhere.[20]

We recruited FGD participants at the health centers visited, from the same pool of interviewed participants. In health centers where CHWs assisted with MDR-TB patient care, we also recruited CHWs for FGDs. FGD questions focused on describing the stages of treatment and comparing the impact of patient- and provider-reported barriers and facilitators on treatment adherence over time. During the FGDs, labeled notecards were used to help participants visualize the direction and relative impact each barrier and facilitator had on adherence. Using the data gathered in this stage, we drafted the stock-and-flow diagram for MDR-TB disease trajectory shown in the results section, and the first draft of causal loop diagrams (CLD) that reflect changes over the period of treatment (Appendix A).

The study was approved by the institutional review boards of the University of North Carolina at Chapel Hill (US), Asociación Benéfica PRISMA (Peru), the Dirección Regional de Salud Callao, Dirección de Salud IV Lima Este, and Dirección de Salud II Lima Sur.

Model refinement

The model refinement stage was guided by the results in the model development stage. The literature review consisted of 136 PubMed search strategies designed to identify articles

within the field of TB that studied factors associated with adherence. Selection of the number and terms for the search strategies was determined from the model develop during the first stage and in consultation with a librarian. Minor adjustments and additions made to the search strategies were guided by the reviewed literature. We also searched through the reference lists from systematic reviews for additional articles.

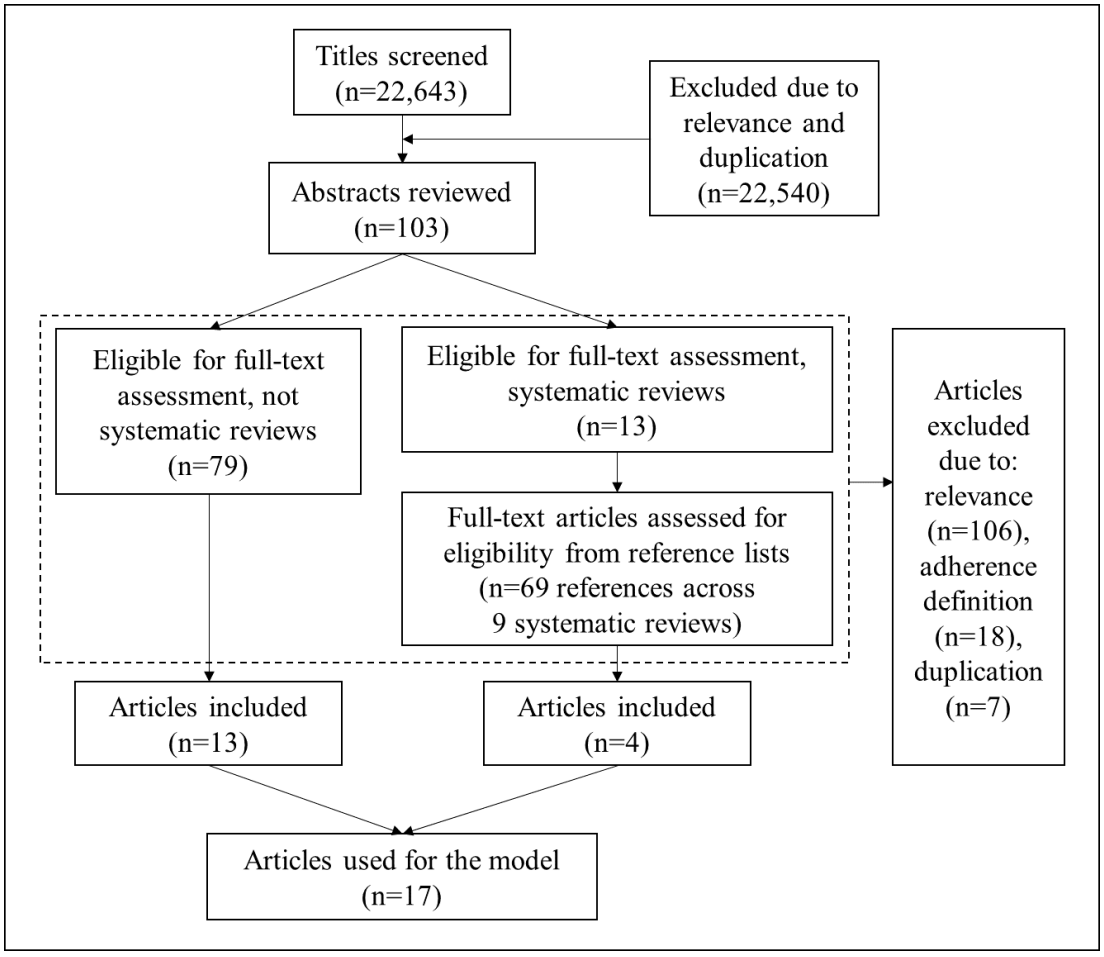
The initial search produced 22,643 results (Figure 3.2); we reviewed their titles for relevance. Our inclusion criteria were TB studies that quantified associations between factors in the context of treatment adherence research. After excluding 22,540 articles based on relevance and duplication, we reviewed 103 abstracts. Among the abstracts, we found 13 systematic reviews and 79 non-systematic reviews for full-text assessment. A total of 17 relevant articles, four from the systematic reviews and 13 from non-systematic reviews, were used for context and content validation of the model.[24]

During the initial search, larger number of articles were found for searches that only included terms for TB and one additional factor. When search terms were combined, the number of results decreased significantly. For example, searching for TB and adherence terms resulted in 3225 article titles, whereas searching for TB, adherence, and financial difficulties returned 26 results. Some combination of searches returned zero results. An example of this is pain from injections. Numerous qualitative studies and our data have shown that pain from injections is a strong determinant for non-adherence and LTFU, yet few related search results were found.

The search strategies (Appendix B) included terms for TB and 16 terms that were identified during interviews, FGDs, and the literature review as relevant and searchable. The matrices below show the count of articles found in the initial search per link (Table 3.1a) and the final count of evidence used for the model per link (Table 3.1b). Empirical evidence was found

for 30 links, including the 10 links originally identified as relevant to adherence during the interviews and FGDs from step 1. In addition to the 17 articles from the literature review, empirical evidence included analyzed data from a previous study.[20] The initial model draft was adjusted and expanded based on the findings from the model refinement stage.

Figure 3.2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for literature review search results on TB and adherence



Model face validation

In the last stage of the model building process, we conducted additional interviews and FGDs with key stakeholders to maximize the model's face validity. These interviews and FGDs were guided by a collaborative planning tool developed by Hovmand et al., which is a script used to make the model-building process more effective.[25] Participants were asked to explain their

interpretation of the model and how it could be improved to match their experiences with the factors that affect adherence. In addition to patients, providers, and CHWs, decision-makers were also interviewed. To finalize the model, we incorporated all the data from interviews, FGDs, and reviewing the literature to finalize the MDR-TB disease trajectory and CLDs.

Table 3.1a Titles screened from the initial PubMed search results for factors associated with TB

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Adherence	3225															
2. Previous LTFU	21	149														
3. Sadness	128	2	627													
4. Side effects from pills	262	4	18	2797												
5. Pain from injections	1			33	43											
6. Time in treatment	97	4	4	50		488										
7. Self-efficacy	6		1				9									
8. Knowledge about disease	248	8	36	70		29	1	3246								
9. Motivation	85		7	2		2	3	16	256							
10. Financial difficulties	26	2	15	8		2		27	1	260						
11. Substance abuse	162	1	49	73	4	15	2	64	18	2	1527					
12. Male (vs. female)	1840	35	424	1662	23	248	5	1749	108	126	8	70399				
13. Employed	174	5	53	55		21		216	14	23	58	1434	3531			
14. Clinic hours	103	52	1	10	1	3	1	64	12	21	18	336	41	626		
15. Feeling healthy	2		4									11			13	
16. Studies	726	13	160	372	9	146	4	796	48	88	215	8676	605	213	2	14505

Titles screened:
n = 22,643 articles

Table 3.1b Literature review evidence for prioritized links in the system dynamics model

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Adherence																
2. Previous LTFU	3															
3. Sadness	2	0														
4. Side effects from pills	1	0	1													
5. Pain from injections	1	0	0	0												
6. Time in treatment	0	0	0	0	0											
7. Self-efficacy	1	0	1	0	0	0										
8. Knowledge about disease	5	0	0	0	0	0	1									
9. Motivation	0	0	0	0	1	0	1	0								
10. Financial difficulties	3	0	1	1	0	0	0	0	0							
11. Substance abuse	6	0	1	1	0	0	0	0	0	1						
12. Male (vs. female)	1	0	1	0	0	0	0	0	0	0	0					
13. Employed	1	0	1	0	0	0	0	0	0	0	0	1				
14. Clinic hours	1	0	0	0	0	0	0	0	0	0	0	0	0			
15. Feeling healthy	1	0	2	0	0	0	0	0	1	0	0	0	0	0		
16. Studies	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	

Links identified in FGDs and interviews*
Additional links identified based on evidence from the literature review (n=17 studies) and Aim 1 data set*

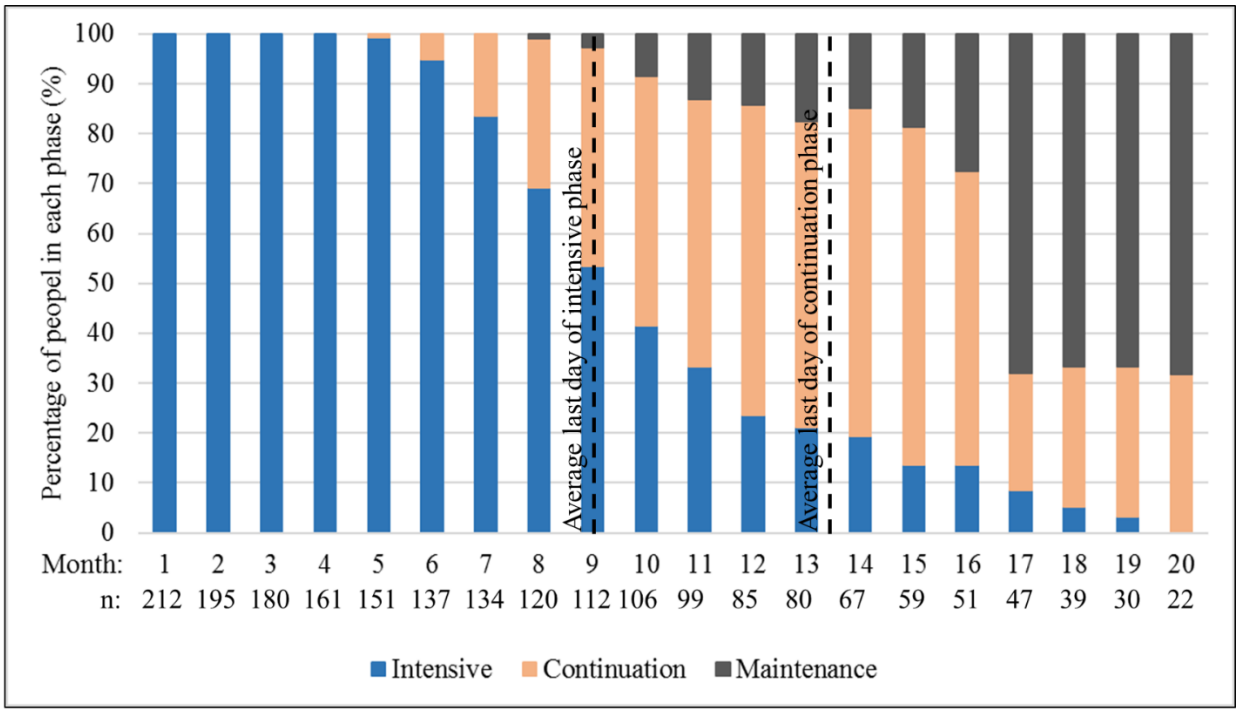
* Numbers indicate the articles (and data set) with evidence for a particular link.

RESULTS

Phases of treatment: intensive, continuation, maintenance

Previous studies have suggested that patients may experience barriers and facilitators to adherence and LTFU differently at different times during treatment.[26,27] In our study, participants identified and described three treatment phases*: intensive, continuation, and maintenance*. The *intensive* phase starts with treatment and ends when patients stop receiving injectable medications. The *continuation* phase starts when injectable medications are stopped and ends when side effects from pills no longer keep patients from returning to normal life (e.g. work and school). During the *maintenance* phase, patients return to their normal lives as side effects from pills no longer subside; this phase lasts through treatment completion.

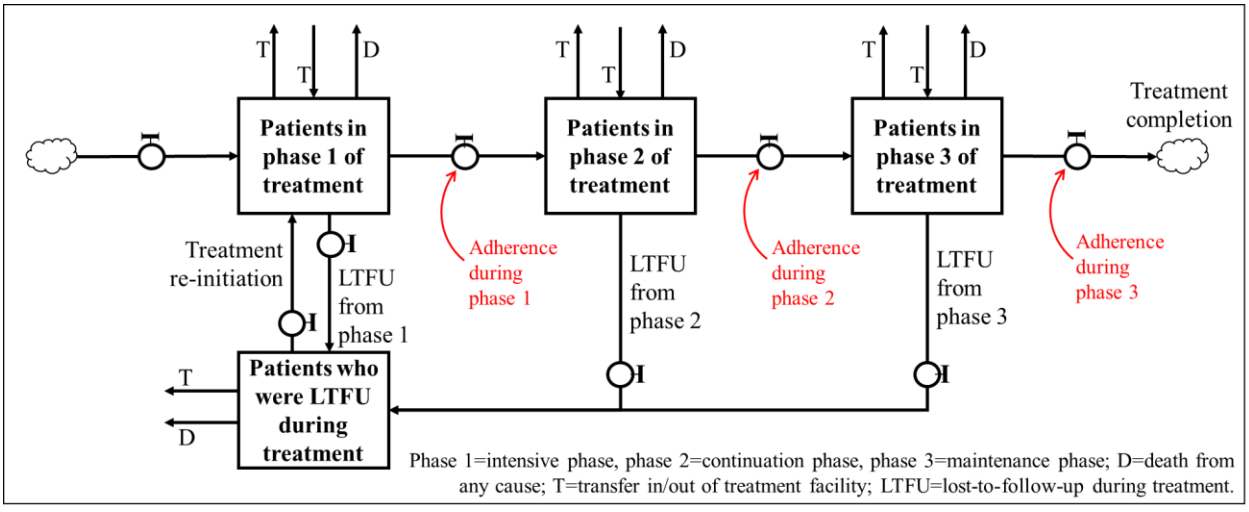
Figure 3.3 Percentage of MDR-TB patients in each phase by month of their treatment



Note: Data was collected from medical charts and questionnaires for 212 adult MDR-TB patients who initiated treatment during 2013 or 2014. Patients who were interviewed at a later date during their treatment contributed more data.

Data from a previous study in Lima was aggregated into months and used to estimate the movements of patients from one phase to the next (Figure 3.3).[20] We observed a clear trend of transition and calculated the average times each patient spends in each phase. Data was limited to the day of data collection or the last day of treatment for LTFU cases. The average time (excluding Sundays) patients had been in treatment at the time of data collection was 243 days [range: 12-771]. The average time a patient spent in the intensive phase was nine months, though some were receiving injectable medications for more than a year. The continuation phase started at about month five and lasted an average of 4.5 months. For the maintenance phase, data count beyond the 20th month of treatment was excluded because there were less than 20 patients' data per month. Data after the 18th month of treatment must be interpreted with caution due to the decline in monthly data available. The phases of treatment are illustrated in the stock-and-flow diagram in Figure 3.4.

Figure 3.4 Stock-and-flow diagram of the treatment progress for MDR-TB patients



The stocks represent people in each of the three phases of treatment and those who have been LTFU during treatment. The cloud on the left is the pool of people who acquire and are diagnosed with MDR-TB. The cloud on the right is the pool of people who complete all

prescribed doses of MDR-TB treatment. The arrows represent the rate at which people move from one stock (or cloud) to another stock (or cloud). The arrows labeled "T" represent patients transferring or moving in and out of the boundaries of the system. The arrows labeled "D" are patients exiting the system due to death, related or unrelated to TB.

A missed dose (e.g. a missed day of treatment) delays treatment completion by one day. Therefore, the rate at which patients move from the stock "patients in phase 1 of treatment" to "patients in phase 2 of treatment" depends on "adherence during phase 1 of treatment", which is measured as a rate (doses taken/doses prescribed during a given period). Similarly, "adherence during phase 2" defines how fast "patients in phase 2 of treatment" move to "patients in phase 3 of treatment", and "adherence during phase 3" defines how fast patients complete treatment. If adherence is "0" for more than 30 consecutive days during any phase, patients move to the stock of "patients who were LTFU during treatment". A percentage of "patients who were LTFU during treatment" re-initiate treatment, thus, they move back into the stock of "patients in phase 1 of treatment".

Literature review results

We refined the initial model using data from an extensive literature review. Most articles found had studied factors associated with TB and MDR-TB LTFU during treatment, also referred to as abandonment, default, non-compliant, or non-adherent. In addition to the scarcity of studies found related specifically to adherence during treatment, many of them used the term interchangeably with "compliance" to indicate LTFU as non-adherent or non-compliant.[28,29,30] The definitions for compliance, adherence, non-compliance, non-adherence, and LTFU-related terms varied across articles.

The measurement for adherence also differed by article. Some authors measured adherence as binary with cut-offs such as rate (e.g. adherent if dosages taken >90% of the time) and day count (e.g. >7 of missed dosages considered non-adherent). Others used scales or did not report how they measured adherence. Sources of adherence data also varied from treatment daily logs to patient-reported scales. Factors associated with adherence were also reported in different units depending on the method of analysis (e.g. odd ratios, adjusted odd ratios, beta coefficients, relative risks).

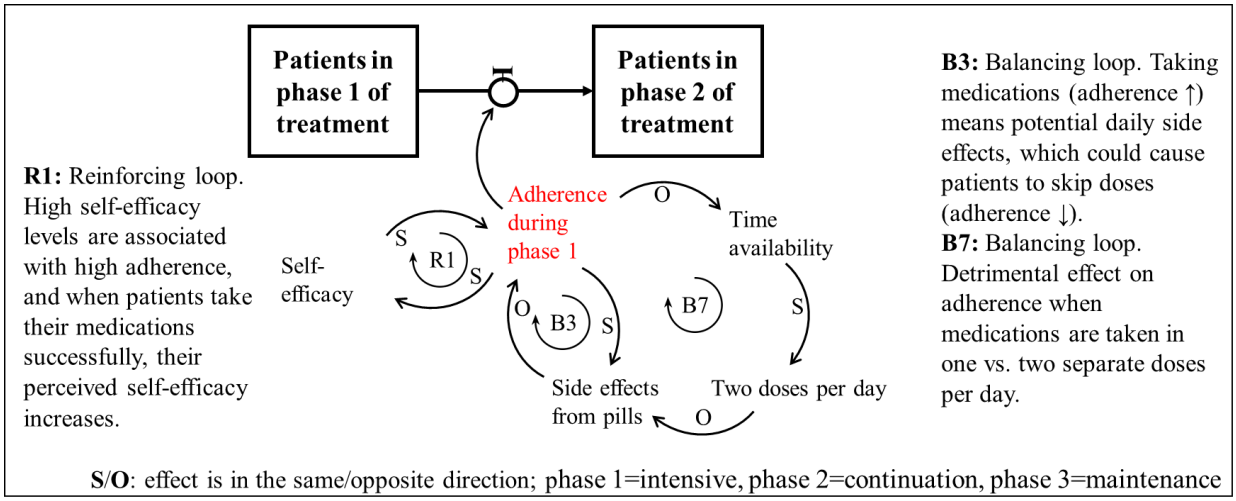
The 17 articles that resulted from the literature review search were used to refine the system dynamics model, generating a second model draft (Appendix C and D). Following the literature review, we conducted six additional interviews with providers and decision-makers, and one FGD with four patients (model face validation) to make final adjustments to the model. The CLDs developed based on interviews, FGDs, and the literature reviews are described below.

Causal loop diagrams and feedback loops

The final model was developed using qualitative SD methods. The structural challenges of developing an SD model are that it must reflect perceived reality, be sensitive to circumstantial changes, and provide information that is useful in theory and practice.[31] The elements of an SD model are the accumulation of flows into stocks (Figure 3.5) and feedback among its variables. A CLD is part of the structure of an SD model which includes its relevant variables and their interactions. Understanding this structure is what makes it possible to ascertain a system's behavior over time.[14] Within a CLD, feedback loops occur when output from one variable eventually influences input to that same variable, which can be used to identify leverage points for changes in the system.

In the stock-and-flow diagram (Figure 3.5), "adherence during phase 1" influences the rate at which patients move to the stock of "patients in phase 2 of treatment". The example in Figure 3.5 illustrates patient flow from the intensive to the continuation phase of treatment and a sample of factors that influence adherence rate – the flow – during the intensive phase (e.g. self-efficacy, side effects from pills, time availability, and time between doses). The arrows represent the links between factors, which could either be positive or negative causal links. Positive causal links are identified by the letter "S" for factors that change in the same direction; negative causal links connect factors that change in opposite directions and are identified by the letter "O".

Figure 3.5 Selected factors in stock-and-flow, and causal loop diagrams of the treatment progress for MDR-TB patients



A reinforcing loop, "R", is a closed cycle in which the effect of a change in any variable within it propagates through the loop and returns to the variable reinforcing the initial deviation. In a balancing loop, "B", the effect through the cycle will return an effect in the opposite direction. In the case of "B7", for example, when adherence is high, patients have less free time available. Due to several barriers, patients are more likely to take all medications from the day in one dose, instead of returning for their second dose in the evening. One dose per day is associated with higher frequency and severity of side effects, which makes it more likely for

patients to skip doses while recovering. Without breaking the B7 feedback loop, the system gets caught in a vicious cycle that decreases adherence.

CLD and feedback loops during the intensive phase

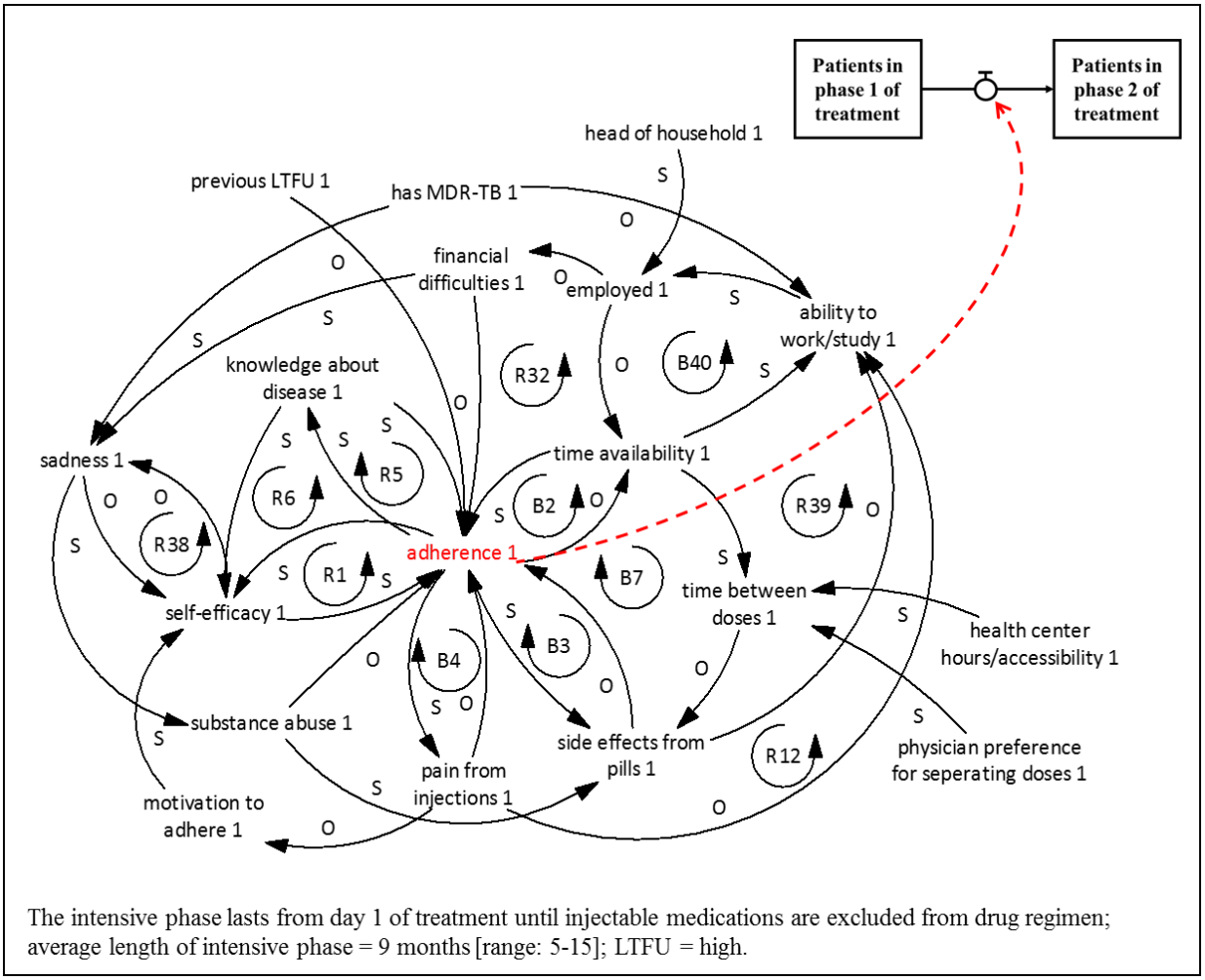
The CLDs summarizing the factors and links identified during the model building process are illustrated in Figures 3.6a-3.6c. During model development (Figure 3.6a), 17 factors were identified through interviews, FGDs, and the literature review as key barriers and facilitators to adherence. Only naturally occurring facilitators were included; intervention, or intervention-like facilitators were excluded from the model. The links between these factors produced a CLD structure with 15 reinforcing loops and 26 balancing loops (Appendix E). We included a selection of these feedback loops to describe the main features of the diagram. The complete reference list used for the model and the links for which evidence was found are described in Appendices D and E.

The factors in the CLDs were grouped into four categories: biomedical (e.g. side effects), cognitive (e.g. self-efficacy), socioeconomic (e.g. financial difficulties), and convenience (e.g. time availability). These factors made up balancing and reinforcing loops. The balancing loops described the barriers that arise just from having MDR-TB or taking treatment, such as side effects, pain from injections, and time availability. For example, key stakeholders reported that high adherence rates decrease the time available to work/study, causing unemployment and more financial difficulties, which also has been strongly associated with sadness, low adherence, and LTFU in evidence from the literature.

The three types of reinforcing loops that emerged from the CLD and resulted in improved adherence when patients were receiving injectable medications (intensive phase) were: i) those that could be mitigated by increasing self-efficacy (e.g. R1, R6), ii) those that could be mitigated

by increasing knowledge (e.g. R5, R6), and iii) those that naturally improved because the very discomfort of the disease keeps patients from working or studying, freeing time for treatment (e.g. R12, R15). To design interventions that target adherence, the leverage points in the system are key to changing its course or reinforcing positive influences. The feedback loops that can be mitigated are potential leverage points in this model.

Figure 3.6a Intensive phase CLD of factors associated with MDR-TB treatment adherence



The intensive phase lasts from day 1 of treatment until injectable medications are excluded from drug regimen; average length of intensive phase = 9 months [range: 5-15]; LTFU = high.

The outer loop R39 shows the negative cycle of barriers that some patients face. When patients are sad about their diagnosis and they have problems with substance abuse, this could worsen their side effects, decrease their ability to work, increase financial difficulties, and result

in more sadness or even depression. Unless someone intervenes, patients will continue facing these barriers daily, which often results in poor adherence or LTFU. The loop B40 illustrates the barrier of time limits in a day; if a patient is employed, this decreases their time available, which decreases their ability to work more during that day. The complex interactions of these barriers and facilitators that affect adherence link back to the rate at which "patients in phase 1 of treatment" flow into the stock of "patients in phase 2 of treatment" (dotted red line).

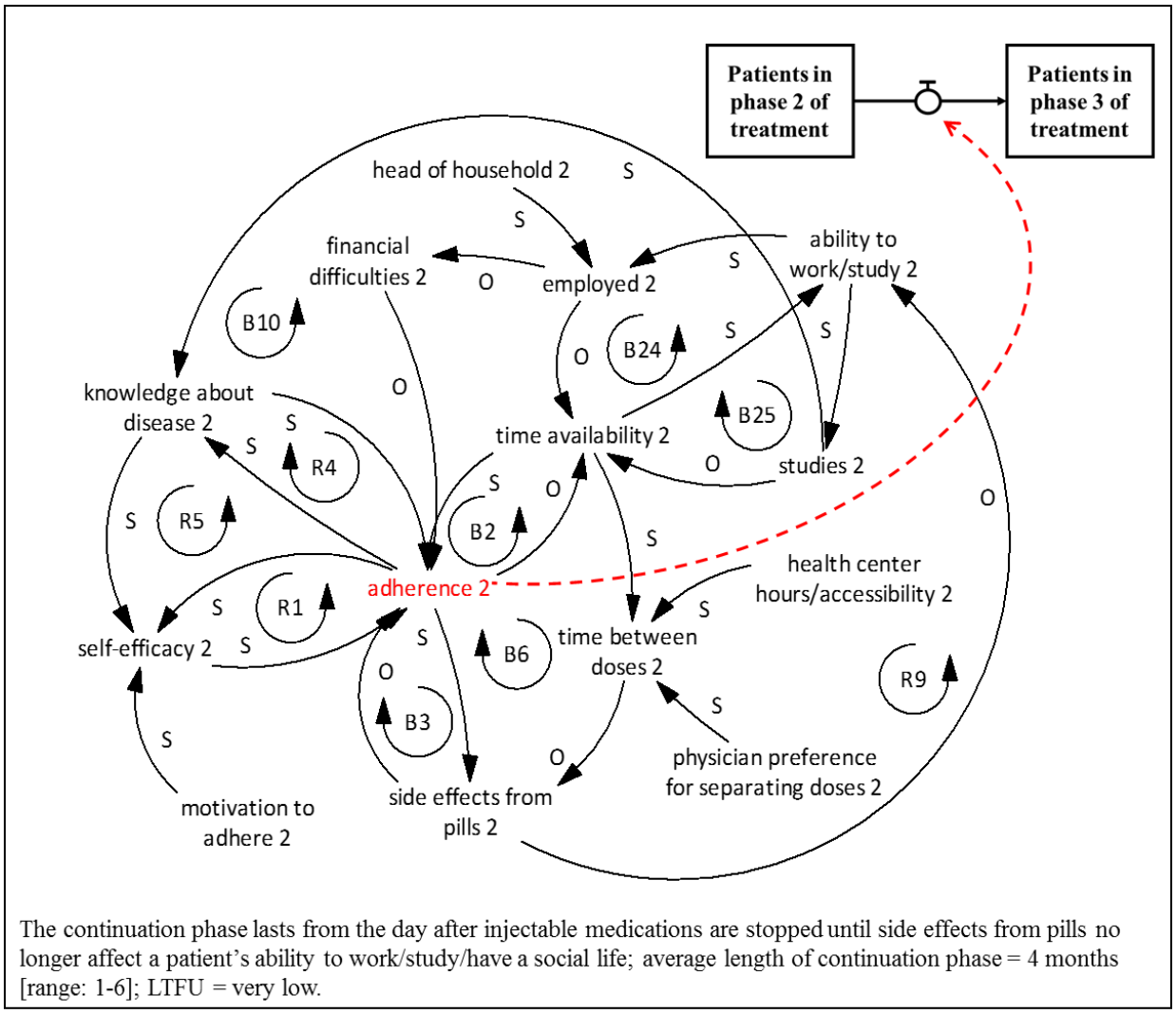
We found evidence on the CLD's links and their directionality from the interviews, FGDs, and literature review. However, evidence of the relative impact of each of these factors on adherence or each other is scarce. Data from interviews and FGDs show that during the intensive phase, financial difficulties, sadness, side effects, and injections have the strongest associations with lower adherence. The relative quantitative effects are not always comparable because of differences in measurement and methods used in the literature. Another aspect to consider is that the percentage of patients experiencing each of these barriers likely varies by context and time.

CLD and feedback loops during the continuation phase

Once a patient is taken off the injectable medications, they move on to the continuation phase of treatment and experience left-over side effects from the pills. In this phase (Figure 3.6b), five reinforcing loops and 22 balancing loops were generated from the structure of the CLD (Appendix E). Most of the patients who were high-risk for LTFU have already stopped taking medications by the end of the intensive phase (particularly those with a history of LTFU). The largest differences in factors between the intensive and continuation phases are the disappearance of "sadness" and "pain from injections" as barriers to adherence, and the addition of "studies". Patients previously told not to attend school/university classes are free to return during phase due to their negative BK status, so long as it does not interfere with treatment.

This phase, when patients experience left-over side effects without the pain from injections, was recognized as the time when patients are least likely to be LTFU or miss doses. Participants reported that side effects from medications affect patients the most during this phase (B3, B6), but patients have gained knowledge about the importance of adherence from previous months in treatment (R4). Financial difficulties could be a significant barrier during the continuation phase more than during the intensive phase since patients may have forgone income for several months due to their disease. However, by this time many patients report finding financial support in family members or friends, which alleviates the burden.

Figure 3.6b Continuation phase CLD of factors associated with MDR-TB treatment adherence



The continuation phase lasts from the day after injectable medications are stopped until side effects from pills no longer affect a patient's ability to work/study/have a social life; average length of continuation phase = 4 months [range: 1-6]; LTFU = very low.

Except for side effects, most barriers experienced during the continuation phase were reported as having a smaller effect on patients than during the intensive phase. In most cases this perception comes from growing accustomed to having MDR-TB and the problems associated with this disease, the reinforcement of self-efficacy through knowledge of the disease (R5), motivation to adhere, and adherence itself (R1). Stakeholders also reported that some patients are offered incentives to adhere through external research projects or are paired with community health workers (CHWs) by this phase. These incentives become essential for patients who face complex barriers to adherence.

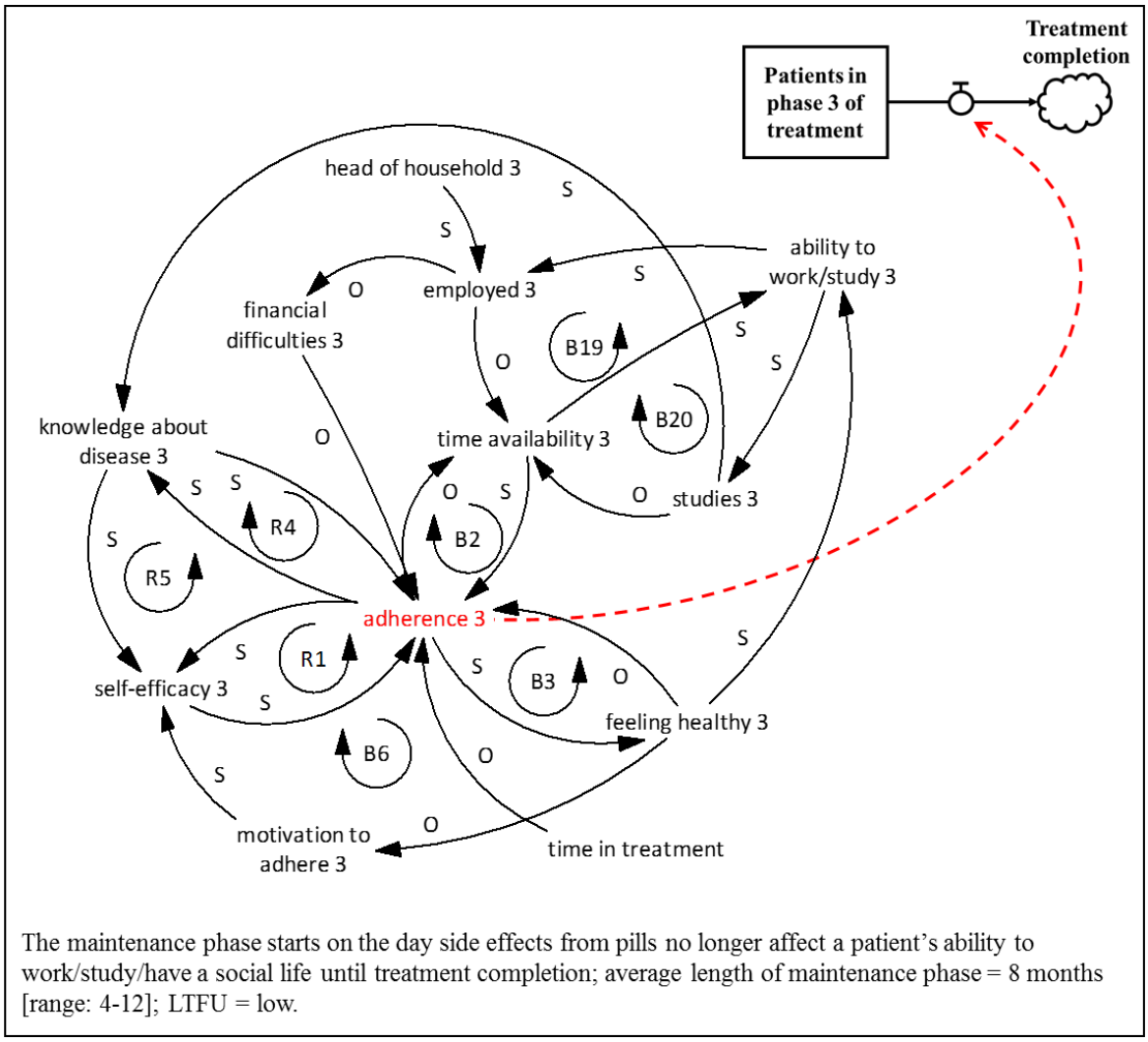
CLD and feedback loops during the maintenance phase

When side effects no longer affect a patient's ability to work or study, patients gradually return to their normal lives (Figure 3.6c). In this phase's CLD we found eight reinforcing loops and 12 balancing loops (Appendix E). Stakeholders reported a slight increase in LTFU and a drop in adherence. These changes were mainly attributed to "feeling healthy" (B3) and the long "time in treatment" patients had already endured. Additionally, patients have mostly returned to their normal lives during this phase, which means they are spending more time at work, studying, socializing, and engaging in other activities that may be prioritized over treatment (B2).

Since motivation to adhere decreases when a patient feels healthy, a refresher on why it is important to adhere to and complete treatment may play an important role in improving adherence during the maintenance phase (R4, R5). This was also reported during interviews and FGDs. Patients who have made it this far need a reminder of what they know about MDR-TB and newly found motivation to increase their self-efficacy. In Peru, approximately 60% of MDR-TB patients will complete treatment, 30% will be LTFU, and 10% will either die or fail

treatment. The rate of LTFU cases who return to treatment is unknown; however, a recent study from the Philippines reported that at least one-third of them wanted to return to treatment.[32]

Figure 3.6c Maintenance phase CLD of factors associated with MDR-TB treatment adherence



The maintenance phase starts on the day side effects from pills no longer affect a patient's ability to work/study/have a social life until treatment completion; average length of maintenance phase = 8 months [range: 4-12]; LTFU = low.

DISCUSSION

We applied qualitative systems mapping to bring a feedback perspective to understanding the complex structure of MDR-TB treatment adherence barriers and facilitators. We used this approach because adherence is the result of the behavior of a multifactorial, dynamic, and nonlinear complex system. As such, the usual tools used (e.g. simple linear models not validated with system stakeholders) coupled with human limitations (e.g. bounded rationality) could

generate misperceptions about the behavior of this system.[33] In the field of TB for example, the global effects of MDR- and XDR-TB were not anticipated when first-line medications were widely made available, a sign that our understanding of the system is often narrow and flawed.

Studies have shown that our misperceptions are mainly due to the oversimplification of systems and our inability to infer the dynamics of complex causal maps.[34,35] Our study aimed at overcoming these misperceptions using SD's stock-and-flow and causal loop diagrams to develop the foundation for an adherence dynamics model. We based our model on an extensive review of the literature, and interviews and FGDs with key stakeholders, to identify the key drivers of adherence and their relationships. The model highlights the intensive, continuation, and maintenance phases of MDR-TB treatment and several conceptual insights to understand the system barriers to adherence. These insights are crucial to designing interventions that address adherence barriers effectively at various times during treatment.

For MDR-TB patients, the decision to take or not take their medications is one they make every day for at least 18 months while facing numerous barriers. This means that timing and sequencing of strategies matters. Evidence from our study also showed that effective interventions must be tailored to meet patients' needs – varying by treatment phase and personal circumstances. For example, patients' knowledge about MDR-TB is one of the facilitators for adherence during the intensive phase, however, during the maintenance phase it is likely the most influential factor for achieving high adherence rates. By the time patients begin returning to their normal lives during the maintenance phase, they feel better and have been in treatment for approximately one year, so they need reminders (knowledge) to prioritize treatment through completion.

The model could also be used to determine what types of interventions could be most effective alone, or in combination with others. No one strategy is likely to improve adherence rate to 100%. However, the leverage points identified in the model may result in interventions that are more effective than without their identification. In the model, we see that biomedical factors (e.g. side effects and pain from injectable medications) are present in the intensive and continuation phases of treatment (B3, B4). Consequently, socioeconomic barriers arise, including unexpected healthcare costs. Patients' emotional reactions to the changes in their lives could become serious psychosocial barriers (R38), and inconveniences such as limited hours of operation at health centers could decrease adherence for patients who have other responsibilities (B2).

Multiple barriers could happen simultaneously (R39), which is why interventions targeting only one type of barrier may not result in substantial improvements on treatment adherence. Per our model, it is likely that resources could be most effectively used as combined interventions during the intensive phase of treatment, when multiple barriers make adherence most difficult. As adherence barriers become less difficult to overcome in the continuation and maintenance phases, it may be more cost-effective to implement fewer and simpler interventions (e.g. education during the maintenance phase).

After determining which barriers should be addressed to improve adherence, we also need to make decisions about *how* to address them. For the example of patients' knowledge (strengthening R5 and R6, Figure 3.6a), we must make strategic choices about the timing, frequency, duration, and person who will deliver this knowledge. If patients do not have a good relationship with their physician, a nurse or CHW may need to deliver the intervention. Patients are physically and emotionally overwhelmed during the first weeks of treatment more than at any

other time. Thus, the intervention may need to be delivered with higher frequency during the intensive phase, compared to later times, to ensure patients digest the information and turn it into knowledge.

Finetuning *how* to implement these interventions in randomized controlled trials could be costly or unethical in high-TB burden settings. Our model could be quantified to run simulations that compare the comparative effectiveness or cost-effectiveness of implementing one or more interventions at different points during treatment. Additionally, the model could also be used to finetune an intervention by simulating its effects on adherence (or treatment outcomes) under different values for timing, frequency, duration, and person who delivers the intervention.

Our study has shown that we need to go beyond describing the associated factors to improve daily adherence and prevent LTFU. This requires a shift from linear to systems thinking, and from outcome- to implementation-driven research. The frequent terms "comprehensive" and "patient-centered" in the literature limit practitioners' ability to replicate and scale-up interventions in different settings. Practitioners need detailed descriptions of the intervention's components and *how* they resulted in positive treatment outcomes to also be available in the literature. Lastly, we need a unified definition of adherence as prescribed doses taken per day and measured as a continuous rate until we have another evidence-based option. This will prevent arbitrary decisions about patients' non-adherence and their impact on research outcomes.

LIMITATIONS

Since our model was defined in part by the existing literature, it partially reflects the deficits in current knowledge about MDR-TB treatment adherence. Many mechanisms, particularly changes over time, are not well-understood. Further empirical research and

simulation models that include the key barriers and facilitators as well as their relationships are needed to enhance the reliability of our model. However, this qualitative model building attempt is important to find innovative ways to conduct research and implement interventions targeting treatment adherence. It is also an important first step towards quantifying and empirically validating simulation models for treatment adherence.

FUTURE DIRECTIONS

The next step is to develop a quantitative simulation model of MDR-TB treatment adherence. The quantitative model would be able to predict the adherence behavior of patients in response to one or multiple interventions. Parameterization of the model will allow for the identification of intervention leverages and priorities as a tool to inform decision-making for National TB Programs.

CONCLUSION

The system that makes up MDR-TB treatment adherence barriers and facilitators is complex. Our system dynamics mapping has revealed three perceived phases of treatment as well as the interactions among the barriers and facilitators with their corresponding feedback loops. Future research is needed to validate and expand upon our initial model. However, the many feedback loops are important in shaping MDR-TB treatment outcomes, and should be considered when designing interventions. System dynamics methodologies could also be used to identify and describe the complex systems for other public health problems.

REFERENCES

1. World Health Organization. Global tuberculosis report 2015. 2015. Available from: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1

2. Chung-Delgado K, Guillen-Bravo S, Revilla-Montag A, Bernabe-Ortiz A. Mortality among MDR-TB Cases: Comparison with Drug-Susceptible Tuberculosis and Associated Factors. PLoS ONE. 2015 Mar 19;10(3). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4366185/

3. Cadosch D, Abel Zur Wiesch P, Kouyos R, Bonhoeffer S. The Role of Adherence and Retreatment in De Novo Emergence of MDR-TB. PLoS Comput Biol. 2016 Mar;12(3):e1004749.

4. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. PloS One. 2013;8(7):e70064.

5. Bastard M, Sanchez-Padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, et al. Effects of Treatment Interruption Patterns on Treatment Success Among Patients With Multidrug-Resistant Tuberculosis in Armenia and Abkhazia. J Infect Dis. 2015 May 15;211(10):1607–15.

6. Thomas BE, Shanmugam P, Malaisamy M, Ovung S, Suresh C, Subbaraman R, et al. Psycho-Socio-Economic Issues Challenging Multidrug Resistant Tuberculosis Patients: A Systematic Review. PloS One. 2016;11(1):e0147397.

7. Liefooghe R, Muynck AD. The dynamics of tuberculosis treatment adherence. JPMA J Pak Med Assoc. 2001 Jan;51(1):3–9.

8. Tupasi TE, Gupta R, Quelapio MID, Orillaza RB, Mira NR, Mangubat NV, et al. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLoS Med. 2006 Sep;3(9):e352.

9. van den Hof S, Collins D, Hafidz F, Beyene D, Tursynbayeva A, Tiemersma E. The socioeconomic impact of multidrug resistant tuberculosis on patients: results from Ethiopia, Indonesia and Kazakhstan. BMC Infect Dis. 2016 Sep 5;16:470.

10. 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(12):e0144936.

11. Rajeswari R, Muniyandi M, Balasubramanian R, Narayanan PR. Perceptions of tuberculosis patients about their physical, mental and social well-being: a field report from south India. Soc Sci Med 1982. 2005 Apr;60(8):1845–53.

12. Hontelez JAC, Lurie MN, Bärnighausen T, Bakker R, Baltussen R, Tanser F, et al. Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A

Model Comparison Study. PLoS Med. 2013 Oct;10(10). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3805487/

13. London School of Hygiene & Tropical Medicine. TB Modelling Group. 2016. Available from: http://tbmodelling.lshtm.ac.uk/

14. Meadows DH. Thinking in Systems: A Primer. Wright D, editor. White River Junction, Vt: Chelsea Green Publishing; 2008. 240 p.

15. Leischow SJ, Milstein B. Systems Thinking and Modeling for Public Health Practice. Am J Public Health. 2006 Mar;96(3):403–5.

16. Guariguata L, Guell C, Samuels TA, Rouwette EAJA, Woodcock J, Hambleton IR, et al. Systems Science for Caribbean Health: the development and piloting of a model for guiding policy on diabetes in the Caribbean. Health Res Policy Syst. 2016 Oct 26;14. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5080771/

17. Atkinson J-AM, Wells R, Page A, Dominello A, Haines M, Wilson A. Applications of system dynamics modelling to support health policy. Public Health Res Pract. 2015 Jul 9;25(3):e2531531.

18. Microsoft. Microsoft Excel. Redmond, Washington: Microsoft; 2010.

19. Ventana Systems, Inc. Vensim DSS Software. 2016.

20. Alegria-Flores K, Wiesen CA, Weiner BJ, Becerra NN, Tovar MA, Evans CA: An innovative approach for designing and implementing drug-resistant tuberculosis treatment adherence interventions. In the 47th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union). Liverpool: The Union; 2016: S96.

21. PAHO WHO | Tuberculosis. Available from: http://www.paho.org/hq/index.php?option=com_topics&view=article&id=59&Itemid=40776&lang=en

22. Ministerio de Salud, Peru. Resolución Ministerial 715-2013/MINSA. Norma Técnica de Salud para la Atención Integral de las Personas afectadas por Tuberculosis. 2013.

23. WHO | Pursue high-quality DOTS expansion and enhancement. WHO. Available from: http://www.who.int/tb/dots/en/

24. Eckerd A, Landsbergen D, Desai A. The Validity Tests Used by Social Scientists and Decision Makers. In: Conference Proceedings. Washington D.C.; 2011. Available from: http://www.systemdynamics.org/conferences/2011/proceed/papers/P1263.pdf

25. Hovmand PS, Andersen DF, Rouwette E, Richardson GP, Rux K, Calhoun A. Group Model-Building "Scripts" as a Collaborative Planning Tool. Syst Res Behav Sci. 2012 Mar 1;29(2):179–93.

26. Wei X-L, Yin J, Zou G-Y, Zhang Z-T, Walley J, Harwell J, et al. Treatment interruption and directly observed treatment of multidrug-resistant tuberculosis patients in China. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2015 Apr;19(4):413–9.

27. Jakubowiak W, Bogorodskaya E, Borisov S, Danilova I, Kourbatova E. Treatment interruptions and duration associated with default among new patients with tuberculosis in six regions of Russia. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2009 May;13(3):362–8.

28. WHO | Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. WHO. Available from: http://www.who.int/bulletin/volumes/86/3/07-043802/en/

29. Haynes RB, Sackett DL. Determinants of compliance: the disease and the mechanics of treatment. Baltimore, MD, USA: Johns Hopkins University Press; 1979. 49-62 p.

30. Conrad P. The meaning of medications: another look at compliance. Soc Sci Med 1982. 1985;20(1):29–37.

31. Sargent RG. Verification and validation of simulation models. J Simul. 2013 Feb 1;7(1):12–24.

32. Mangan JM, Tupasi TE, Garfin AMCG, Lofranco V, Orillaza-Chi R, Basilio R, et al. Multidrug-resistant tuberculosis patients lost to follow-up: self-reported readiness to restart treatment. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2016 Sep;20(9):1205–11.

33. Sterman J, Sterman JD. Business Dynamics: Systems Thinking and Modeling for a Complex World with CD-ROM. HAR/CDR edition. Boston u.a.: McGraw-Hill Education; 2000. 1008 p.

34. Paich M, Sterman JD. Boom, Bust, and Failures to Learn in Experimental Markets. Manag Sci. 1993;39(12):1439–58.

35. Kampmann C, Sterman JD. Feedback complexity, bounded rationality, and market dynamics. Cambridge, MA; 1998.

CHAPTER IV: MERGING SYSTEM DYNAMICS AND IMPLEMENTATION SCIENCE TO IMPROVE PUBLIC HEALTH STRATEGIES (AIM 3)

OVERVIEW

Background. The goal of implementation science is to determine what is required to influence the full and effective use of public health innovations in practice. However, implementation strategies are often designed without consideration of the full processes of healthcare service delivery. For extended treatments, the timing and targeting of interventions could have short- or long-term implications, and have positive or negative consequences. In this study, we applied system dynamics methodology to simulate alternate scenarios for implementation strategies' timing and targets, and estimated their comparative effects on health outcomes.

Methods. We parameterized and calibrated a system dynamics model for the context of multidrug-resistant tuberculosis in Peru. The model was parameterized using data from the literature and calibrated using longitudinal patient-level data from Lima, Peru. We compared single- and multi-pronged scenarios in three sets of simulations, which targeted adherence and loss-to-follow-up within three distinct phases of treatment (intensive, continuation, and maintenance).

Results. In the single-pronged scenarios, we found that a 5% improvement in treatment completion could be achieved by increasing the adherence rate by 11% or reducing the LTFU daily probability by 1% during the intensive phase. For the multi-pronged scenarios, increasing

adherence rates to 90% and decreasing LTFU daily probabilities in half during both the intensive and maintenance phases improved treatment completion by 10%. To achieve 80% treatment completion, adherence rates must reach 95% and LTFU daily probabilities must decrease to one-tenth of their baseline values in all treatment phases.

Conclusion. We successfully turned a qualitative system dynamics model into a simulation platform to inform intervention design. Our findings showed that we must understand implementation timing and targets to translate knowledge into practice. System dynamics is a malleable tool that implementation scientists could use to improve public health strategies and guide the allocation of resources.

BACKGROUND

The integration of implementation science approaches within public health work is growing. In implementation science, the goal is to determine what is required to influence the full and effective use of innovations in practice.[1] In addition to knowing an innovation is effective, we need to also understand why, how, when, and for whom it works.[2] For chronic diseases, or long treatments, timing is particularly important because even small changes in implementation barriers and context can have serious implications on treatment outcomes.[3,4,5] However, implementation strategies are often designed without consideration of the complexity of healthcare service delivery processes.[6]

While some healthcare needs are acute (e.g., diagnosing a short-term illness and prescribing medication), other services can be prolonged – requiring care through multiple and often distinct phases of recovery or stabilization. Among populations suffering from chronic conditions, intervening during one phase could positively or negatively affect later phases of treatment.[3] Additionally, the same intervention could have different effects on outcomes

depending on the phase of treatment in which it is implemented. An interesting example is the treatment for multidrug-resistant tuberculosis (MDR-TB), which requires daily adherence to treatment for at least 18 months.[7] During treatment, patients face barriers that cause them to skip some doses or stop treatment altogether (e.g. side effects, work/family commitments, lack of knowledge about disease, migration, etc.). The types of barriers and their influence on treatment adherence change over time. Lack of understanding about how the timing and targets of interventions affect treatment outcomes could result in ineffective implementation strategies and misallocation of resources.[8]

In this study, we will illustrate how system dynamics (SD) simulation modeling can be used to estimate implementation requirements to achieve improvements in health outcomes, for each target for change under consideration. SD is a modeling technique that uses feedback loops and stock-and-flow diagrams to illustrate and simulate complex systems.[9] We parameterized and calibrated a SD stock-and-flow diagram of the MDR-TB treatment trajectory in Lima, Peru.[10] We used this platform to model implementation strategy timing and targets that could improve treatment outcomes. We seek to illustrate, in this paper, how simulation platforms such as this could be used to inform implementation strategy design and be adapted to test specific strategies in different contexts.

METHODS

We used Microsoft Excel (2010) and Vensim DSS (2016) software to analyze an SD model adapted from a previously reported qualitative model.[11,12] SD is a methodology and mathematical modeling technique used to identify critical points for system behavior change through the mapping and modeling of its interconnected elements.[9] SD modeling applies a participatory approach to model-building to diagram the stocks, flows, internal feedback loops,

and time delays of a system.[13] The SD approach is particularly useful in explaining why systems are resistant to policy implementation and planned change, and produce mathematical models that allow policy makers to understand the potential effects of alternative interventions.

SD is used extensively by engineers and environmental scientists, and to guide intervention implementation for public health problems such as service operations, diabetes, and substance abuse.[14] An example of mathematical simulation tools used to study complex systems in health is the sexually transmitted disease stochastic microsimulation model, which evaluates behavioral interventions, treatments, and programmatic strategies.[15] In the field of TB, the TB Modelling and Analysis Consortium has been modelling the natural history and epidemiology of TB through a simulation platform.[16]

Model context

Tuberculosis (TB) is the leading cause of death from infectious disease worldwide.[7] Compared to drug-susceptible TB, MDR-TB is far deadlier and current treatments are expensive, lengthy, and often cause severe side-effects.[17] Missing treatment doses could result in poor treatment outcomes, further transmission of MDR-TB, and amplified resistance to drugs.[18-20] As is the case for patients across multiple chronic diseases, treatment adherence is very difficult for many MDR-TB patients who face biological, financial, psychosocial, and systemic barriers throughout treatment.[18,21,22] These barriers interact with facilitators at multiple levels, creating a complex system that we have not explained or resolved with past or current public health strategies.[21,23]

In the case of TB, the most recognized and widely implemented strategy is the World Health Organization (WHO) directly observed therapy (DOT), in which trained individuals observe patients taking their TB medications 1-2 times daily.[24,25] However, its advantage

over self-administered treatment has no scientific basis.[24,26,27] Furthermore, low adherence and high numbers of patients lost-to-follow-up (LTFU) have resulted in growing resistance to drugs, and a dwindling global TB decline since 2000 of less than 1.5% per year.[7] To date, little is known about *how* to effectively implement strategies that improve MDR-TB treatment outcomes like treatment completion and death.[19,28]

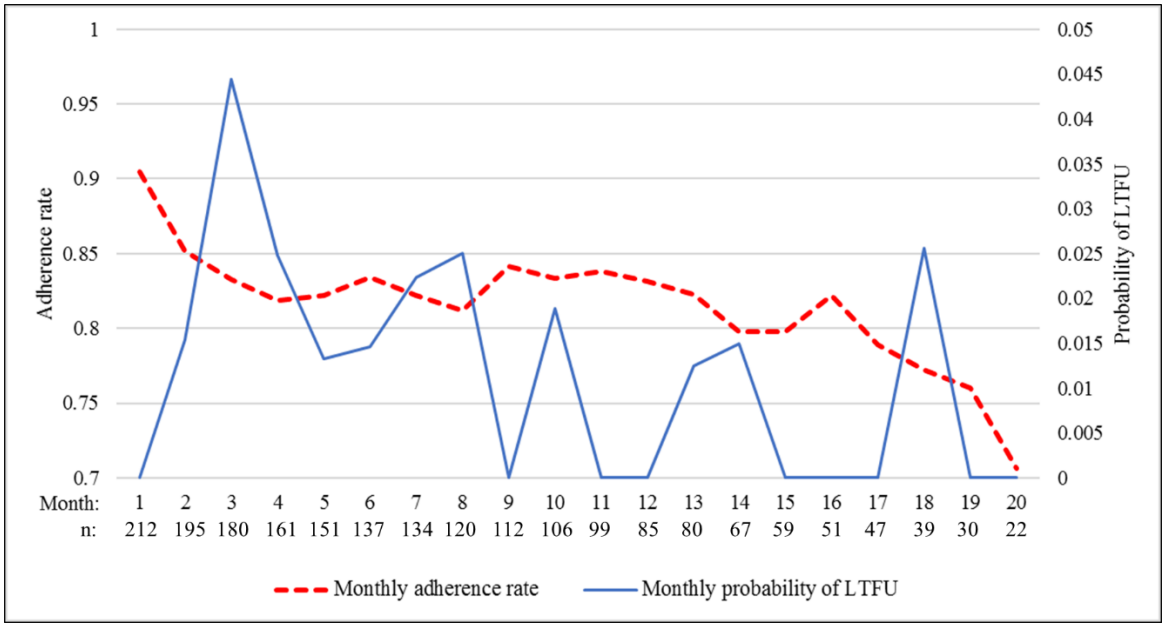
This qualitative model was developed with boundaries and rules grounded in the context of Peru's national TB program (NTP).[29] Within the Latin America and the Caribbean region, Peru accounts for 3.1% of the population, but has 35.3% of the region's MDR-TB cases.[30] Its capital, Lima, has 54% of the country's TB cases, 76% of the MDR-TB cases, and 89% of extremely drug-resistant tuberculosis (XDR-TB) cases.[31]

In Peru, MDR-TB treatment lasts for at least 18 calendar months and follows the WHO's DOT strategy.[32] Community health workers (CHWs) who are able to take the medications to MDR-TB patients are scarce, so a typical patient must go to a public health center administered by the Ministry of Health Monday through Saturday, excluding national holidays, to take their medications so they can be supervised as they swallow their pills. In addition to pills, patients are expected to be on injectable medications for approximately the first six months of treatment (or until obtaining four consecutive negative cultures, tested monthly) unless otherwise specified by their physician; and an LTFU case is defined as a patient who missed doses for 30 continuous days or more.

To recreate the treatment trajectory for MDR-TB patients, we gathered data from a sample of 212 adult patients who initiated treatment between 2013 and 2014 in Lima.[33] Data from medical charts were used to estimate their average monthly adherence rate and probability of LTFU (Figure 4.1). Patients whose data was gathered at a later date during their treatment

contributed more treatment-months of data. Data was available through the day of data collection, or the last day of treatment for LTFU cases. Local data from Peru's national TB program showed similar trends for LTFU timing. The average time, excluding Sundays and holidays, patients had been in treatment at the time of data collection was 243 days (range: 12-771). Data count beyond the 20th month of treatment was excluded because there were fewer than 20 patients' data per month.

Figure 4.1 Patient treatment adherence rate and LTFU by month



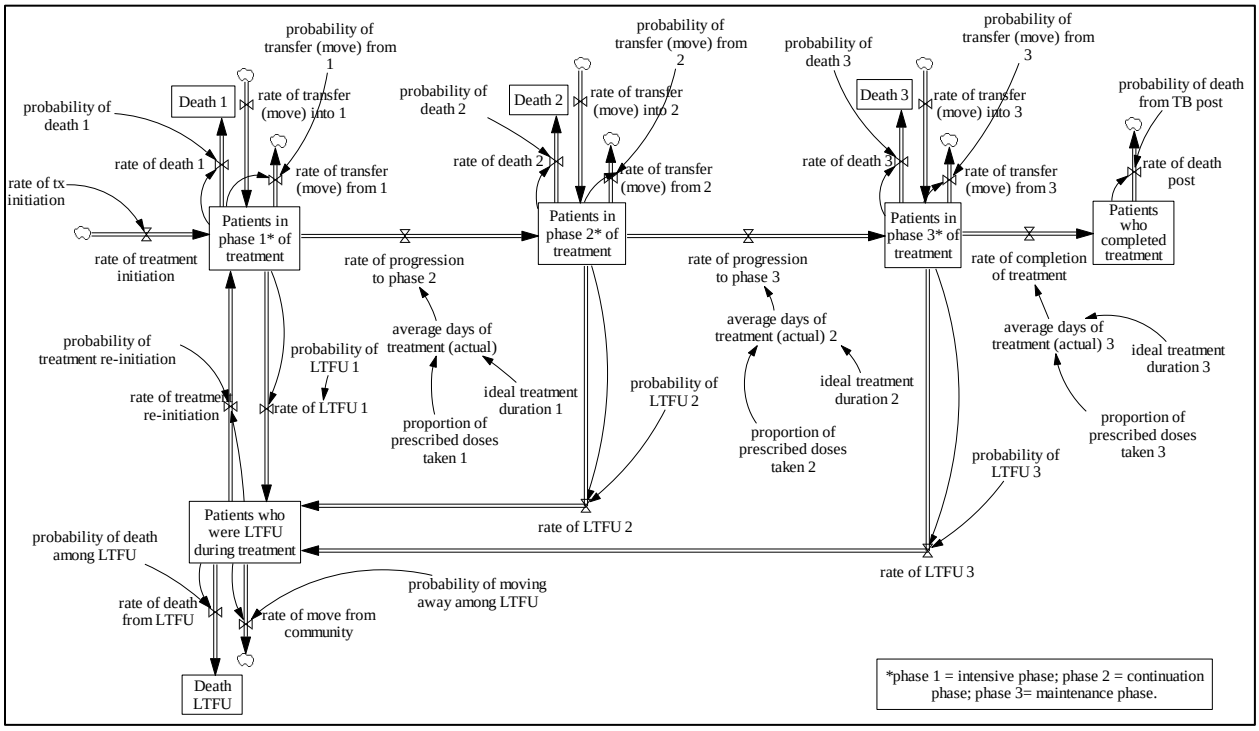
The average treatment adherence rate through the date of data collection, or last day of treatment, was 80% (including LTFU cases while still in treatment). From the start of treatment, adherence rate drops fast between the first and fourth months, plateauing between 81% and 83% until the average last day of the intensive phase. Between the ninth and fourteenth months, there is a slight increase in adherence rate, remaining below 85%. After the 16th month, adherence rates decrease quickly again. However, data after the 16th month must be interpreted with caution due to the decrease in sample size in the later months of treatment. Most (83%) of the LTFU

happened during the first nine months of treatment. A decline in monthly probability of LTFU was observed after the 9th month followed by another peak around the 18th month.

Model development

SD often uses a community-based participatory approach to model development, where the model is built with input from key stakeholders.[34] The qualitative model-building process followed this approach through interviews and focus group discussions with stakeholders in Lima, Peru, for face validation. The model's development was also grounded on scientific evidence; it included information gathered through an extensive PubMed literature review on TB and MDR-TB treatment adherence.[10]

Figure 4.2 System dynamics stock-and-flow diagram of the treatment trajectory for MDR-TB patients



The qualitative SD stock-and-flow diagram in Figure 4.2 illustrates adult MDR-TB patients' disease transitions from treatment initiation to final treatment outcome. The stocks in the model represent people moving from one phase of treatment to the next: becoming LTFU,

dying, or transferring in and out of treatment. For simplicity, other uncommon outcomes in the context of Lima, such as 'unknown' (incomplete or missing data) and 'treatment failure' (e.g. XDR-TB) are included within rates of transfer out of treatment stocks. Differentiation between primary and acquired MDR-TB was not considered because it does not affect the design of interventions that target adherence. Co-infection with human immunodeficiency virus (HIV) was not considered because such cases constitute a small proportion of all MDR-TB cases in Peru.

The qualitative model differentiates among three phases of treatment that were defined by stakeholders, which are supported in the research literature.[10] During the first treatment phase, *intensive*, patients receive a painful injectable drug in their buttocks in addition to receiving pills. The intensive phase is perhaps the most difficult one since patients must accept their disease status and adjust to the new routine, side effects from the medications, and stigma from their communities. When patients enter the second phase of treatment, *continuation*, they stop receiving the injectable drug, but persistent side effects from the pills keep them from returning to work, school, or other 'normal life' activities. In the third and last phase of treatment, which we will call the *maintenance* phase, side effects no longer affect patients' ability to return to 'normal life'. Patients can be LTFU during any of these treatment phases and, if symptoms continue to return, patients must re-initiate treatment from day one. The earlier patients are LTFU, the more likely it is that they are still infectious or that they will become infectious again.

Model parameterization, calibration, and testing

For the parameterization and calibration of the model, we followed guidelines by the International Society for Pharmacoeconomics and Outcomes Research, and the Society for Medical Decision Making.[35,36] Parameterization is the process of deciding and defining the

parameters necessary for the specification of a model. Calibration involves systematic adjustments of model parameter estimates so that the model output more accurately reflects real-world data. The model calibration process is iterative and includes making model parameter changes, re-running the model, re-assessing the results goodness of fit between model and data, and if needed, further adjusting the inputs.

Table 4.1 Model parameters*

VARIABLE	TYPE	DESCRIPTION
Patients in phases 1, 2, 3 of treatment	Stock	The prevalence of patients in phases 1, 2, and 3 of treatment
Patients who were LTFU during treatment	Stock	The prevalence of patients who were LTFU during treatment
Patients who completed treatment	Stock	The prevalence of patients who completed treatment
Death 1, 2, 3	Stock	The prevalence of patients who died during phases 1, 2, and 3 of treatment
Death LTFU	Stock	The prevalence of patients who died after they had been LTFU
Probability of death 1, 2, 3	Constant	The daily probabilities that a patient will die during phases 1, 2, and 3 of treatment
Probability of death among LTFU	Constant	The daily probability that a patient will die after being LTFU during treatment
Rate of death 1, 2, 3	Rate	Death rates for patients during phases 1, 2 , and 3 of treatment
Rate of death from LTFU	Rate	Death rate for patients after they have been LTFU
Rate of transfer (move) into 1, 2, 3	Rate	The rates at which patients transfer, or move, into the system during phases 1, 2, and 3 of treatment
Rate of transfer (move) from 1, 2, 3	Rate	The rates at which patients transfer, or move, out of the system during phases 1, 2, and 3 of treatment
Rate of move from community	Rate	The rate at which patients who were LTFU during treatment move out of the system
Probability of transfer (move) from 1, 2, 3	Constant	The daily probabilities that a patient will transfer or move out of the system during phases 1, 2, and 3 of treatment
Probability of moving away among LTFU	Constant	The daily probability that a patient who was LTFU during treatment will transfer or move out of the system
Rate of treatment initiation	Constant	The expected number of diagnosed MDR-TB patients who start treatment each day
Rate of progression to phases 2, 3	Rate	The rates at which patients move from phase 1 to phase 2, and from phase 2 to phase 3 during treatment
Rate of completion of treatment	Rate	The rate at which patients move from phase 3 to treatment completion
Proportion of prescribed doses taken 1, 2, 3	Constant	The average proportions of prescribed doses taken by patients during phases 1, 2, and 3 of treatment
Ideal treatment duration 1, 2, 3	Constant	Number of days a person would be in treatment during phases 1, 2, and 3, if their adherence rate was 1 (no missed doses)
Average days of treatment (actual) 1, 2, 3	Constant	The actual average number of days a person spends in phases 1, 2, and 3 of treatment (includes missed doses)
Rate of LTFU 1, 2, 3	Rate	LTFU rates for patients during phases 1, 2, and 3 of treatment
Probability of LTFU 1, 2, 3	Constant	The daily probabilities that a patient will be LTFU during phases 1, 2, and 3 of treatment
Rate of treatment re-initiation	Rate	The rate at which patients who were LTFU during treatment return to begin treatment again
Probability of treatment re-initiation	Constant	The daily probability of re-starting treatment among patients who were LTFU during treatment

*phase 1 of treatment = intensive phase; phase 2 of treatment = continuation phase; phase 3 of treatment = maintenance phase

The parameters in the model are defined in Table 4.1 and the inputs and sources are described in Table 4.2. Wherever possible, data was obtained from Peru's NTP and the National Institute of Statistics and Informatics (INEI). Another major data source was a previous study

conducted with MDR-TB patients in Lima, which collected data from patients' daily treatment adherence logs, among other variables. Except for patients' daily treatment adherence logs, the dataset was cross-sectional. A detailed description of this dataset can be found elsewhere.[33] Wherever possible, calculations at each phase of treatment included values found in this study and the published literature.

Table 4.2 Model inputs and sources*

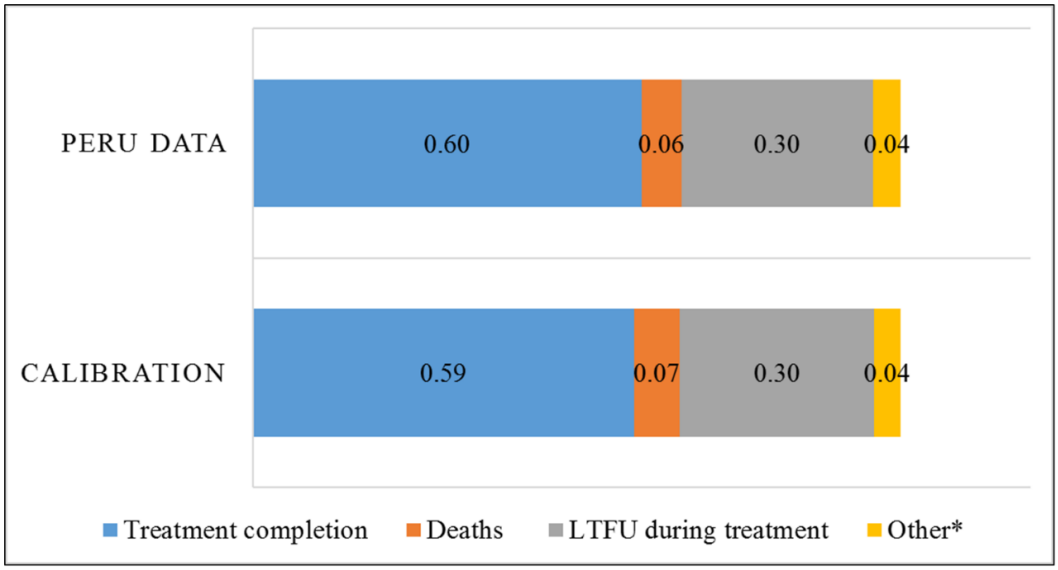
VARIABLE	DESCRIPTION	INITIAL VALUE	CALIBRATED VALUE	SOURCE
Probability of death 1	The daily probability that a patient will die during phase 1 of treatment*	0.00012	0.00015	INEI, NTP
Probability of death 2	The daily probability that a patient will die during phase 2 of treatment*	0.00012	0.00005	NTP
Probability of death 3	The daily probability that a patient will die during phase 3 of treatment*	0.00012	0.00003	NTP
Probability of death among LTFU	The daily probability that a patient will die after being LTFU during treatment	0.0007	0.00013	Emvudu 2011
Rate of transfer (move) into 1	The rate at which patients transfer, or move, into the system during phase 1	0.003	0.0001	Aim 1
Rate of transfer (move) into 2	The rate at which patients transfer, or move, into the system during phase 2	0.003	0.001	Aim 1
Rate of transfer (move) into 3	The rate at which patients transfer, or move, into the system during phase 3	0.003	0.001	Aim 1
Probability of transfer (move) from 1	The daily probability that a patient will transfer or move out of the system during phase 1	0.0003	0.0012	Aim 1
Probability of transfer (move) from 2	The daily probability that a patient will transfer or move out of the system during phase 2	0.0003	0.00005	Aim 1
Probability of transfer (move) from 3	The daily probability that a patient will transfer or move out of the system during phase 3	0.0003	0.0001	Aim 1
Probability of moving away among LTFU	The daily probability that a patient who was LTFU during treatment will transfer or move out of the system	0.0005	0.0004	Aim 1
Rate of treatment initiation	The expected number of diagnosed MDR-TB patients who start treatment each day	2.4	3.2	NTP
Proportion of prescribed doses taken 1	The average proportion of prescribed doses taken by patients during phase 1	0.81	-	Aim 1
Proportion of prescribed doses taken 2	The average proportion of prescribed doses taken by patients during phase 2	0.94	-	Aim 1
Proportion of prescribed doses taken 3	The average proportion of prescribed doses taken by patients during phase 3	0.85	-	Aim 1
Ideal treatment duration 1	Number of days a person would be in treatment during phase 1, if their adherence rate was 1 (no missed doses)	152	-	Aim 1
Ideal treatment duration 2	Number of days a person would be in treatment during phase 2, if their adherence rate was 1 (no missed doses)	101	-	Aim 1
Ideal treatment duration 3	Number of days a person would be in treatment during phase 3, if their adherence rate was 1 (no missed doses)	202	-	Aim 1
Probability of LTFU 1	The daily probability that a patient will be LTFU during phase 1 of treatment	0.0013	0.0012	NTP
Probability of LTFU 2	The daily probability that a patient will be LTFU during phase 2 of treatment	0.0003	0.0002	NTP
Probability of LTFU 3	The daily probability that a patient will be LTFU during phase 3 of treatment	0.0005	0.0005	NTP
Probability of treatment re-initiation	The daily probability of re-starting treatment among patients who were LTFU during treatment	0.00054	0.00054	Marx 2012

*phase 1 of treatment = intensive phase; phase 2 of treatment = continuation phase; phase 3 of treatment = maintenance phase

We initially parameterized the model using the values found in Table 4.2. The model's time step was one day; meaning that the values for the model's parameters were transformed to this scale. At time zero, the model had zero persons in all the stocks. Baseline input parameters were used to calculate the prevalence in each of the stocks each day through mathematical

functions embedded in the model. For example, a stock is the integral of the net flow added to the initial value of the stock, and the net flow is the outflow subtracted from the inflow.[9] The model excluded Sundays and holidays because patients generally do not have access to DOT during those days in Peru. Exclusion of these days resulted in a total of 302 MDR-TB treatment days per year per patient. We ran the model for 10 treatment years to let the model transition from disease-free to endemic equilibrium, where the number of new cases entering the system matches the number of cured cases exiting it.[37]

Figure 4.3. MDR-TB treatment outcomes calibrated to data from Peru (2012)



*Includes patients who transfered health centers, failed treatment, or those without conclusive data for treatment outcomes.

The model was calibrated using the most recent (2012) MDR-TB treatment outcome results from the NTP (Figure 4.3).[38] This calibration helped align the model with real world data for key parameters, and characterize their growth rate over each treatment phase. The process was iterative, in that every time the model reached equilibrium (measured at 10 treatment years), we compared it to the outcomes from Peru and used the discrepancies and

insights gained to improve the model. This process was repeated until the model produced outcomes similar to those in Peru.

The qualitative model was developed with initial face validation [10] and grounded in the published literature. We tested the model via calibration to real systems data (Figure 4.3), goal-seeking (e.g. what-if) analyses, and tests under extreme value conditions. The analyses and tests were conducted under the methodological assumption that if the model did not behave as expected, it would be recalibrated; these analyses and tests also helped compare the overall behavior changes when intervention targets were varied in different treatment phases, and guide the design of plausible implementation strategies.[39]

For the tests under extreme value conditions, we first simulated perfect adherence rate (100%) in each treatment phase. Then we simulated extremely low daily probabilities of LTFU (<0.01%) in each treatment phase. We summarized the results for each of these scenarios and compared them to the baseline (calibrated) treatment outcomes. In addition to the main treatment outcomes – treatment completion, deaths, LTFU during treatment, and other (transfers and other uncommon outcomes) – we also compared the average total number of days a patient would be in treatment across scenarios. The results from the extreme value conditions tests can be found in Appendix F.

Model simulations

Three sets of model simulations were run. In the first set of scenarios, we varied intervention timing (by phase) and target (adherence or LTFU), to determine how much change in each would be required to realize a fixed percent improvement in treatment completion for more targeted (single-pronged) interventions. In the second set, six combination scenarios were run, estimating the impact of optimistic but realistic improvement scenarios, to inform treatment

targets. Finally, we solved for changes required within multi-pronged intervention scenarios that would produce previously observed treatment completion rates of 80% and 83% (currently desired targets). In each scenario, the model was simulated for five intervention years, after reaching an equilibrium (i.e., after running for 10 treatment-years). Results from the simulated treatment outcomes were illustrated using the same bar charts as Peru's NTP for the purposes of comparison and communication to stakeholders.

The first set of simulations used goal-seeking, or what-if analysis, which consists of estimating the change that would be required to achieve a fixed improvement in an outcome.[40] In the first three goal-seeking analyses, we allowed adherence rates in each phase to increase (to a maximum of 1, or perfect adherence) to reach treatment completion targets of 1% and 5% improvements. In the next three goal-seeking analyses, we allowed LTFU rates to decrease to a minimum of 0 (no LTFU) to reach treatment completion targets of 1% and 5% improvements. At baseline, adherence rates during the intensive, continuation, and maintenance phases of treatment, were 0.81, 0.94, and 0.85, and LTFU probabilities were 0.0012, 0.0002, and 0.0005 (correspond to 20%, 2%, and 11% LTFU rates for each phase), respectively (Table 4.2).[33]

In the second set of simulation analysis, we sought to understand the maximum impact of combination (multi-pronged) scenarios, including:

1. *Full Intensive*: All intervention efforts on the intensive phase of treatment to reach 100% adherence and less than 0.01% daily probability of LTFU.
2. *Full Maintenance*: All intervention efforts on the maintenance phase of treatment to reach 100% adherence and less than 0.01% daily probability of LTFU.
3. *Full Combo*: All intervention efforts on the intensive and maintenance phases of treatment to reach 100% adherence and less than 0.01% daily probability of LTFU.

4. *Practical Intensive*: Intervention efforts on the intensive phase of treatment to reach 90% adherence and decrease LTFU by 50%.
5. *Practical Maintenance*: Intervention efforts on the maintenance phase of treatment to reach 90% adherence and decrease LTFU by 50%.
6. *Practical Combo*: Intervention efforts are combined on the intensive and maintenance phases of treatment to reach 90% adherence and decrease LTFU by 50%.

Within the published literature, the best MDR-TB treatment outcomes in Peru were reported in the 1990s, when the DOT strategy was first implemented for MDR-TB patients in the shantytowns of Lima. The reported treatment completion rate was 83%, LTFU 8%, death 8%.[41] To find out what timing and target combination could reach similar treatment completion as in the study from the 1990s, we ran a last set of analysis in which we identified two scenarios: *Plan X* and *Plan Z.* We used goal-seeking analyses, varying adherence and LTFU separately, and at different treatment phases. The goal in Plan X was to achieve a treatment completion rate of 80%. In Plan Z, we sought to achieve 83% treatment completion.

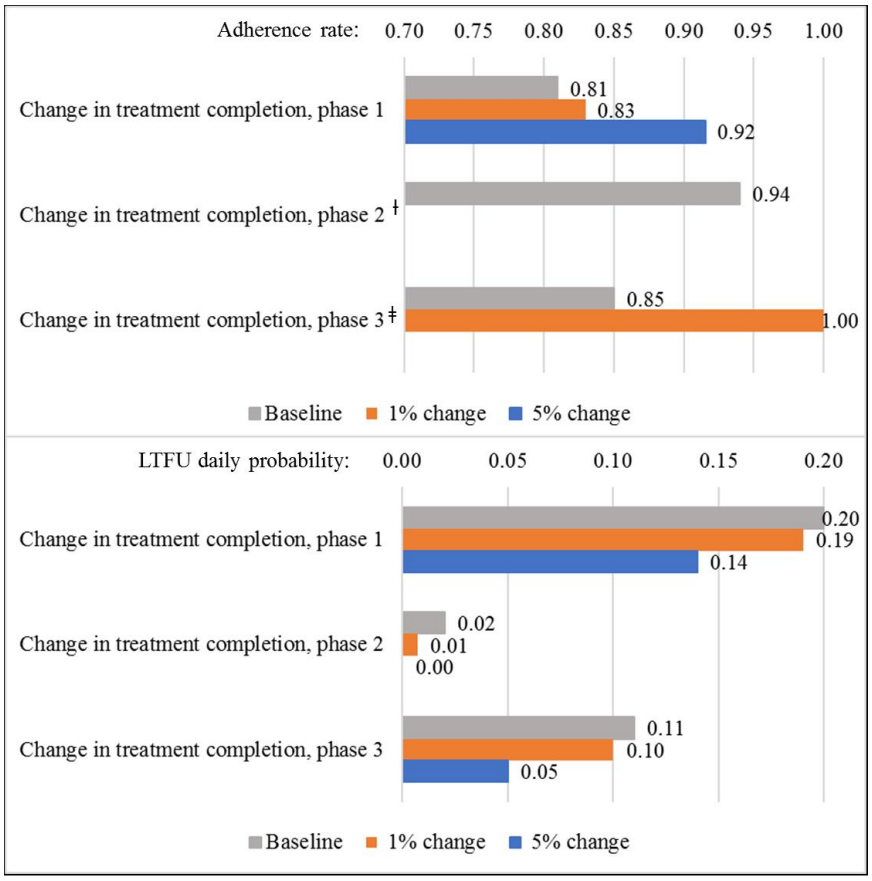
RESULTS

The results from the three sets of simulations – 1% and 5% goal-seeking analysis, six combined interventions, and 80% and 83% treatment completion goal-seeking analysis – are listed below. Additional 1% and 5% goal-seeking analyses can be found in Appendix G.

We highlighted the findings for the goal-seeking analysis of improving treatment completion rates by 1% and 5% in Figure 4.4. To improve treatment completion by 1% during the intensive phase (phase 1), adherence rate had to increase from 0.81 to 0.83, and LTFU daily probability had to decrease from 0.2 to 0.19. A 5% improvement in treatment completion needed an increase of 0.11 in adherence rate (0.81 to 0.92) and a decrease of 0.06 in LTFU daily probability (0.2 to 0.14). Improving adherence rate alone could not improve treatment

completion by 5% during the maintenance phase (phase 3) or by 1% during the continuation phase (phase 2). Improving LTFU daily probability alone did not reach a 1% improvement on treatment completion during the continuation phase (phase 2).

Figure 4.4. Changes in adherence rates and LTFU daily probability needed in each phase* of treatment to increase treatment completion by 1% and 5%

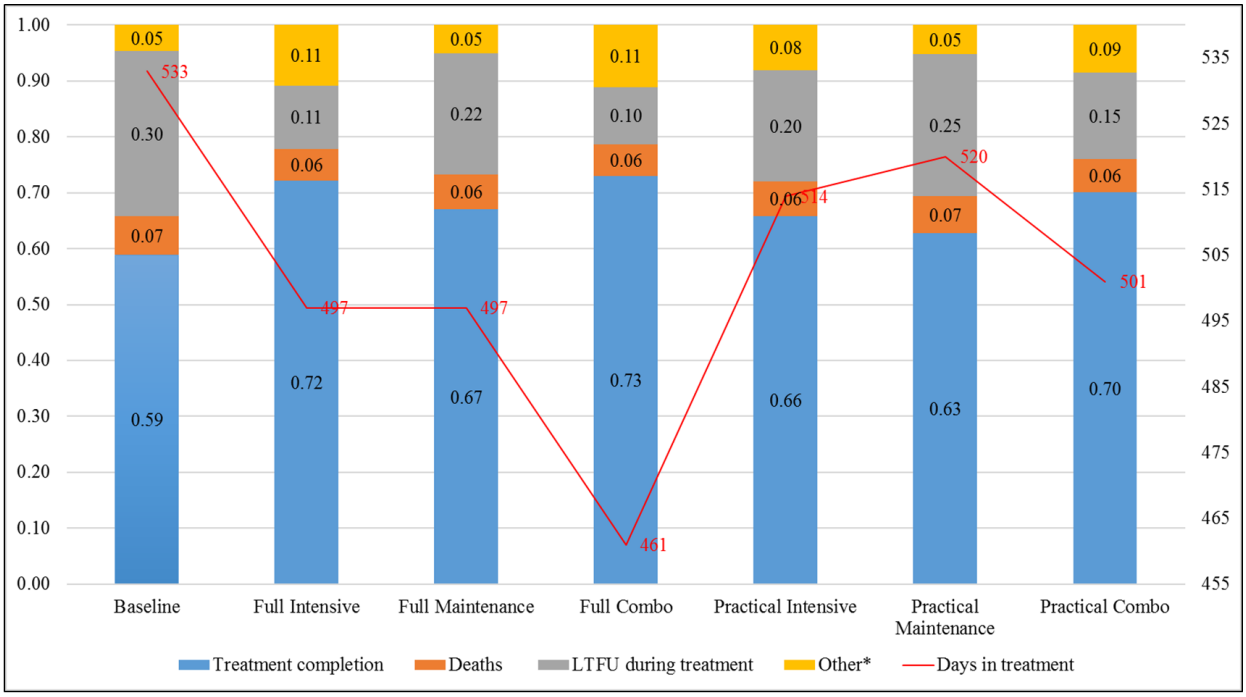


*Phase 1 = intensive phase, phase 2 = continuation phase, phase 3= maintenance phase. ǂ Not possible to improve treatment outcomes by 5% or 1 %; ǂ Not possible to improve treatment outcomes by 5%.

In Figure 4.5, the simulations for combined targets in policy scenarios Full Intensive, Full Maintenance, Full Combo, Practical Intensive, Practical Maintenance, and Practical Combo, showed that treatment outcomes are optimized when adherence is maximized and LTFU minimized during both, the intensive and the maintenance phase; however, it is only slightly better than only maximizing adherence and minimizing LTFU only during the intensive phase. In Full Intensive, 72% of patients completed treatment (1% lower than Full Combo), 10% were

LTFU during treatment (1% higher than Full Combo), and death rate was the same (6%) as in Full Combo. The average total days of treatment was estimated to 497 for Full Intensive and Full Maintenance, but decreased to 461 days for Full Combo.

Figure 4.5 Six policy scenarios and their effects on treatment outcomes

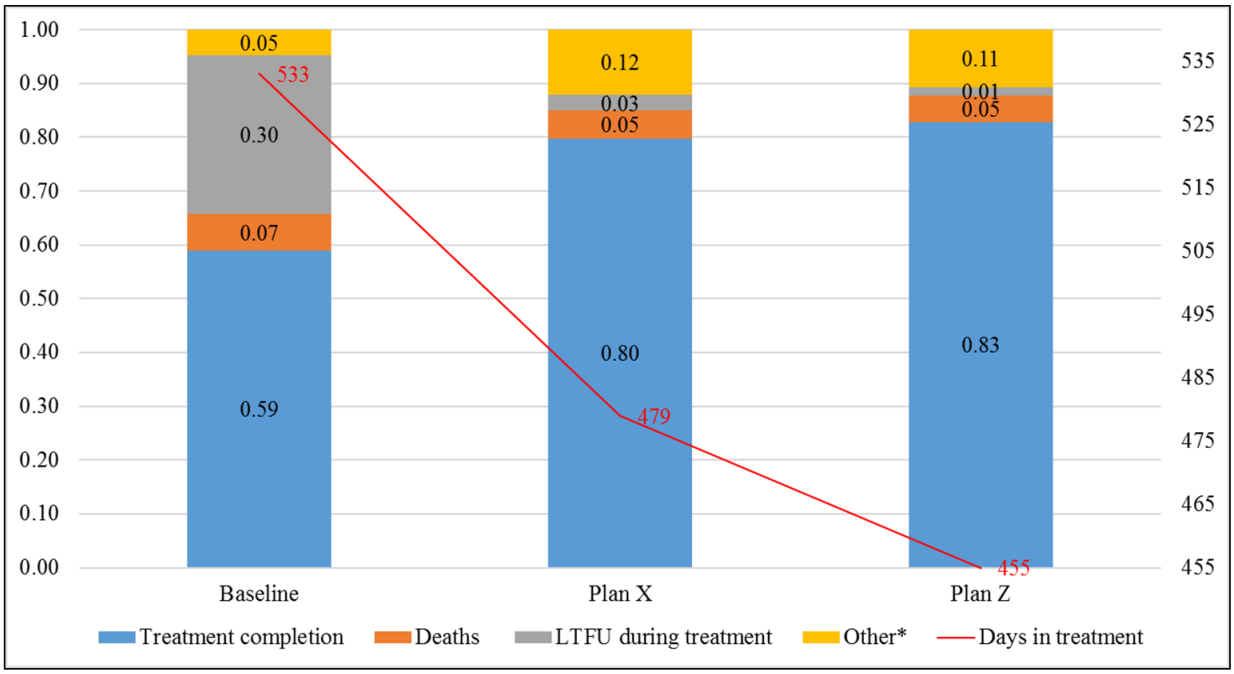


* Includes patients who transfered, failed treatment, or without conclusive treatment outcomes. Baseline represents values from the calibrated model; **Full Intensive**: 100% adherence and <0.01% LTFU daily probability during the intensive phase; **Full Maintenance**: 100% adherence and <0.01% LTFU daily probability during the maintenance phase; **Full Combo**: 100% adherence and <0.01% LTFU daily probability during the intensive and maintenance phases; **Practical Intensive**: 90% adherence and 50% reduction in LTFU during the intensive phase; **Practical Maintenance**: 90% adherence and 50% reduction in LTFU during the maintenance phase; **Practical Combo**: 90% adherence and 50% reduction in LTFU during the intensive and maintenance phases. For each scenario, the average total days in treatment are shown in red.

In scenarios Practical Intensive, Practical Maintenance, and Practical Combo, intervention target objectives were set at slightly lower (practical) standards, resulting in slightly worse outcomes than the first three scenarios. When adherence rate was increased to 90% and LTFU decreased by 50% in both, the intensive and the maintenance phases of treatment (Practical Combo), treatment completion rate reached 70% and LTFU decreased to 15%. Average treatment days remained above 500 for these three scenarios, with the lowest value observed in Practical Combo, at 501 days. Overall, intervention targets that focus their resources

on the intensive phase are more successful than those that focus on the maintenance phase, and a combined intervention implemented during these two phases produced the best treatment outcomes for MDR-TB patients. This was consistent with the results from the tests under extreme value conditions.

Figure 4.6 Policy goal-seeking scenarios Plan X and Plan Z and their effects on treatment outcomes



*Includes patients who transfered health centers, failed treatment, or those without conclusive data for treatment outcomes. Baseline represents values from the calibrated model; **Plan X**: 95% adherence and 1/10 of the calibrated LTFU daily probability during all three phases; **Plan Z**: 100% adherence and 1/20 of the calibrated LTFU daily probability during all three phases. For each scenario, the average total days in treatment are shown in red.

We simulated the goal-seeking scenarios for Plans X and Z to achieve results similar to those from the successful 1990s study. A combined intervention would have to increase adherence to 95% and decrease LTFU daily probability by a tenth throughout treatment to reach 80% treatment completion rate (Figure 4.6). To reach 83% treatment completion, adherence would need to be maintained at 100% and LTFU probability at one twentieth its calibrated value (Plan Z). Average total days in treatment decreased to 479 days in Plan X and 455 days (the ideal/minimum treatment length) in Plan Z.

DISCUSSION

This analysis illustrates how SD methods can be used to transform clinic-based performance data (i.e., adherence and LTFU) into metrics decision makers use as the basis of program monitoring and resourcing; inform strategic planning about what it would take, targeting different "leverage points" for action, to produce a desired change in outcomes; support the development of realistic program targets; and, estimate change requirements to realize a desired outcome target. In this illustration, the complexity studied was the timing and target for change. We compared scenarios to learn about the 'what' (target) and the 'when' (timing) that make an implementation strategy most effective within a specific context. This understanding moved us closer to influencing the full and effective use of innovations in practice. Our model can be used as a decision-making tool in the context of Peru and MDR-TB; however, SD models are flexible and can be applied to many other settings, diseases, and research questions.

Certain health conditions, such as MDR-TB, require patients to adhere to long and difficult treatment regimens. Patients need different types of support throughout treatment, but health systems have limited resources. To our knowledge, this is the first study bringing together implementation science and SD to optimize intervention implementation strategies and improve health outcomes. The impact of effectively implemented interventions go beyond short-term improvement in adherence and outcomes. For MDR-TB, higher adherence means less patients infecting others, developing further resistance to drugs, restarting treatment, or dying. Higher adherence also results in less total days in treatment, which lessens the burden on health care services providers and the health system in general.

Data from Figure 4.1 showed that the first few months of MDR-TB treatment (intensive phase) is when patients' adherence levels quickly drop and most LTFU cases occur, and that

these indicators do not follow similar trends. The results from this study confirms what is suggested by these trends: in this context, interventions are most effective when implemented during the intensive phase. the model also aids in understanding the relative effects of strategies targeting adherence vs. LTFU, and provides insight into how the timing and targets could be combined to reach specific programmatic goals.

For Lima and based on our findings, we would recommend starting with an intervention that matches the targets in the Practical Combo scenario (Figure 4.5), which increases treatment completion from 60% to 70% and reduces total treatment time by 32 days. In this scenario, adherence rates must reach 90%, and LTFU rates cut by half during the intensive and maintenance phases. The next step should be to reach 80% treatment completion, for which adherence rate would need to improve to 95% and LTFU daily probability would need to decrease by one-tenth across all phases of treatment (Figure 4.6). Without combining timing and targets, achieving results above 73% completion rate would be very difficult if not impossible. This information could help national TB programs set reasonable goals for a specific timeframe based on their resources. If costs of achieving specific targets were calculated for a sustainable implementation strategy, the model could be expanded to simulate its cost-savings and lives saved over time, compared to continuing with the status quo.

The 1990's study was implemented within a trial, with resources that are not usually available in Lima. To run their psychosocial support groups, they had nurses and mental health practitioners who were well-trained, willing to work with MDR-TB patients, and compensated appropriately; this approach was unsustainable. Other successful MDR-TB studies implemented interventions such as CHWs, or comprehensive approaches that included active TB case finding, effective treatment, prevention, and patient support. We do not know what (timing, content,

delivery person, frequency, etc.) about these interventions was effective. However, we could test similar sustainable implementation strategies for specific targets and contexts to compare their impact with the application of implementation science and SD. The same is true for other diseases where adherence is key to treatment success.

Another way to expand this decision-making tool in the context of MDR-TB is to simulate targets closer to adherence with the information-motivation-behavioral skills (IMB) model. A previous study applied the IMB model to MDR-TB and showed that adherence is highest when patients have knowledge of the importance of adherence (information), want to take their medications (motivation), and believe they have the skills and resources necessary to take their medications (behavioral skills).[33] According to that study, the difference in adherence rate between a patient with low vs. high behavioral skills is as much as 27% (2.2 points vs. 4 points using a 5-point scale). Even in the scenario Plan X, the largest improvement necessary in adherence, required during the intensive phase, would be 14% (moving adherence from 81% to 95%). This translates into a 0.9-point increase in average behavioral skills. Our tool could be expanded to simulate strategies that increase behavioral skills – CHWs, educational workshops, and psychosocial support groups – in different treatment phases to evaluate their comparative impact.

The visualization of a system structure to understand its behavior is also a benefit of using SD methodology.[10] In our model, for example, the simulated behavior for the outcome "LTFU" is the result of forces pulling in opposite directions. In Figure 4.2, we can see that as we approach the desired treatment outcomes there are fewer patients flowing into the LTFU stock, which means that more people remain in the stocks with patients moving through the phases of treatment. On the other hand, improved outcomes also mean there are fewer patients LTFU, and

therefore, less of them re-initiating treatment. This decreases the number of patients in the phase 1 treatment stock and then the rest of the phases, and the rate at which patients move into the LTFU stock. This explains the range of values simulated for the outcome "LTFU" under various scenarios and can be easily detected visually and then confirmed quantitatively with simulated estimates from the model.

Other uses for SD methodology are planning for the future and avoiding unintended consequences. In the case of MDR-TB, this means predicting the types of technologies that would have positive long-term effects, instead of investing in ones that are likely to fail outside of the trial setting.[42] More specifically, focusing resources on technologies that are likely to decrease adherence barriers during the intensive and maintenance phases. The elimination of injectable medications and milder side effects are part of the solution, but they are not enough. As shown in a previous study, access to treatment for patients who cannot make it to the health center and psychosocial support are also essential to improve adherence and minimize LTFU.[10]

Perhaps one of the main limitations of SD modeling is that it requires expertise in modeling and computation, as do other modeling techniques. Another drawback is that an SD model could become exceedingly complicated with large number of variables and their mathematical relationships.[9] However, we need to apply methodologies that best fit the complex health system where we implement interventions if we intend to understand and improve them.[43] As a tool, SD is very malleable and can adapt to fit different types of systems and settings to answer research questions. It can also model processes that take a long time to turn into outcomes, and test strategies without at relatively low cost. That is the why SD has been

applied for decades in the fields of business and engineering, and has recently emerged in public health fields such as HIV, diabetes, and operational research.[14,44]

Limitations

We calibrated the equilibrium state to local treatment outcome data from 2012 and tested the model with available data that allowed our estimates to be consistent with the observed treatment outcomes in Lima. We had the total numbers for the daily probabilities of deaths, and other uncommon outcomes such as treatment failure and transfers reported post-treatment, but we did not find enough data to differentiate these probabilities between treatment periods prior to calibration. The effect of interventions, such as improved adherence and LTFU, on these uncommon treatment outcomes in different periods of treatment is unknown. However, the daily probabilities for these events are small and its qualitative effect do not affect our policy recommendations. As further data becomes available, the model will need to be validated and adapted to fit different contexts.

CONCLUSIONS

We successfully quantified a qualitative MDR-TB treatment model, and used it as a simulation platform to inform intervention design and decision-making. The simulations showed that interventions aiming to improve MDR-TB treatment outcomes must consider timing and multiple targets during the design of implementation strategies. The application of SD methods to compare implementation strategies could reveal new information about system behavior that affects the design of interventions, and its benefits are not limited by field or setting. Complex systems simulations could be added to the implementation scientist toolbox to support decision-making, improve healthcare service delivery and guide the allocation of resources. SD models

could be further developed to identify cost-effective implementation strategies that close the gap between knowledge and practice for numerous public health problems in various settings.

REFERENCES

1. Implementation Science Defined | NIRN Project site. http://nirn.fpg.unc.edu/learn-implementation/implementation-science-defined. Accessed 13 Mar 2017.

2. Ridde V. Need for more and better implementation science in global health. BMJ Global Health. 2016;1:e000115.

3. Herman DB, Mandiberg JM. Critical Time Intervention: Model Description and Implications for the Significance of Timing in Social Work Interventions. Research on Social Work Practice. 2010;20:502–8.

4. Working Group on Management of Congenital Heart Diseases in India. Consensus on timing of intervention for common congenital heart disease. Indian Pediatr. 2008;45:117–26.

5. Vanderwert RE, Marshall PJ, Iii CAN, Zeanah CH, Fox NA. Timing of Intervention Affects Brain Electrical Activity in Children Exposed to Severe Psychosocial Neglect. PLOS ONE. 2010;5:e11415.

6. Ramdas K, Teisberg E, Tucker A. Four Ways to Reinvent Service Delivery. SSRN Scholarly Paper. Rochester, NY: Social Science Research Network; 2012. https://papers.ssrn.com/abstract=2335946. Accessed 14 Mar 2017.

7. WHO | Global tuberculosis report 2016. WHO. http://www.who.int/tb/publications/global_report/en/. Accessed 18 Feb 2017.

8. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implement Sci. 2013;8:139.

9. Meadows DH. Thinking in Systems: A Primer. White River Junction, Vt: Chelsea Green Publishing; 2008.

10. Alegria-Flores K, Hassmiller Lich KL, Van Rie A, Weiner BJ, Becerra Herrera N: Complex systems: Visualizing multidrug-resistant tuberculosis treatment adherence in a causal loop diagram. In the 21st Annual Conference of The Union-North American Region. Vancouver: The Union-NAR; 2017: 11.

11. Microsoft. Microsoft Excel. Redmond, Washington: Microsoft; 2010.

12. Ventana Systems, Inc. Vensim DSS Software. 2016.

13. Leischow SJ, Milstein B. Systems Thinking and Modeling for Public Health Practice. Am J Public Health. 2006 Mar;96(3):403–5.

14. Atkinson J-AM, Wells R, Page A, Dominello A, Haines M, Wilson A. Applications of system dynamics modelling to support health policy. Public Health Res Pract. 2015;25:e2531531.

15. Hontelez JAC, Lurie MN, Bärnighausen T, Bakker R, Baltussen R, Tanser F, et al. Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study. PLoS Med. 2013;10. doi:10.1371/journal.pmed.1001534.

16. London School of Hygiene & Tropical Medicine. TB Modelling Group. 2016. http://tbmodelling.lshtm.ac.uk/. Accessed 4 Nov 2016.

17. Abubakar I, Zignol M, Falzon D, Raviglione M, Ditiu L, Masham S, et al. Drug-resistant tuberculosis: time for visionary political leadership. Lancet Infect Dis. 2013;13:529–39.

18. Bastard M, Sanchez-Padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, et al. 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.

19. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. PLoS ONE. 2013;8:e70064.

20. Cadosch D, Abel Zur Wiesch P, Kouyos R, Bonhoeffer S. The Role of Adherence and Retreatment in De Novo Emergence of MDR-TB. PLoS Comput Biol. 2016;12:e1004749.

21. Thomas BE, Shanmugam P, Malaisamy M, Ovung S, Suresh C, Subbaraman R, et al. Psycho-Socio-Economic Issues Challenging Multidrug Resistant Tuberculosis Patients: A Systematic Review. PLoS ONE. 2016;11:e0147397.

22. Deshmukh RD, Dhande DJ, Sachdeva KS, Sreenivas A, Kumar AMV, Satyanarayana S, et al. Patient and Provider Reported Reasons for Lost to Follow Up in MDRTB Treatment: A Qualitative Study from a Drug Resistant TB Centre in India. PLoS ONE. 2015;10:e0135802.

23. Liefooghe R, Muynck AD. The dynamics of tuberculosis treatment adherence. J Pak Med Assoc. 2001;51:3–9.

24. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2007;:CD003343.

25. Newell JN, Baral SC, Pande SB, Bam DS, Malla P. Family-member DOTS and community DOTS for tuberculosis control in Nepal: cluster-randomised controlled trial. Lancet. 2006;367:903–9.

26. 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:e0150511.

27. Pasipanodya JG, Gumbo T. A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients. Clin Infect Dis. 2013;57:21–31.

28. Frick M, Zhang A. Patient-Centered TB Treatment Will Require Modernizing Directly-Observed Therapy. Speaking of Medicine. 2013. Available from: http://blogs.plos.org/speakingofmedicine/2013/10/30/patient-centered-tb-treatment-will-require-modernizing-directly-observed-therapy/

29. Ministerio de Salud, Peru. Resolución Ministerial 715-2013/MINSA. Norma Técnica de Salud para la Atención Integral de las Personas afectadas por Tuberculosis. 2013.

30. PAHO WHO | Tuberculosis. Available from: http://www.paho.org/hq/index.php?option=com_topics&view=article&id=59&Itemid=40776&lang=en

31. Ministerio de Salud (2013). Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis. Available from: http://www.tuberculosis.minsa.gob.pe/

32. World Health Organization. WHO | Guidelines for the programmatic management of drug-resistant tuberculosis. WHO. 2011. http://www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/en/.

33. Alegria-Flores K, Wiesen CA, Weiner BJ, Becerra NN, Tovar MA, Evans CA: An innovative approach for designing and implementing drug-resistant tuberculosis treatment adherence interventions. In the 47th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union). Liverpool: The Union; 2016: S96.

34. Community Based System Dynamics | Peter Hovmand | Springer. http://www.springer.com/us/book/9781461487623. Accessed 14 Mar 2017.

35. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-4. Med Decis Making. 2012 Oct;32(5):701–11.

36. Vanni T, Karnon J, Madan J, White RG, Edmunds WJ, Foss AM, et al. Calibrating models in economic evaluation: a seven-step approach. Pharmacoeconomics. 2011 Jan;29(1):35–49.

37. Vynnycky E, White R. An Introduction to Infectious Disease Modelling. 1 edition. New York: Oxford University Press; 2010.

38. Alarcón Guizado VA: Tuberculosis en el Perú: Situación actual y desafíos. 4ta Jornada Científica de Investigación Peruana para el Control de la Tuberculosis, Lima, March 16-17, 2016.

39. Sterman J. Business Dynamics: Systems Thinking and Modeling for a Complex World. Irwin: McGraw-Hill; 2000.

40. O'Brien J, Marakas G. Management Information Systems. 10 edition. New York: McGraw-Hill Education; 2010.

41. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcántara F, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med. 2003;348:119–28.

42. Khan F: Meta-analysis of Short-Course MDR-TB Treatment Regimens. 21st Annual Conference The Union-North America Region; Vancouver, 2017.

43. Northridge ME, Metcalf SS. Enhancing implementation science by applying best principles of systems science. Health Res Policy Syst. 2016;14:74.

44. Aarons GA, Sommerfeld DH, Chi BH, Ezeanolue EE, Sturke R, Guay L, et al. Concept Mapping of PMTCT Implementation Challenges and Solutions Across 6 sub-Saharan African Countries in the NIH-PEPFAR PMTCT Implementation Science Alliance. J Acquir Immune Defic Syndr. 2016;72 Suppl 2:S202-206.

CHAPTER V: CONCLUSION

The dissertation project's global hypothesis was that *how* we implement strategies that target adherence to improve MDR-TB treatment outcomes is key to understanding and solving this complex public health problem. The analyses in Aims 1-3 show that adherence is a complex behavior and we need interventions that are designed to improve the patients' information, motivation, and behavioral skills with implementation strategies that are intentionally chosen and measured. Implementation strategies – *what, when, how, who* – must be evidence-based and have a long-term sustainability plan. Adherence, and LTFU, should be monitored during treatment, while interventions are finetuned to fit the context and maximize its impact prior to scaling-up. Though LTFU is an extension of adherence (LTFU is defined as zero adherence for a month of more), their determinants are not identical and we should consider interventions accordingly. The application of implementation science and SD methodology could facilitate and fast-track the process of improving these strategies, close the gap between knowledge and practice, and inform the allocation of resources to minimizing waste.

In Aim 1, the theory-based IMB model was applied in the context of MDR-TB. The model showed that adherence is a function of behavioral skills (self-efficacy), which is in turn is a function of knowledge and motivation. Therefore, implementation strategies could use these three indicators to design, monitor, and evaluate intervention components that target adherence. The direct effect of provider's work engagement on adherence is a reminder that we also must train, motivate, protect, and support the overworked staff who work in highly infectious

environments. As other studies have shown, previous LTFU was a strong driver for lower adherence.[1] However, even when the past cannot be changed, we should explore how to overturn its negative implications. Finally, one more idea for intervention components surging from Aim 1 and supported by the literature would be social support.[2] It does not seem to matter who it comes from, as long as the patient perceives being supported emotionally and/or financially by someone, it has an indirect positive effect on MDR-TB treatment adherence.

The second aim served to develop a qualitative SD model of the complex system that results in adherence in the context of the MDR-TB treatment trajectory. One of the most interesting findings was that the determinants of adherence differ in direction and magnitude over time. This means that one-size does not fit all, and intervention design should consider timing, targets, and intensity. Another finding was that few published studies focused on adherence as a continuous measure of daily behavior compared to as a binary definition for LTFU post-treatment. This hinders our ability to learn about the adherence process that results in poor outcomes (including LTFU). In the reviewed literature, studies usually focused or reported only on one or two aspects of this complex system of elements, connections, and time. These oversimplifications result in misperceptions and our inability to infer the dynamics of the complex system of adherence behavior, all of which could cause inefficiencies and unintended negative consequences over time.[3,4] The visual SD representation of MDR-TB treatment adherence was useful in generating insights and future directions for implementation research.

In Aim 3, the qualitative model was parameterized, calibrated, and validated using SD methodology as a tool for implementation science research. Various intervention implementation scenarios were simulated to compared their effect on treatment outcomes using SD simulations. The inferred relationships between timing, targets, and intensity, and treatment outcomes from

Aim 2 were confirmed with the quantified model. Most specifically, interventions implemented during the intensive phase of treatment had the greatest impact, and targeting LTFU daily probabilities had a greater impact than targeting adherence on treatment outcomes. This is in line with the trends of daily adherence and LTFU cases over time, which shows that the determinants of these two variables are not identical. According to our estimates, interventions that combined timing and targets, with moderately high intensity resulted in significant improvements in treatment outcomes. The decision-making tool resulting from the application of SD methodology to conduct implementation science research could improve healthcare service delivery and guide the allocation of resources.

Beyond the lessons from Aim 3, SD methodology has much more to offer to the field of implementation science. The questions of what, why, how, when, and for whom an intervention is effective can be programmed in SD, and simulated to fit a specific context by changing the corresponding model inputs. These are questions that could otherwise be complicated to ask in a randomized clinical trial or would not fit the more commonly used linear regression models. There is also the advantage of visualizing mental models for complex systems. Group model-building exercises clarify some aspects of a system's behavior even before the quantification of the model. This is what happened for the qualitative model in Aim 2, which produced several hypotheses that were later confirmed in Aim 3, quantitatively. Adding SD methodology to the implementation science toolbox could support research that translates knowledge into practice.

The results of this dissertation also have implications for the field of MDR-TB and TB at large. The study from the 1990s,[5,6] achieved 83% treatment completion even when their diagnostic and treatment options were more limited than they are now, but their implementation strategy (psychosocial support groups in a trial setting) were not sustainable. We could attain

similar results with implementation strategies that are evidence-based and likely to have long-term sustainability. In this dissertation, the IMB model was applied to MDR-TB treatment to understand the basic determinants of adherence (Aim 1); we expanded on the IMB model by developing a broader qualitative map of the barriers and facilitators to adherence over time using SD methodology to visualize the problem (Aim 2); and generated a simulation platform to compare options for implementation strategies and predict their impact on treatment outcomes (Aim 3). The findings show that reducing the length of treatment is important, but investments would have a greater impact by supporting patients, particularly during the intensive phase of treatment. Lastly, daily adherence and LTFU are essential indicators for poor treatment outcomes and national TB programs would benefit from collecting and analyzing this data to measure and improve the impact of their interventions in real-time.

Patients experience daily barriers to adherence. Healthcare service providers usually do not have the resources they need to recognize or address these barriers, which results in low fidelity to DOT. Auxiliary services such as psychologists, nutritionists, and CHWs are stretched thin across the health centers' catchment population, and providers would rather not work with TB patients for fear of infection. In a city where treatment completion is 60% and LTFU reaches 30%, effective solutions are desperately needed.

This story is not unique to Lima, and examples of successful interventions are spread across the world. We should learn from these lessons to find the most cost-effective solutions. Implementation science can help us identify the questions we should be asking, such as *how* are successful interventions implemented. SD methodology can help us answer those questions through group model-building and simulations. As evidence builds, the SD model could incorporate this data and become a more robust decision-making tool. This tool could aid in

promoting evidence-based policy-decision making not just for TB, but also for other complex public health problems. This tool could be further adapted to conduct comparative cost-effectiveness and cost-benefit analyses to inform resource allocation in resource-limited settings. Thus, improving the effective allocation of resources at local, national, and global levels.

The IMB model, SD methodology, and implementation science could play an important role in translating evidence into practice. For MDR-TB, these tools have been successfully used in this project to develop, test, and apply a model that describes how treatment adherence, and consequently, treatment outcomes, could be improved. Future research should focus on improving the robustness of the SD model through a longitudinal study to answer questions related to costs and to finetune intervention implementation strategies. The author hopes that the results of this dissertation become a small but significant step towards decreasing the global burden of MDR-TB and improving the lives of patients.

REFERENCES

1. Tola HH, Tol A, Shojaeizadeh D, Garmaroudi G. Tuberculosis Treatment Non-Adherence and Lost to Follow Up among TB Patients with or without HIV in Developing Countries: A Systematic Review. Iran J Public Health. 2015 Jan;44(1):1–11.

2. Thomas BE, Shanmugam P, Malaisamy M, Ovung S, Suresh C, Subbaraman R, et al. Psycho-Socio-Economic Issues Challenging Multidrug Resistant Tuberculosis Patients: A Systematic Review. PLoS ONE. 2016;11(1):e0147397.

3. Kampmann C, Sterman JD. Feedback complexity, bounded rationality, and market dynamics. Cambridge, MA; 1998.

4. Paich M, Sterman JD. Boom, Bust, and Failures to Learn in Experimental Markets. Manag Sci. 1993;39(12):1439–58.

5. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcántara F, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med. 2003;348:119–28.

6. 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. Global Public Health. 2007 Oct 1;2(4):404–17.

APPENDIX A. FIRST MODEL DRAFT

The first draft of the causal loop diagrams (CLD) for each period of treatment was based on the initial round of interviews and focused group discussions (FGDs) with key stakeholders.

Figure 3.A1 Intensive phase CLD of factors associated with MDR-TB treatment adherence, first model draft

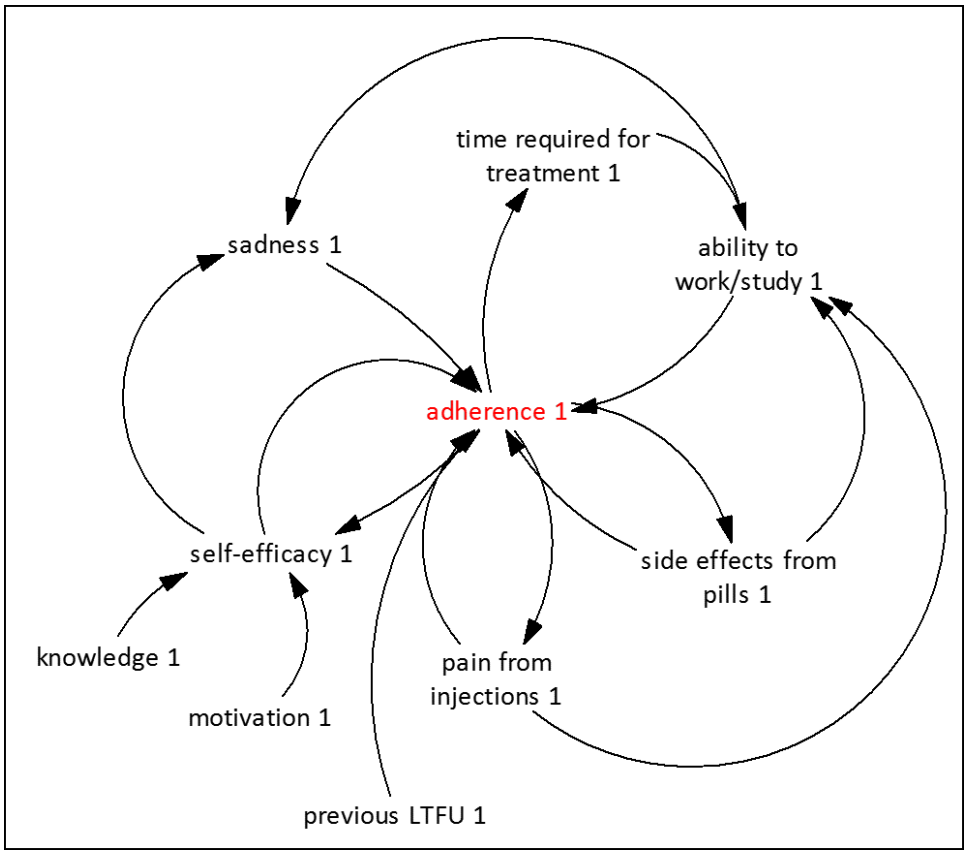


Figure 3.A2 Continuation phase CLD of factors associated with MDR-TB treatment adherence, first model draft

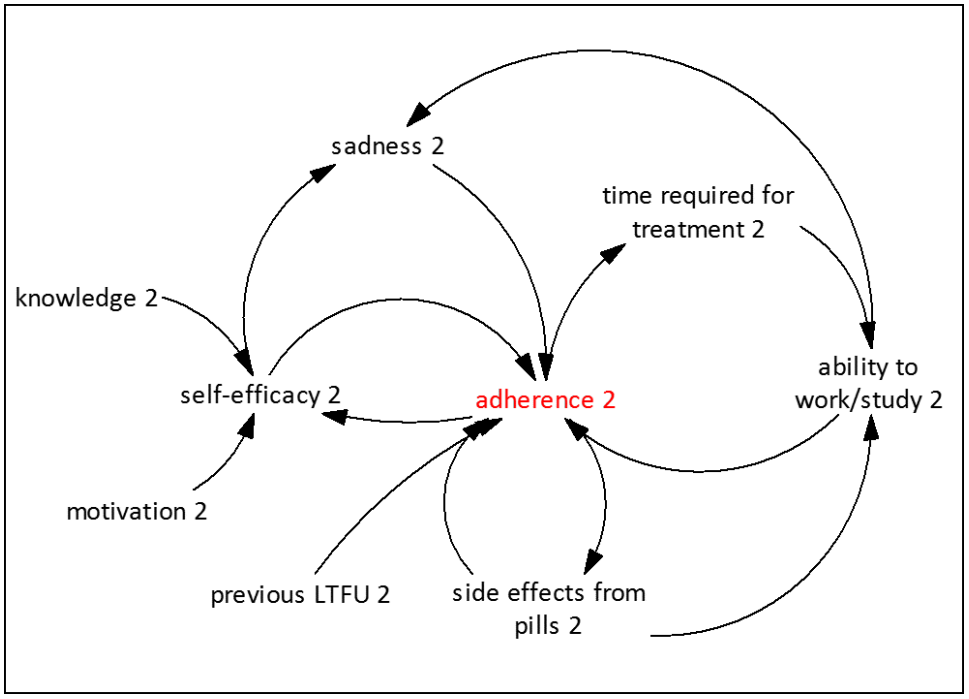
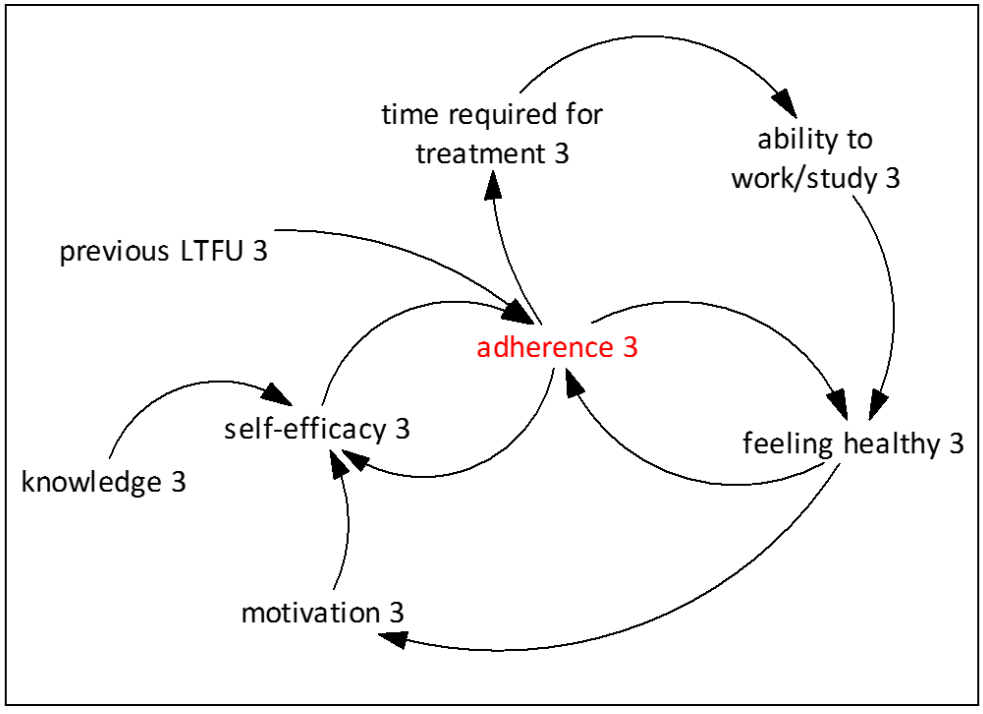


Figure 3.A3 Maintenance phase CLD of factors associated with MDR-TB treatment adherence, first model draft



APPENDIX B. LITERATURE REVIEW SEARCH STRATEGIES

Literature search strategies were developed combining PubMed terms for TB and the factors that were identified in the first model draft.

Total search strategies: 136

Source: PubMed

Search date: August 4, 2016

Total search results = 22,643 titles

Exploratory search for systematic reviews:

Terms	Search strategy	Results
MDR-TB and all terms related to adherence and LTFU, limited to systematic reviews	(“mdr-tb” OR “Tuberculosis, Multidrug Resistant” [mh]) AND (“fidelity” OR "adherence" OR "compliance" OR "abandon" OR "default" OR “irregular” OR "lost to follow up"[mh]) AND “systematic review”	13
TB and all terms related to adherence and LTFU, limited to systematic reviews	"Tuberculosis"[mh] AND (“fidelity” OR "adherence" OR "compliance" OR "abandon" OR "default" OR “irregular” OR "lost to follow up"[mh]) AND “systematic review”	48

Search of tuberculosis AND individual terms (not limited to systematic reviews):

Terms	Search strategy	Results
Adherence	"Tuberculosis"[mh] AND (“fidelity” OR "adherence" OR "compliance" OR “irregular”)	3225
Previous LTFU	"Tuberculosis"[mh] AND (“history of abandonment” OR “history of default” OR “previous abandonment” OR “previous default” OR “incomplete treatment” OR "lost to follow up"[mh])	149
Sadness, depression	"Tuberculosis"[mh] AND (“depression”[mh] OR “sad” OR “despair” OR “mental health” OR “psychosocial” OR “stigma” OR “self-esteem” OR “social isolation” OR “loneliness” OR “shame”)	627
Side effects from pills	"Tuberculosis"[mh] AND (“side effects” OR “adverse reactions” OR “drug toxicity” OR “drug-related side effects and adverse reactions”[mh])	2797
Pain from injectable drugs	"Tuberculosis"[mh] AND (“side effects” OR “adverse reactions” OR “drug toxicity” OR “drug-related side effects and adverse reactions”[mh]) AND (“injection” OR “injectable”)	43

Time in treatment	"Tuberculosis"[mh] AND (“time in treatment” OR “length of treatment” OR “duration of treatment” OR “treatment duration”)	488
Ability to work/study	"Tuberculosis"[mh] AND (“work” OR “have a job” OR “time to work” OR “school” OR “go to school” OR “time to study” OR “normal life”)	16930
Behavioral skills	"Tuberculosis"[mh] AND (“behavioral skills” OR “self efficacy”[mh])	9
Information	"Tuberculosis"[mh] AND (“information” OR “patient medication knowledge”[mh])	3246
Motivation	"Tuberculosis"[mh] AND (“motivation”[mh] OR “incentive” OR “disincentive”)	256
Financial difficulties	"Tuberculosis"[mh] AND (“financial difficulties” OR “catastrophic costs” OR “cost of illness”[mh] OR “economic burden of disease”)	260
Substance abuse, drugs	"Tuberculosis"[mh] AND (“substance abuse” OR “substance-related disorders”[mh] OR “drug dependence” OR “drug addiction”)	1527
Sex	"Tuberculosis"[mh] AND (“sex” OR “gender” OR “male” OR “female” OR “men” OR “women”)	70399
Employed	"Tuberculosis"[mh] AND (“work” OR “have a job” OR “time to work” OR “employed”)	3531
Substance abuse, alcohol	"Tuberculosis"[mh] AND (“alcohol addiction” OR “alcohol dependence” OR “alcohol abuse”)	143
Clinic hours	"Tuberculosis"[mh] AND (“clinic hours” OR “hours of operation” OR “accessibility”)	626
Feeling better	"Tuberculosis"[mh] AND (“feel healthy” OR “feel better”)	13
Studies	"Tuberculosis"[mh] AND (“school” OR “go to school” OR “time to study”)	14505

Examples of combined searches:

Terms	**Search strategy**	**Results**
Adherence & depression	"Tuberculosis"[mh] AND (“fidelity” OR "adherence" OR "compliance" OR “irregular”) AND (“depression”[mh] OR “sad” OR “despair” OR “mental health” OR “psychosocial” OR “stigma” OR “self-esteem” OR “social isolation” OR “loneliness” OR “shame”)	128
Adherence & side effects from pills	"Tuberculosis"[mh] AND (“fidelity” OR "adherence" OR "compliance" OR "abandon" OR "default" OR “irregular” OR "lost to follow up"[mh]) AND (“side effects” OR “adverse reactions” OR “drug toxicity” OR “drug-related side effects and adverse reactions”[mh])	262

APPENDIX C. REFERENCES FOR NUMBERED LINKS IN THE MODEL

Table 3.C1 Matrix with labeled links

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Adherence																
2. Previous LTFU	1															
3. Sadness	2	16														
4. Side effects from pills	3	17	30													
5. Pain from injections	4	18	31	43												
6. Time in treatment	5	19	32	44	55											
7. Self-efficacy	6	20	33	45	56	66										
8. Knowledge about disease	7	21	34	46	57	67	76									
9. Motivation	8	22	35	47	58	68	77	85								
10. Financial difficulties	9	23	36	48	59	69	78	86	93							
11. Substance abuse	10	24	37	49	60	70	79	87	94	100						
12. Male (vs. female)	11	25	38	50	61	71	80	88	95	101	106					
13. Employed	12	26	39	51	62	72	81	89	96	102	107	111				
14. Clinic hours	13	27	40	52	63	73	82	90	97	103	108	112	115			
15. Feeling healthy	14	28	41	53	64	74	83	91	98	104	109	113	116	118		
16. Studies	15	29	42	54	65	75	84	92	99	105	110	114	117	119	120	

Table 3.C2 List of references used as empirical evidence for the links in the model

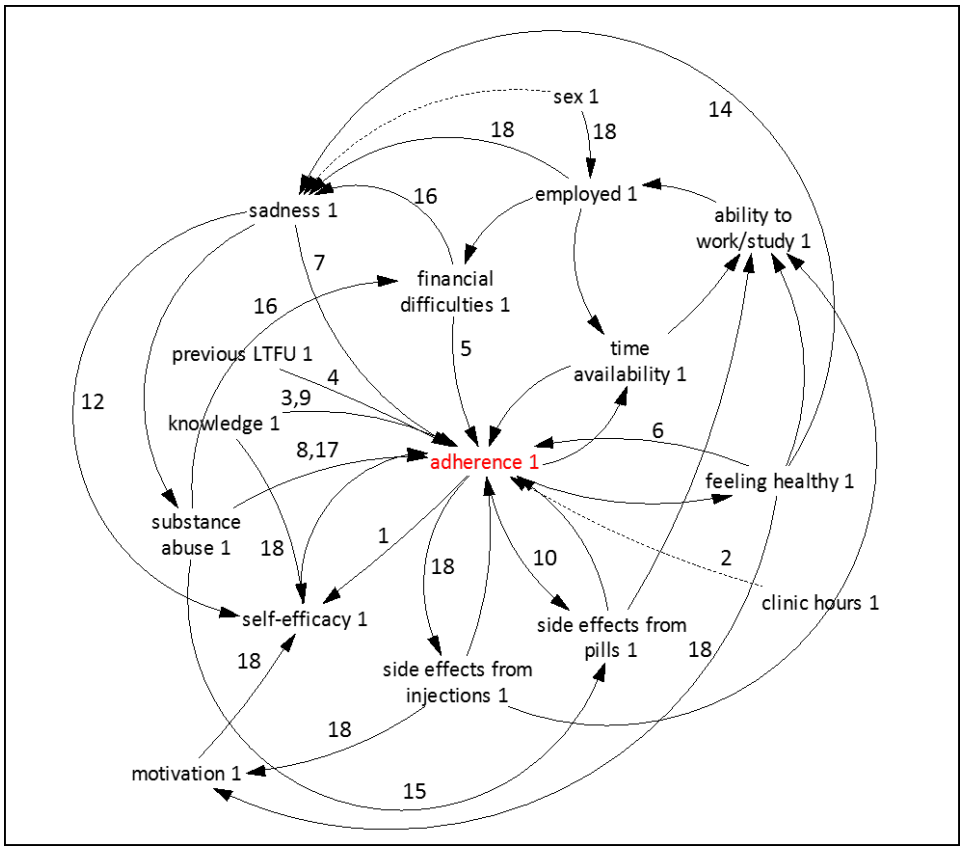
No	**Reference**	**Link # from matrix**
1	Morisky DE, Malotte CK, Ebin V, Davidson P, Cabrera D, Trout PT, et al. Behavioral interventions for the control of tuberculosis among adolescents. Public Health Rep. 2001;116:568–74.	6
2	Naing NN, D'Este C, Isa AR, Salleh R, Bakar N, Mahmod MR. Factors contributing to poor compliance with anti-TB treatment among tuberculosis patients. Southeast Asian J Trop Med Public Health. 2001;32:369–82.	10, 13
3	O'Boyle SJ, Power JJ, Ibrahim MY, Watson JP. Factors affecting patient compliance with anti-tuberculosis chemotherapy using the directly observed treatment, short-course strategy (DOTS). Int J Tuberc Lung Dis. 2002;6:307–12.	7, 9, 12
4	Salami AK, Oluboyo PO. Management outcome of pulmonary tuberculosis: a nine year review in Ilorin. West Afr J Med. 2003;22:114–9.	1, 10
5	Woith WM, Larson JL. Delay in seeking treatment and adherence to tuberculosis medications in Russia: a survey of patients from two clinics. Int J Nurs Stud. 2008;45:1163–74.	2, 9
6	Ibrahim LM, Hadejia IS, Nguku P, Dankoli R, Waziri NE, Akhimien MO, et al. Factors associated with interruption of treatment among Pulmonary Tuberculosis patients in Plateau State, Nigeria. 2011. Pan Afr Med J. 2014;17:78.	7, 14
7	Theron G, Peter J, Zijenah L, Chanda D, Mangu C, Clowes P, et al. Psychological distress and its relationship with non-adherence to TB treatment: a multicentre study. BMC Infect Dis. 2015;15:253.	2, 7, 10, 37, 38

8	Méda ZC, Lin Y-T, Sombié I, Maré D, Morisky DE, Chen Y-MA. Medication-adherence predictors among patients with tuberculosis or human immunodeficiency virus infection in Burkina Faso. J Microbiol Immunol Infect. 2014;47:222–32.	1, 7, 9, 10
9	Bam TS, Gunneberg C, Chamroonsawasdi K, Bam DS, Aalberg O, Kasland O, et al. Factors affecting patient adherence to DOTS in urban Kathmandu, Nepal. Int J Tuberc Lung Dis. 2006;10:270–6.	7
10	Kisambu J, Nuwaha F, Sekandi JN. Adherence to treatment and supervision for tuberculosis in a DOTS programme among pastoralists in Uganda. Int J Tuberc Lung Dis. 2014;18:799–803.	3
11	Wei X-L, Yin J, Zou G-Y, Zhang Z-T, Walley J, Harwell J, et al. Treatment interruption and directly observed treatment of multidrug-resistant tuberculosis patients in China. Int J Tuberc Lung Dis. 2015;19:413–9.	11
12	Robinson-Smith G, Johnston MV, Allen J. Self-care self-efficacy, quality of life, and depression after stroke. Arch Phys Med Rehabil. 2000;81:460–4.	33
13	Masumoto S, Yamamoto T, Ohkado A, Yoshimatsu S, Querri AG, Kamiya Y. Prevalence and associated factors of depressive state among pulmonary tuberculosis patients in Manila, The Philippines. Int J Tuberc Lung Dis. 2014;18:174–9.	30
14	Rajeswari R, Muniyandi M, Balasubramanian R, Narayanan PR. Perceptions of tuberculosis patients about their physical, mental and social well-being: a field report from south India. Soc Sci Med. 2005;60:1845–53.	41
15	Keshavjee S, Gelmanova IY, Shin SS, Mishustin SP, Andreev YG, Atwood S, et al. Hepatotoxicity during treatment for multidrug-resistant tuberculosis: occurrence, management and outcome. Int J Tuberc Lung Dis. 2012;16:596–603.	49
16	Louwagie GM, Wouters E, Ayo-Yusuf OA. Poverty and substance use in South African tuberculosis patients. Am J Health Behav. 2014;38:501–9.	36, 100
17	Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. PLoS ONE. 2013;8:e70064.	10
18	Aim 1 dataset	1, 4, 10, 15, 39, 41, 48, 58, 76, 77, 92, 98, 111, 117

APPENDIX D. SECOND MODEL DRAFT

The second model draft incorporated data collected during the literature review into the first model draft. The links are labeled with numbers for some of the articles that had empirical evidence to support the relationships. The complete list of articles and the links supported by each one can be found in Appendix C.

Figure 3.D1 Intensive phase CLD of factors associated with MDR-TB treatment adherence, second model draft



As an indirect link example, the gender (sex) of the patient is frequently found to have a statistically significant association with LTFU in multivariate analyses. We found one multivariate analysis where the association between sex and treatment interruption (adherence proxy) had p-value=0.046. Stakeholders had reported that sex did not play a direct role to adherence; however, they explained that the head of a household is often responsible for the

family income, and men had a slightly higher probability of being the head of a household than women in Lima, Peru. Thus, our link sex→adherence is indirect.

The default criterion was to incorporate statistically significant evidence into the model as direct links. A few exceptions were made for indirect links when evidence was inconclusive (univariate analysis or t-tests) or stakeholders had reported a detailed description of the indirect link. When evidence from the literature did not coincide with the data from interviews and FGDs, we used dotted lines for links. The links in dotted lines were further discussed with stakeholders during the final round of interviews and FGDs.

Figure 3.D2 Continuation phase CLD of factors associated with MDR-TB treatment adherence, second model draft

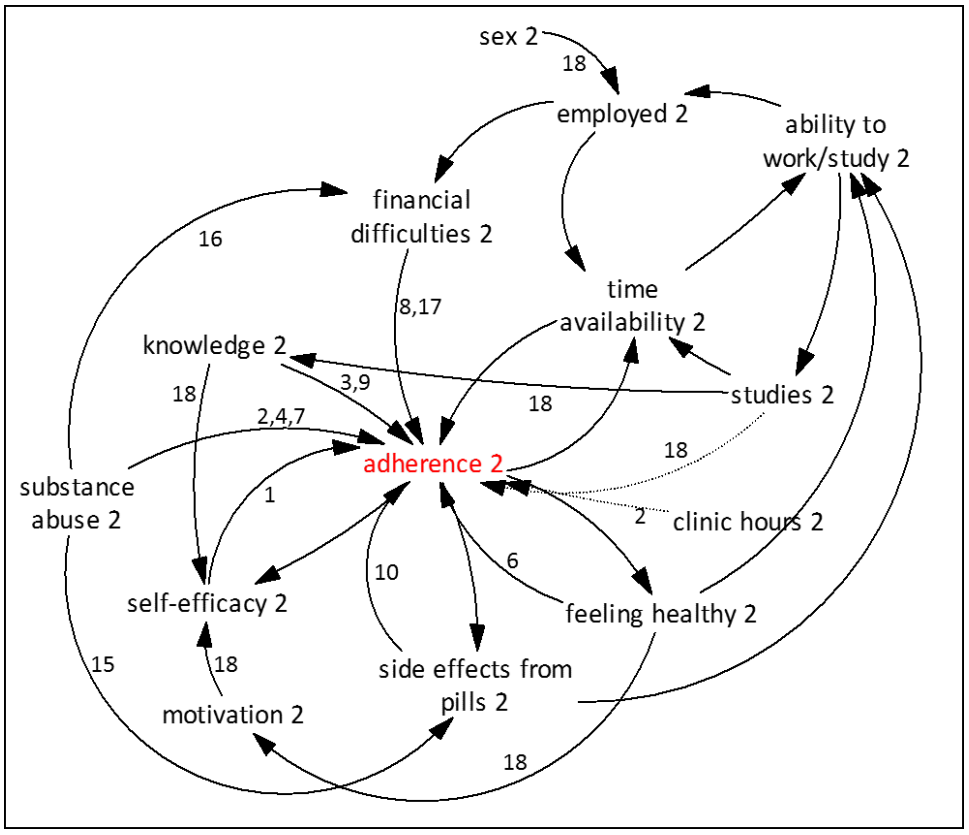
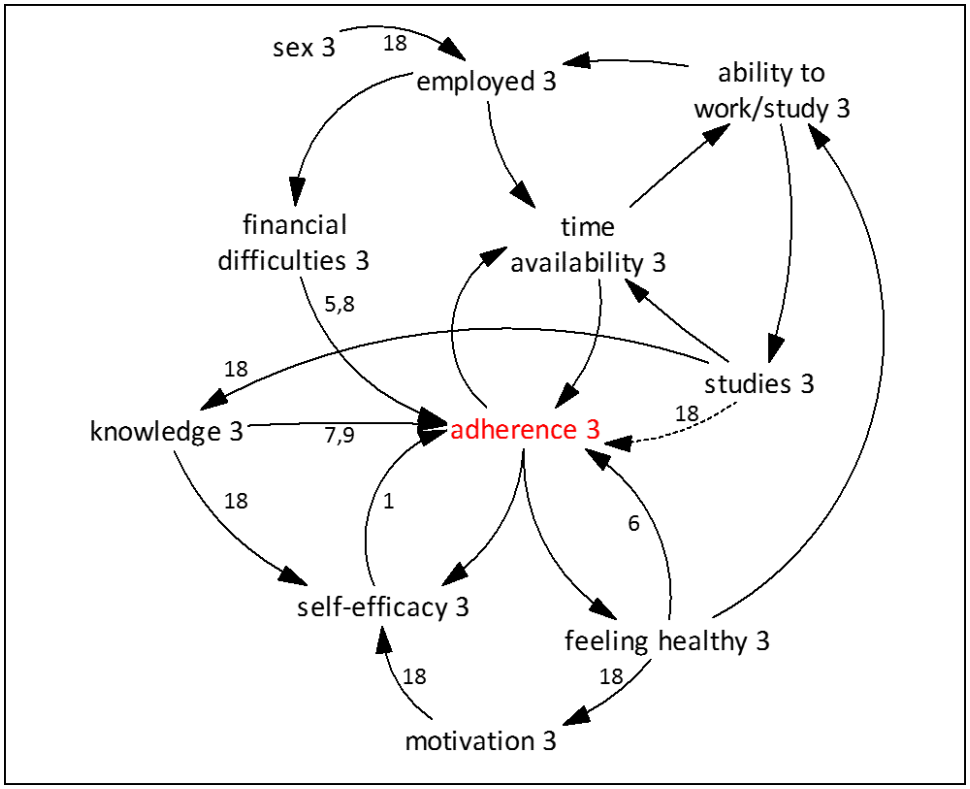


Figure 3.D3 Maintenance phase CLD of factors associated with MDR-TB treatment adherence, second model draft



APPENDIX E. FEEDBACK LOOPS BY TREATMENT PHASE

(*included in the model)

INTENSIVE PHASE

No	Length	Variables	Name	Category
R1*	2	Adherence, self-efficacy, adherence	building/losing confidence	Cognitive
B2*	2	Adherence, time availability, adherence	time/adherence trade-off	Convenience
B3*	2	Adherence, side effects from pills, adherence	comfort/adherence trade-off	Biomedical
B4*	2	Adherence, pain from injections, adherence	comfort/adherence trade-off	Biomedical
R5*	2	Adherence, knowledge about disease, adherence	more/no change in knowledge acquisition	Cognitive
R6*	3	Adherence, knowledge about disease, self-efficacy, adherence	adherence perpetuated through knowledge acquisition and confidence	Cognitive
B7*	4	Adherence, time availability, time between doses, side effects from pills, adherence	B2 extends to affect B3	Convenience – biomedical
R8	4	Adherence, self-efficacy, sadness, substance abuse, adherence	Adherence perpetuated when confidence mitigates destructive behavior	Cognitive – biomedical
B9	4	Adherence, pain from injections, motivation to adhere, self-efficacy, adherence	B4 is amplified through motivation and self-efficacy	Biomedical – cognitive
R10	5	Adherence, knowledge about disease, self-efficacy, sadness, substance abuse, adherence	Adherence perpetuated when knowledge acquisition and confidence mitigate destructive behavior	Cognitive – biomedical
B11	5	Adherence, pain from injections, ability to work/study, employed, financial difficulties, adherence	B4 is amplified through accessibility to resources	Biomedical – socioeconomic
R12*	5	Adherence, pain from injections, ability to work/study, employed, time availability, adherence	Adherence is perpetuated when discomfort is mitigated by freed time	Biomedical – convenience
B13	5	Adherence, side effects from pills, ability to work/study, employed, financial difficulties, adherence	B3 is amplified through accessibility to resources	Biomedical – socioeconomic
R14	5	Adherence, self-efficacy, sadness, substance abuse, side effects from pills, adherence	Adherence is perpetuated when confidence mitigates destructive behavior and discomfort	Cognitive – biomedical
R15	5	Adherence, side effects from pills, ability to work/study, employed, time availability, adherence	Adherence is perpetuated when discomfort is mitigated by freed time	Biomedical – convenience

B16	5	Adherence, time availability, ability to work/study, employed, financial difficulties, adherence	B2 is amplified through accessibility to resources	Convenience – socioeconomic
R17	6	Adherence, knowledge about disease, self-efficacy, sadness, substance abuse, side effects from pills, adherence	Adherence perpetuated when knowledge acquisition and confidence mitigate destructive behavior and discomfort	Cognitive – biomedical
B18	6	Adherence, pain from injections, motivation to adhere, self-efficacy, sadness, substance abuse, adherence	B4 is amplified when confidence levels influence destructive behavior	Biomedical – cognitive – biomedical
B19	7	Adherence, pain from injections, motivation to adhere, self-efficacy, sadness, substance abuse, side effects from pills, adherence	B4 and B3 are amplified when confidence levels influence destructive behavior	Biomedical – cognitive – biomedical
B20	7	Adherence, time availability, ability to work/study, employed, financial difficulties, sadness, self-efficacy, adherence	B2 influences accessibility to resources and confidence level	Convenience – socioeconomic – cognitive
B21	7	Adherence, time availability, ability to work/study, employed, financial difficulties, sadness, substance abuse, adherence	B2 influences accessibility to resources and destructive behavior	Convenience – socioeconomic – cognitive – biomedical
B22	7	Adherence, side effects from pills, ability to work/study, employed, financial difficulties, sadness, self-efficacy, adherence	B3 influences accessibility to resources and confidence level	Biomedical – convenience – socioeconomic – cognitive
B23	7	Adherence, time availability, time between doses, side effects from pills, ability to work/study, employed, financial difficulties, adherence	B2 influences comfort and accessibility to resources	Convenience – biomedical – convenience – socioeconomic
B24	7	Adherence, side effects from pills, ability to work/study, employed, financial difficulties, sadness, substance abuse, adherence	B3 influences accessibility to resources and destructive behavior	Biomedical – convenience – socioeconomic – cognitive – biomedical
B25	7	Adherence, pain from injections, ability to work/study, employed, financial difficulties, sadness, substance abuse, adherence	B4 influences accessibility to resources and destructive behavior	Biomedical – convenience – socioeconomic – cognitive – biomedical
B26	7	Adherence, pain from injections, ability to work/study, employed, financial difficulties, sadness, self-efficacy, adherence	B4 influences accessibility to resources and confidence level	Biomedical – convenience – socioeconomic – cognitive
R27	7	Adherence, pain from injections, ability to work/study, employed, time availability, time between	B4 influences time needed to mitigate discomfort caused by the pills	Biomedical – convenience

		doses, side effects from pills, adherence		
B28	8	Adherence, pain from injections, ability to work/study, employed, financial difficulties, sadness, substance abuse, side effects from pills, adherence	B4 influences accessibility to resources and destructive behavior that could mitigate discomfort	Biomedical – convenience – socioeconomic – cognitive – biomedical
B29	8	Adherence, self-efficacy, sadness, substance abuse, side effects from pills, ability to work/study, employed, time availability, adherence	R1 influences destructive behavior, discomfort, and time for adherence	Cognitive – biomedical – convenience
B30	8	Adherence, time availability, ability to work/study, employed, financial difficulties, sadness, substance abuse, side effects from pills, adherence	B2 influences accessibility to resources and destructive behavior that could amplify B3	Convenience – socioeconomic – cognitive – biomedical
R31	8	Adherence, self-efficacy, sadness, substance abuse, side effects from pills, ability to work/study, employed, financial difficulties, adherence	adherence perpetuated by confidence, regardless of destructive behavior, discomfort, and accessibility to resources	Cognitive – biomedical – convenience – socioeconomic
R32*	9	Adherence, knowledge about disease, self-efficacy, sadness, substance abuse, side effects from pills, ability to work/study, employed, financial difficulties, adherence	Adherence perpetuated when knowledge acquisition and confidence mitigate destructive behavior, discomfort, and accessibility to resources	Cognitive – biomedical – socioeconomic
B33	9	Adherence, knowledge about disease, self-efficacy, sadness, substance abuse, side effects from pills, ability to work/study, employed, time availability, adherence	R6 influence on destructive behavior and discomfort are mitigated by time restrictions	Cognitive – biomedical – convenience
B34	9	Adherence, time availability, time between doses, side effects from pills, ability to work/study, employed, financial difficulties, sadness, self-efficacy, adherence	B2 extended through discomfort, accessibility to resources, and confidence level	Convenience – biomedical – convenience – socioeconomic – cognitive
B35	9	Adherence, time availability, time between doses, side effects from pills, ability to work/study, employed, financial difficulties, sadness, substance abuse, adherence	B2 extended through discomfort, accessibility to resources, and destructive behavior	Convenience – biomedical – convenience – socioeconomic – cognitive – biomedical
B36	10	Adherence, pain from injections, motivation to adhere, self-efficacy, sadness, substance abuse, side effects from pills, ability to	B4 extended through confidence, destructive behavior, discomfort, and accessibility to resources	Biomedical – cognitive – biomedical – convenience – socioeconomic

		work/study, employed, financial difficulties, adherence		
R37	10	Adherence, pain from injections, motivation to adhere, self-efficacy, sadness, substance abuse, side effects from pills, ability to work/study, employed, time availability, adherence	adherence is perpetuated when discomfort and confidence are mitigated by freed time	Biomedical – cognitive – biomedical – convenience
R38*	2	Sadness, self-efficacy, sadness	sadness perpetuated through confidence	Cognitive
R39*	6	Sadness, substance abuse, side effects from pills, ability to work/study, employed, financial difficulties, sadness	Sadness perpetuated through destructive behavior, discomfort and accessibility to resources	Cognitive – biomedical – convenience – socioeconomic
B40*	3	Ability to work/study, employed, time availability, ability to work/study	time limits for employment	Convenience
B41	5	Ability to work/study, employed, time availability, time between doses, side effects from pills, ability to work/study	health limits for employment	Convenience – biomedical

CONTINUATION PHASE

No	**Length**	**Variables**	**Name**	**Category**
R1*	2	Adherence, self-efficacy, adherence	building/losing confidence	Cognitive
B2*	2	Adherence, time availability, adherence	time/adherence trade-off	Convenience
B3*	2	Adherence, side effects from pills, adherence	comfort/adherence trade-off	Biomedical
R4*	2	Adherence, knowledge about disease, adherence	more/no change in knowledge acquisition	Cognitive
R5*	3	Adherence, knowledge about disease, self-efficacy, adherence	adherence perpetuated through knowledge acquisition and confidence	Cognitive
B6*	4	Adherence, time availability, time between doses, side effects from pills, adherence	B2 extends to affect B3	Convenience – biomedical
B7	5	Adherence, side effects from pills, ability to work/study, studies, knowledge about disease, adherence	B3 amplified through knowledge acquisition	Biomedical – cognitive
B8	5	Adherence, time availability, ability to work/study, studies, knowledge about disease, adherence	B2 amplified through knowledge acquisition	Convenience – cognitive
R9*	5	Adherence, side effects from pills, ability to work/study, studies, time availability, adherence	disabling effect of adherence frees time for adherence	Biomedical – convenience

B10*	5	Adherence, time availability, ability to work/study, studies, knowledge about disease, adherence	B2 influences knowledge acquisition	Convenience – cognitive
R11	5	Adherence, side effects from pills, ability to work/study, employed, time availability, adherence	disabling effect of adherence frees time for adherence	Biomedical – convenience
B12	5	Adherence, side effects from pills, ability to work/study, studies, knowledge about disease, adherence	B3 influences knowledge acquisition	Biomedical – convenience – cognitive
B13	5	Adherence, side effects from pills, ability to work/study, employed, financial difficulties, adherence	B3 is amplified through accessibility to resources	Biomedical – convenience – socioeconomic
B14	5	Adherence, time availability, ability to work/study, employed, financial difficulties, adherence	B2 is amplified through accessibility to resources	Convenience – socioeconomic
B15	6	Adherence, time availability, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	B2 amplified through knowledge acquisition, regardless of confidence	Convenience – cognitive
B16	6	Adherence, side effects from pills, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	B3 amplified through knowledge acquisition, regardless of confidence	Biomedical – cognitive
B17	6	Adherence, side effects from pills, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	B3 is amplified through knowledge acquisition and confidence level	Biomedical – convenience – cognitive
B18	6	Adherence, time availability, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	B2 is amplified through knowledge acquisition and confidence level	Convenience – cognitive
B19	7	Adherence, time availability, time between doses, side effects from pills, ability to work/study, studies, knowledge about disease, adherence	B2 amplified through discomfort and knowledge acquisition	Convenience – biomedical – cognitive
B20	7	Adherence, time availability, time between doses, side effects from pills, ability to work/study, studies, knowledge about disease, adherence	B2 is amplified through discomfort and knowledge acquisition	Convenience – biomedical – convenience – cognitive
B21	7	Adherence, time availability, time between doses, side effects from pills, ability to work/study, employed, financial difficulties, adherence	B2 is amplified through discomfort and accessibility to resources	Convenience – biomedical – convenience – socioeconomic
B22	8	Adherence, time availability, time between doses, side effects from pills, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	B2 amplified through discomfort and knowledge acquisition, regardless of confidence	Convenience – biomedical – cognitive

B23	8	Adherence, time availability, time between doses, side effects from pills, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	B2 is amplified through discomfort, knowledge acquisition, and confidence level	Convenience – biomedical – convenience – cognitive
B24*	3	Ability to work/study, employed, time availability, ability to work/study	time limits for employment	Convenience
B25*	3	Ability to work/study, studies, time availability, ability to work/study	time limits for studying	Convenience
B26	5	Ability to work/study, studies, time availability, time between doses, side effects from pills, ability to work/study	health limits for studying	Convenience – biomedical
B27	5	Ability to work/study, employed, time availability, time between doses, side effects from pills, ability to work/study	health limits for employment	Convenience – biomedical

MAINTENANCE PHASE

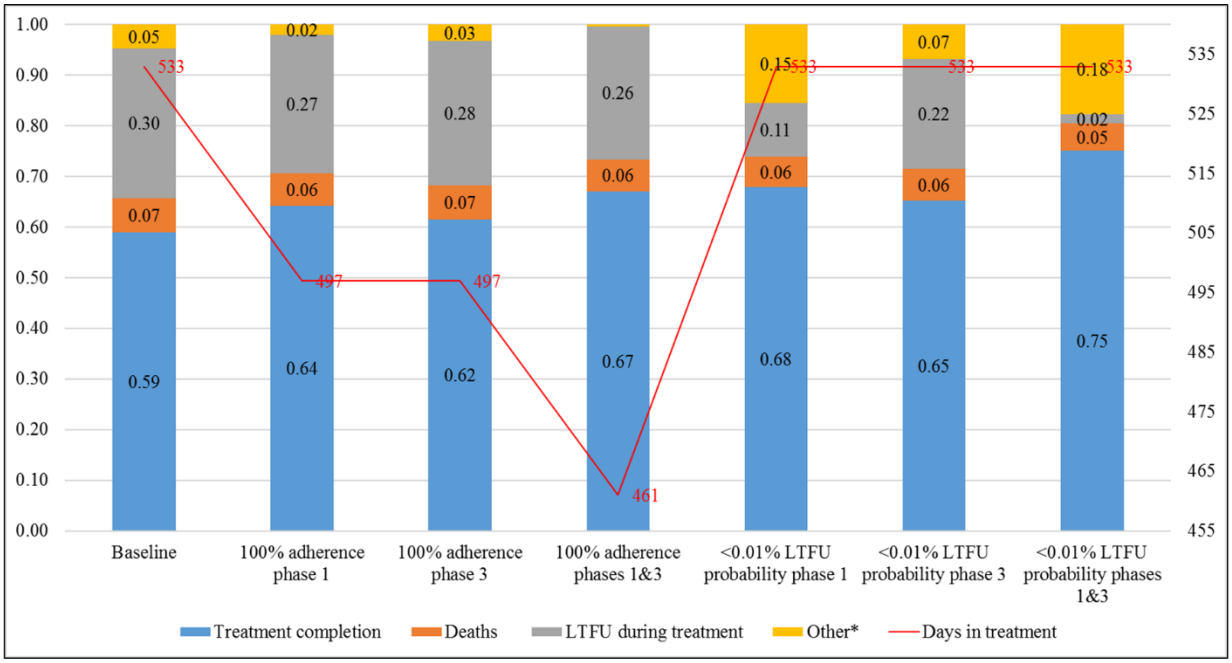
No	**Length**	**Variables**	**Name**	**Category**
R1*	2	Adherence, self-efficacy, adherence	building/losing confidence	Cognitive
B2*	2	Adherence, time availability, adherence	time/adherence trade-off	Convenience
B3*	2	Adherence, feeling healthy, adherence	justification for non-adherence	Biomedical
R4*	2	Adherence, knowledge about disease, adherence	more/no change in knowledge acquisition	Cognitive
R5*	3	Adherence, knowledge about disease, self-efficacy, adherence	adherence perpetuated through knowledge acquisition and confidence	Cognitive
B6*	4	Adherence, feeling healthy, motivation to adhere, self-efficacy, adherence	B3 amplified through confidence level	Biomedical – cognitive
B7	5	Adherence, time availability, ability to work/study, studies, knowledge about disease, adherence	B2 amplified through knowledge acquisition	Convenience – cognitive
R8	5	Adherence, feeling healthy, ability to work/study, studies, knowledge about disease, adherence	adherence perpetuated because knowledge acquisition mitigates B3	Biomedical – cognitive
B9	5	Adherence, feeling healthy, ability to work/study, studies, time availability, adherence	B3 amplified through B2	Biomedical – convenience
B10	5	Adherence, time availability, ability to work/study, studies, knowledge about disease, adherence	B2 amplified through knowledge acquisition	Convenience – cognitive

B11	5	Adherence, time availability, ability to work/study, employed, financial difficulties, adherence	B2 amplified through accessibility to resources	Convenience – socioeconomic
B12	5	Adherence, feeling healthy, ability to work/study, employed, time availability, adherence	B3 amplified through B2	Biomedical – convenience
R13	5	Adherence, feeling healthy, ability to work/study, employed, financial difficulties, adherence	adherence perpetuated through accessibility to resources	Biomedical – convenience – socioeconomic
R14	5	Adherence, feeling healthy, ability to work/study, studies, knowledge about disease, adherence	adherence perpetuated through knowledge acquisition	Biomedical – convenience – cognitive
B15	6	Adherence, time availability, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	B2 amplified because knowledge acquisition mitigates confidence	Convenience – cognitive
R16	6	Adherence, feeling healthy, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	adherence perpetuated because knowledge acquisition and confidence mitigate B3	Biomedical – cognitive
B17	6	Adherence, time availability, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	B2 amplified through knowledge acquisition and confidence level	Convenience – cognitive
R18	6	Adherence, feeling healthy, ability to work/study, studies, knowledge about disease, self-efficacy, adherence	adherence perpetuated through knowledge acquisition and confidence level	Biomedical – convenience – cognitive
B19*	3	Ability to work/study, employed, time availability, ability to work/study	time limits for employment	Convenience
B20*	3	Ability to work/study, studies, time availability, ability to work/study	time limits for studying	Convenience

APPENDIX F. RESULTS FOR TESTS UNDER EXTREME VALUE CONDITIONS

The simulation results of the tests under extreme value conditions are shown in Figure 5. Interventions during the continuation phase were excluded due to the small effects observed from the goal-seeking analyses. Overall, minimizing the daily probability of LTFU has a greater positive effect on treatment outcomes than maximizing adherence rates across all treatment phases. Additionally, improving either intervention target during the intensive phase had a larger positive effect on outcomes than improvements made during the maintenance phase. The largest improvement on treatment outcomes was seen in the scenario where LTFU is minimized in both the intensive and maintenance phases (75% treatment completion, 2% LTFU, 5% death).

Figure 4.B Effects of extreme value conditions for adherence rate and daily probability of LTFU, by phase of treatment, on treatment outcomes

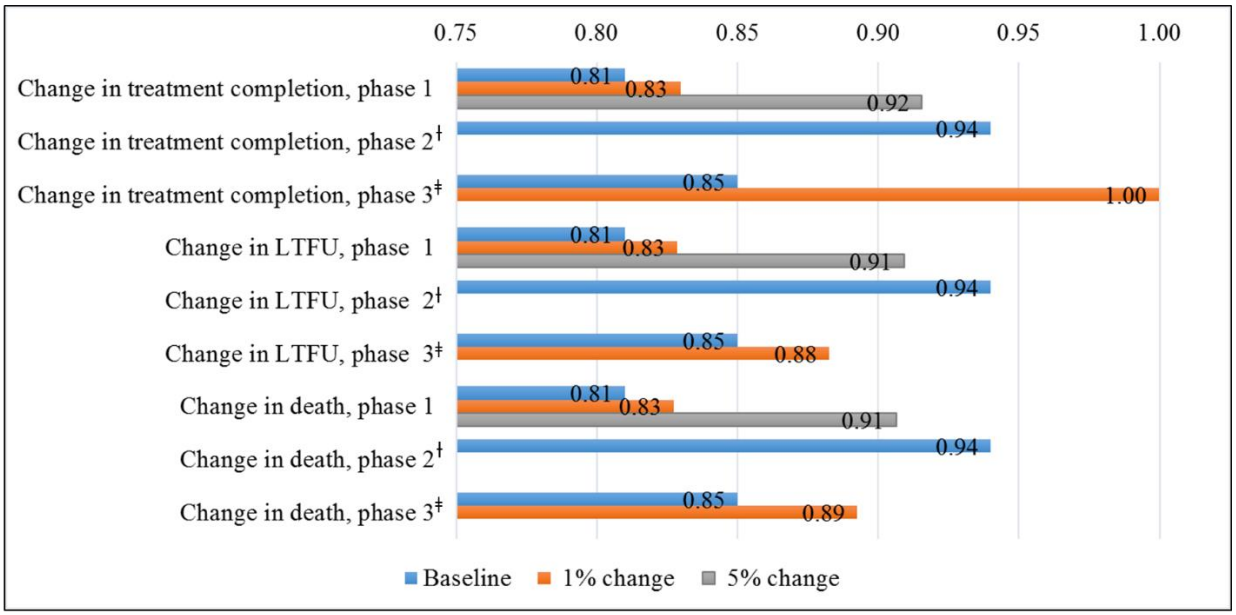


* Includes patients who transfered, failed treatment, or without conclusive treatment outcomes. Baseline represents values from the calibrated model; 100% adherence rates and less than 0.01% daily LTFU probabilities were simulated during the intensive phase (1), maintenance phase (3), or intensive and maintenance phases (1 and 3) of treatment; For each scenario, the average total days in treatment are shown in red.

APPENDIX G. RESULTS FOR GOAL-SEEKING ANALYSES

In the first set of goal-seeking analyses, we estimated the changes in adherence rate that would be needed to improve treatment outcomes by 1% and 5% in each treatment phase. At baseline in the continuation phase, adherence rate is already high (94%) and LTFU rate was low (2%). Thus, even an increase to 100% adherence rate could not improve treatment outcomes by 1% because there is not much space for improvement (Figures 3). Changes in adherence rates to 91% or higher during the intensive phase of treatment improved the treatment outcomes by 5%. Changes in adherence during the maintenance phase of treatment improved treatment outcomes by 1%, but were not enough to improve them by 5% in any of the treatment phases.

Figure 4.A1 Changes in adherence rates needed in each phase* of treatment to increase specified outcomes by 1% and 5%

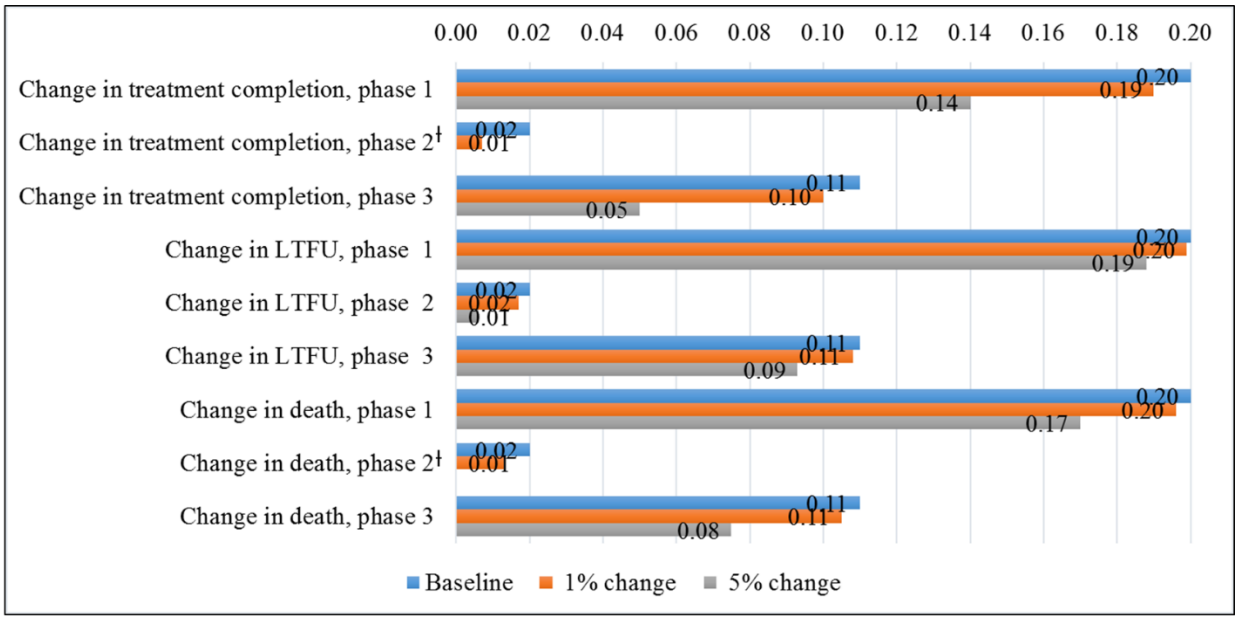


*Phase 1 = intensive phase, phase 2 = continuation phase, phase 3= maintenance phase. †Not possible to improve treatment outcomes by 5% or 1 %; ‡Not possible to improve treatment outcomes by 5%.

For the second set of goal-seeking analyses, small changes in LTFU probability during the intensive and maintenance phases of treatment were sufficient to achieve 1% and 5% improvements in treatment outcomes (Figure 4). Even though 5% improvements in outcomes

were possible for the continuation phase's LTFU rate, only 1% improvements were possible for treatment completion and deaths by changes in LTFU probability.

Figure 4.A2 Changes in LTFU rates needed in each phase* of treatment to increase specified outcomes by 1% and 5%



*Phase 1 = intensive phase, phase 2 = continuation phase, phase 3= maintenance phase. ǂ Not possible to improve treatment outcomes by 5%.

APPENDIX H. KEY VARIABLE LIST

CATEGORY	CONSTRUCT VARIABLE	DATA SOURCE	ITEM DESCRIPTION
Outcome (treatment adherence)	Adherence rate	Clinic records	The proportion of prescribed doses taken since treatment started. Reported in clinical records.
	Adherence category	Patient	Adherence categories at “>90% of the time”, “50%-90% of the time”, and “<50% of the time” since the start of treatment.
	Adherence Scale	Patient	Constructed by a 6-item questionnaire; a combination of binary (“yes” and “no”) and continuous answers.
Predictor	Adherence Information, Motivation, Behavioral Skills	Patient	Constructed by a 30-item questionnaire on a 5-point scale from "strongly disagree" to "strongly agree".
	Provider Work Engagement	Provider	Constructed by a 9-item questionnaire on a 7-point scale from "never" to "always/every day".
	Previous TB treatment	Patient	Whether the patient has previously been treated for TB or MDR-TB; "yes" or "no", binary.
Controls	Sex	Patient, Provider	Born "female" or "male", binary.
	Age	Patient, Provider	Reported age on the day of data collection; continuous.
	Treatment regimen	Clinic records	Patient's current treatment type (drug combination)
	Smear sputum (SS) status	Clinic records	Patient's current SS status; "+" or "-", binary.
	Clinic is walking distance	Patient	If the patient walks to the clinic, it takes them <30min; "yes" or "no", binary.
	Monthly income	Patient	Patient reported income for the past month.
	Substance dependency	Patient	Patient reported addiction status to alcohol, cocaine, or any other drug; "yes" or "no", binary.
	Occurrence of side effects	Patient	Patient reported incident(s) of side effects since treatment started; "yes" or "no", binary.
	Household members	Patient	Patient-reported count of household members; Contin.
	DOT location	Patient	Patient reported most common location of DOT; "clinic only", "home only", "work only", "combination of these", and "other", categorical.
	Diagnosis delay	Clinic records	Time elapsed between MDR-TB diagnostic test (Xpert or DST) and diagnosis results; days, continuous.
	Incentives received	Patient	Patient reported incentives received to adhere since tx started; options will include food bag, cash, gifts, workshops, psychosocial support groups; categorical.
	Time working in TB unit	Provider	Provider reported length of time working at this TB unit; measured in months and years, continuous.
	Children at home	Provider	Provider reported number of children at home; continuous.
	Uses mask	Provider	Provider reported use of protective mask >0 times to treat patients in the past 2 weeks; "yes" or "no", binary.
	Takes prophylaxis	Provider	Provider reported taking prophylaxis since they started working at the TB unit; "yes" or "no", binary.

	Trainings attended	Provider	Provider reported MDR-TB trainings attended since they started working at the TB unit; count.
	Providers per clinic	Clinic	Number of healthcare providers working directly with MDR-TB patients in a TB clinic; count.
	CHW-to-patient	Clinic	Number of CHWs assigned to MDR-TB patients at a TB clinic over the number of MDR-TB patients; continuous
	TB prevalence	Clinic	Number of TB patients registered per TB clinic; count.
	MDR-TB prevalence	Clinic	Number of MDR-TB patients registered per TB clinic; count.
	Outcome: MDR-TB cohort	Clinic	Number of MDR-TB patients with recorded outcomes in the past 12 months (per clinic).
	Outcome: Cured	Clinic	Number of MDR-TB patients cured in the past 12 months.
	Outcome: Completion	Clinic	Number of MDR-TB patients who defaulted from treatment in the past 12 months.
	Outcome: Default	Clinic	Number of MDR-TB patients who defaulted from treatment in the past 12 months.
	Outcome: Failure	Clinic	Number of MDR-TB patients whose treatment failed in the past 12 months.
	Outcome: Death	Clinic	Number of MDR-TB patients who died in the past 12 months.
	Supporting staff per clinic	Clinic	Number of supporting staff working directly with MDR-TB patients; includes psychiatrists and nutritionists, count.
	Political leaders visit	Clinic	Political leader or member of the Ministry of Health has visited the TB unit in the past year; "yes" or "no", binary.
	Separate TB unit entrance	Clinic	There is an entrance only used by TB or MDR-TB patients in this clinic; "yes" or "no", binary.
	Adherence interventions	Clinic	Types of interventions implemented at the clinic level to improve adherence; options include food bags, cash, gifts, workshops, psychosocial support groups, other; categorical.

APPENDIX I: PATIENT QUESTIONNAIRE

INTERVIEWER ONLY: Patient's name
INTERVIEWER ONLY: Health center's name [blank space]
INTERVIEWER ONLY: Patient's gender F/M
INTERVIEWER ONLY: Date [blank space]

Section A: Basic TB and Medical History

To start, I will ask you a few questions about your history with TB and MDR-TB and other details about your medical history. Please remember that your personal information will not be linked to any of these answers and I am the only one who will access the data.

1. Have you ever been treated for TB or MDR-TB before?

Yes / No [→ Skip to 5 if answer is no]

2. How many times?

[Blank space] / NA

3. The last time you received treatment, did you complete it?

Yes / No / I don't remember [→ skip to 5 if answer is yes or don't remember]

4. What was the main reason for not completing your treatment?

I felt better / I moved / It interfered with my job or school / Due to family problems / Side effects / The injections / I was depressed / Administrative problems at the clinic / Other reason: [blank space]

Have you been diagnosed with any of the following diseases?

5.	Diabetes	Yes/No
6.	Heart disease	Yes/No
7.	Cancer	Yes/No
8.	Diarrhea	Yes/No
9.	Psychiatric problems	Yes/No
10.	Other diseases	[Blank space]

11. The last time you received treatment at the clinic, work, or home, did you have to have an injection as part of your MDR-TB treatment?

Yes / No

12. When did you start your current treatment?

[Black space for date] / DK

13. How long did you have to wait to start your MDR-TB treatment once you were diagnosed?

[Blank space for days] [Blank space for weeks] / DK

14. How many times did you visit the clinic or hospital due to your TB symptoms before you started treatment?

[Blank space for number of visits] / DK

15. What symptoms have you had since you started treatment?
Cough / Cough with blood / Fever / Trouble breathing / Weight loss / Tiredness / Night sweats / Loss of appetite / Diarrhea / Hives, itching / Chest or back pain / Nausea or vomiting / Stomach pain, gastritis / Headache / DK or NA

16. If you needed to undergo surgical procedures during your current MDR-TB treatment, have the clinic personnel address these problems to your satisfaction?

Yes / No / DK / NA

17. If you have existing co-morbidities (such as HIV, diabetes, mental health, etc.) has the clinic personnel address these problems to your satisfaction since you started this MDR-TB treatment?

Yes / No / DK / NA

18. If you have experienced side effects from the medications since the start of this MDR-TB treatment, have the clinic personnel address these problems to your satisfaction?

Yes / No / DK / NA

Indicate how many times in the last month the following has happened to you:

19. You have been drunk: [blank space] days
20. You went to bed very hungry because there was no food at home: [blank space] days
21. You have taken vitamins: [blank space] days
22. How many meals did you eat yesterday? [blank space] times

Section B: Feelings about MDR-TB and treatment

23. What bothers you the most about having MDR-TB?

Having to take medications everyday / Not being able to work or study / Having to get shots / Feeling sad / What others think of me / Being distanced from family and friends / Side effects / NA

24. How often have you felt sad since you were diagnosed with MDR-TB?

Always / Most of the time / Sometimes / Rarely / Never / DK

25. At this moment, how do you feel?

Very bad / Bad / Ok / Good / Very good / DK

As a consequence of your illness, how did your relationship change with your:

26. Family Worse / Same / Better / I don't know
27. Partner Worse / Same / Better / I don't know

28. Friends Worse / Same / Better / I don't know
29. Neighbors Worse / Same / Better / I don't know

30. In the past 2 weeks, when you do not take your medications, what is the most common reason?

I was feeling fine / I was too sick / I was working or studying / I forgot / Side effects / I do not like the shots / Clinic was closed / CHW did not show up / I had family problems / I was traveling / NA / Other

Section C: Health services access and quality

The next section is about your experience with the accessibility and quality of the health services you receive at the health center. Your answers will help us understand how services could be improved.

31. How long does it take you to get to the health center?

Minutes: [blank space] / DK

32. When you come/go to take your medications at the health center with questions about your treatment, how often do your healthcare providers take the time to answer your questions to your satisfaction?

Always / Most of the time / Sometimes / Rarely / Never / I never have questions / I never ask questions / DK

33. When you come/go to the health center, and feel that taking your medications is difficult, how often do your healthcare providers take the time to motivate you to continue with your treatment?

Always / Most of the time / Sometimes / Rarely / Never / I never feel that way / DK

34. Overall, how dissatisfied or satisfied are you with the quality of personal interactions with the nurse or technician who work at the TB clinic?

Very dissatisfied / Dissatisfied / Neutral / Satisfied / Very satisfied / DK

35. Are there things you do not like about going/coming to the health center? If so, what are they?

No / Disrespectful attitude / Long waiting periods / High costs / Too far from home / It interferes with work or school / People can see me and know I am sick / Other reason: [blank space]

Section D: Adherence Level

The next few questions will be about your feelings on taking your medications as prescribed. Please answer as honestly as possible.

36. Do you ever forget to take your MDR-TB medications?

Yes / No / DK

37. Are you careless at times about taking your medications?

Yes / No /DK

38. Sometimes if you feel worse, do you stop taking your medications?

Yes / No /DK

39. Thinking about the last week, how often have you not taken your medications?

[Blank space for number of times]

40. Did you not take any of your medications over the past weekend?

Yes / No / DK

41. Over the past 3 months, how many days have you not taken your medications at all?

2 days or less / more than 2 days / DK

Section E: Information-Motivation-Behavior

In the next section I give you statements about MDR-TB, how you feel about MDR-TB, and some of the activities in a patient's life that may have been affected by MDR-TB. For each statement, please listen carefully and think about whether that statement applies to your experience with MDR-TB. If it is very close to how you feel or what you know, then you can tell me you strongly agree with that statement. The other 4 options for responses will be "I somewhat agree", "I neither agree nor disagree", "I somewhat disagree", and "I strongly disagree". Your honest response to the questions will be the correct answer. Do you have any questions about the responses? Here is the first statement:

42. I know how each of my current MDR-TB medications is supposed to be taken (for example, whether or not my current medications can be taken with food, beverages, or other prescription medications).

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

43. I know what to do if I miss a dose of any of my MDR-TB medications (for example, whether or not to take the missed dosage later).

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

44. Skipping a few of my MDR-TB medications from time to time would not really hurt my health.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

45. I know that the possible side effects of each of my MDR-TB medications are.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

46. As long as I am feeling healthy, missing my MDR-TB medications from time to time is OK.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

47. I understand how each of my MDR-TB medications works in my body to fight MDR-TB

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

48. If I don't take my MDR-TB medications as prescribed, these kinds of medications may not work for me in the future.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

49. I believe that if I take my MDR-TB medications as prescribed, I will live longer.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

50. I know how my MDR-TB medications interact with alcohol and street drugs.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

51. MDR-TB is a very serious illness.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

52. I am worried that other people might realize that I have MDR-TB if they see me taking my MDR-TB medications.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

53. I get frustrated taking my MDR-TB medications because I have to plan my life around them.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

54. I don't like taking my MDR-TB medications because they remind me that I have MDR-TB.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

55. I feel that my healthcare provider takes my needs into account when making recommendations about which MDR-TB medications to take.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

56. Most people who are important to me who know I have MDR-TB support me in taking my medications.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

57. My healthcare provider doesn't give me enough support when it comes to taking my MDR-TB medications as prescribed.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

58. It frustrates me to think that I will have to take these MDR-TB medications for a long time.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

59. I am worried that the MDR-TB medications I have been prescribed will hurt my health.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

60. It upsets me that the MDR-TB medications I have been prescribed can affect the way I feel.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

61. It upsets me that the MDR-TB medications I have been prescribed can cause side effects.

I strongly disagree / I somewhat disagree / I neither agree nor disagree/ I somewhat agree / I strongly agree

For the next set of questions, please listen to the statements I say and tell me whether you think it is "very hard", "hard", "sometimes hard, sometimes easy", "easy", or "very easy" for you.

62. There are times when it is hard for me to take my MDR-TB medications when I drink alcohol or use street drugs.

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

63. How hard or easy is it for you to stay informed about your MDR-TB treatment?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

64. How hard or easy is it for you to get the support you need from others for taking your MDR-TB medications (for example, from friends, family, or doctor)?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

65. How hard or easy is it for you to take your MDR-TB medications on time?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

66. How hard or easy is it for you to take your MDR-TB medications when you are wrapped up in what you are doing?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

67. How hard or easy is it for you to manage the side effects of your MDR-TB medications?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

68. How hard or easy is it for you to remember to take your MDR-TB medications?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

69. How hard or easy is it for you to take your MDR-TB medications because the pills are hard to swallow, taste bad, or make you sick to your stomach?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

70. How hard or easy is it for you to make your MDR-TB medications part of your daily life?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

71. How hard or easy is it for you to take your MDR-TB medications when your usual routine changes (for example, when you travel or when you go out with your friends)?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

72. How hard or easy is it for you to take your MDR-TB medications when you do not feel good emotionally (for example, when you are depressed, sad, angry, or stressed out)?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

73. How hard or easy is it for you to take your MDR-TB medications when you feel good physically and don't have any symptoms of your MDR-TB disease?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

74. How hard or easy is it for you to take your medications when you do NOT feel good physically?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

75. How hard or easy is it for you to talk to your healthcare provider about your MDR-TB medications?

Very hard / Hard / Sometimes hard, sometimes easy / Easy / Very Easy

Section D: Treatment dosages

Some patients are able to come/go to the health centers to take all of their dosages, some are not for various reasons. The following questions are about where you generally take your morning and evening dosages.

76. Right now, do you take your medications twice a day, or only once a day?

Once a day [→ Skip to 83] /Twice a day / DK

77. Generally, where do you take the morning dosage of your MDR-TB treatment?

At the clinic / At work / At school / At home / Another location / DK

78. Generally, who gives you the morning dosage of your MDR-TB treatment?

Healthcare provider / CHW / Self-administered / A friend or family member / Other / DK

79. Generally, where do you take the evening dosage of your MDR-TB treatment?

At the clinic / At work / At school / At home / Another location / DK

80. Generally, who gives you the evening dosage of your MDR-TB treatment?

Healthcare provider / CHW / Self-administered / A friend or family member / I do not take an evening dosage / Other / DK

81. Are you more likely to miss the morning or the evening dosage of your MDR-TB treatment?

Morning / Evening / No difference / DK

82. What makes this dosage more difficult to take?

[Blank space] / DK or NA

Section E: Socio-Economic Status

Now I would like to learn more about the social and economic barriers you have to face as a MDR-TB patient. Some of the questions will be about your current living situation and others about the changes you have experienced since you became ill.

83. What do you do for work right now?

[Blank space]

84. How long were you too sick to continue working/studying before the beginning of your MDR-TB treatment?

Days: [blank space]

85. How much debt does your family have right now?

S/. [Blank space]

86. Your home is:

Owned / Rented / Borrowed / Mortgaged / Other

87. What is the level of education of the head of the household?

None / Elementary school / Some high school or technical school / Completed high school or technical school / Some college / Completed college

88. How many people normally sleep at home?

People: [blank space]

89. Which material predominates on the exterior walls of your house?

Bricks or cement / Adobe / Thatch / Rocks and mud / Wood / Matting / Other

90. Which material predominates on the floors of your house?

Polished wood / Asphalt or similar / Tiles or similar / Wood, filed / Cement / Dirt, sand, or similar / Other

91. How many rooms in your house? – Without considering the bathroom, hallways, kitchen, storage, garage.

Rooms: [blank space]

92. How is water supplied to your house?

Public service inside the house / Public service outside of the house / Pilón / Well / River, stream / Truck tank / Piped water, not potable / Other

93. What kind of bathroom do you have at home?

Public service inside the house / Public service outside of the house / Latrine / Septic hole, dark hole / Use the canal or stream / Do not have a bathroom / Other

94. Do you share your bathroom with members of another household?

Yes / No

95. What kind of lightning do you have at home?

Electricity / Kerosene, gas, petroleum / Candles / None / Other

96. Which type of fuel do you use for cooking?

Electricity / Kerosene, gas, petroleum / Carbon / Wood / Do not cook / Other

Do you have at home…

97.	Working TV	Yes / No
98.	Working radio	Yes / No
99.	Working telephone	Yes / No
100.	Working kitchen	Yes / No
101.	Working refrigerator	Yes / No

How much has having MDR-TB cost you and your family since the symptoms began?

102.	Natural medicines:	[blank space] S/.
103.	Buying more food:	[blank space] S/.
104.	Loss of family income:	[blank space] S/.
105.	Transportation (taxi, bus, etc.)	[blank space] S/.
106.	Clinical exams (X-rays, etc.)	[blank space] S/.
107.	Medications:	[blank space] S/.
108.	Other costs:	[blank space] S/.

109. What was the main activity you were performing last week?

Regular work (salary) / I don't work, but used to have a salary / I was too sick to work or go to school / Unpaid work at home / Independent work (taxi driver, market, etc.) / I was looking for work / Domestic work / Studying / DK

110. What is the monthly household income?

S/. [Blank space]

111. How much does your family spend in food every week?

S/. [Blank space]

112. How many people in your household eat from the food that is bought every week?

S/. [Blank space]

113. What is your total income since the symptoms of this MDR-TB episode started?

S/. [Blank space]

114. How much income has been lost due to MDR-TB since you started having symptoms of ths MDR-TB episode?

S/. [Blank space]

Do you use any drugs?

115. Marijuana Yes / No
116. Cocaine Yes / No
117. Cocaine paste Yes / No
118. Terokal (glue) Yes / No
119. Ecstasy Yes / No
120. Heroine Yes / No

Section F: Local Interventions Targeting Adherence

A. Food Bags

121. Since you started treatment as an MDR-TB patient, have you received food bags from the clinic?

Yes / No [→ skip to 124 if no] / DK

122. How many times have you received food bags from this clinic since the beginning of your MDR-TB treatment?

[blank space] times / DK

123. How would you rate the quality of the items that come in the food bags?

Very good quality / Good quality / Ok / Poor quality / Very poor quality / DK

124. Who benefits from the food bags that you receive from the clinic?

Family / Friends / Only me / Others / DK

B. Social Support

Since you started treatment, which of the following has helped you cope with your illness?

125. Family Yes / No
126. Friends Yes / No

127. Church, faith Yes / No
128. Work Yes / No
129. Healthcare provider Yes / No
130. CHW Yes / No

131. Whose support do you feel you need the most to make it through your treatment?

Family / Friends / Church, faith / Work / Healthcare provider / CHW / Other / DK

132. Have you attended a support group or social events for MDR-TB patients since you started treatment?

Yes / No [→ skip to 135 if answer is no]

133. How many support groups or social events for MDR-TB patients have you attended since you started treatment?

[Blank space for continuous variable]

134. Who organized these support groups or social events?

Church, faith / NGO / Healthcare provider / CHW / Other: [blank space] / DK

135. Would you recommend these support groups or social events to other MDR-TB patients?

Yes / No / DK

C. Community Health Workers

136. Do you need a CHW to bring your medications in order to take your MDR-TB treatment?

Yes / No / NA

137. Have you been assigned a CHW to support you during your treatment?

Yes / No / I don't know [→ skip to 142 if answer is no or I don't know]

138. How often does your current CHW deliver your dosages as agreed?

Always / Most of the time / Sometimes / Never / DK

139. How frequently does the CHW give you new information and/or remind you of important information about your MDR-TB treatment?

Every time s/he visits / Most of the time s/he visits / Sometimes / Rarely / Never / NA

140. How frequently does the CHW motivate you to continue taking your MDR-TB medications?

Every time s/he visits / Most of the time s/he visits / Sometimes / Rarely / Never / NA

141. How much time does the CHW usually spend with you during each visit?

[Blank space for minutes]

142. During the past seven days, how many times did your assigned CHW visited you?

[Blank space] times / NA

D. Financial Assistance

143. Have you received any cash to reimburse you for transportation costs from your home to the clinic since you started MDR-TB treatment?

Yes / No / DK [← skip to 145 if answer is no]

144. Have you received any other financial assistance to support you since you started treatment?

Yes / No / DK

145. If you have received financial assistance (other than for transportation), what was the total amount?

S/.[Blank space] / DK

E. Psychological Support

146. How many appointments with a psychiatrist or therapist have you had since you started treatment?

[Blank space for number of appointments] [→skip to 149 if answer is 0]

147. Do you feel that these visits helped you feel better about your MDR-TB diagnosis?

Yes / No / DK

148. Do you feel that these visits helped you find strength to continue your treatment when it was difficult to do so?

Yes / No / DK

149. How often have you felt sad since you were diagnosed with MDR-TB?

Always / Most of the time / Sometimes / Rarely / Never / DK

F. Nutritional Counseling and Assistance

150. Do you need to take your medications with a beverage or food in order to avoid stomach problems?

Yes, with a beverage / Yes, with food / Yes, with both / No / DK

151. In the past week, when you were given your medications, how often did the health center provide you with beverages or food to drink or eat while you are taking your medications?

Always / Frequently / Sometimes / Not frequently / Never / NA

152. In the past week, when you were given your medications, how often did the CHW bring you beverages or food to drink or eat while you are taking your medications?

Always / Frequently / Sometimes / Not frequently / Never / NA

153. How many appointments with a nutritionist at this health center have you had since you started MDR-TB treatment?

None / 1-2 appointments / >3 appointments / I was never offered that service [→ skip to 155 if answer is none or never offered]

154. Have you changed your diet based on the nutritionist's recommendations?

Yes / No / NA

155. If you have had appointments with a nutritionist, are his/her recommendations about diet changes feasible based on your budget and what is sold in the market?

Yes / No / NA

G. Educational Workshops

156. Have you attended any classes or workshops where you were given information about MDR-TB and/or the facilitators answered your questions about your illness?

Yes / No [→ skip to 160 if answer is no]

157. How many of these classes or workshops have you attended since your MDR-TB diagnosis?

[Blank space] times / NA

158. Who organized these classes or workshops?

Church, faith / NGO / Healthcare provider / CHW / Other / NA

159. Overall, have you learned new things about MDR-TB at these classes or workshops?

Yes / No / DK

160. You would recommend these classes or workshops for other MDR-TB patients?

Yes / No / DK

H. Other Local Interventions

161. Have you received any other incentives, or gifts, or have you been helped in any other way to encourage you to take your MDR-TB medications by anyone? If so, can you tell me what kind?

No / Yes: [blank space]

Section F: Demographics

162. Which of these best describes your situation?

Single / Married / Widowed / Divorced / Separated / In a relationship

163. How many children do you have? Biological and live children only.

[Blank space] children.

164. How long have you lived at your current address?

[Blank space] years, [blank space] months.

165. Where were you born?

In this district / In another district in Lima / In another coastal city / In a city in the mountains / In a city in the Amazon

166. What is the highest grade you completed at school?

None / Elementary / Some high school / Completed high school / Some college / Completed college

167. Have you attended any school this year?

Yes, and still attending / No / Yes, but no longer attending

168. Are you currently working or attending school? If you are not, how come?

Yes / No, I cannot due to symptoms / No, I cannot due to daily treatment / No, I do not want to get others sick / No, I lost my job / No, and was not before I got sick / No, unspecified

Thank you for your time!

APPENDIX J. PROVIDERS QUESTIONNAIRE

Section A: Provider's work history

1. What are the top three most difficult parts of your job? [open ended]

High risk of contracting MDR-TB / Short on personnel / Lack of resources / Low compensation / Work location is unpleasant / Work location is unsafe / Complexity of tasks / Emotional distress / Difficulty of patients' cases / I would rather be in a different field / Other: [blank space]

2. How long have you been working in this healthcare center with MDR-TB patients?

Less than a month / 1-3 months / 3-6 months / 6-12 months / 1-5 years / >5 years

3. How long have you been working with MDR-TB patients, including the time in other health centers?

Less than a month / 1-3 months / 3-6 months / 6-12 months / 1-5 years / >5 years

4. What is the job position you hold at this healthcare center?

Nurse / Lung or TB Specialist / Intern / Physician / Nurse assistant / Other: [blank space]

Section B: Work Safety

Some healthcare workers in TB units worry about becoming infected with TB or MDR-TB. The following questions are about your feelings and concerns about your safety at work.

5. If you worry about becoming infected with MDR-TB at work, how much do you worry about it?

It never worries me / It worries me a little / It worries me a lot

6. If you worry about someone at home becoming infected with MDR-TB because of your work with MDR-TB patients, how much do you worry about it?

It never worries me / It worries me a little / It worries me a lot / I live alone

7. In the seven days, how many days have you used a mask while MDR-TB patients take their medications?

Every day / 1-2 days / 3-4 days / 5-7 days / 0 days

8. At the health center you currently work at, have you ever been provided with masks to wear while you care for MDR-TB patients (N95 type)?

Yes / No, but it has been offered for free / No, it has not been offered for free / I do not remember

9. Thinking of all the years you have worked with MDR-TB patients at this and other health centers, have you ever taken prophylaxis?

Yes / No, but it has been offered for free / No, it has not been offered for free / I do not remember

10. Some health centers are located in dangerous parts of the city. In general, how safe do you feel coming to, and leaving from, work?

Unsafe / Barely safe / Mostly safe / Completely safe

Section C: Provider's work engagement

The following 17 statements are about how you feel at work. Please listen to each statement carefully and decide if you ever feel this way about your work here at the healthcare center. If you have never had this feeling, we will assign a "0" (zero) to this statement. If you have had this feeling, we will assign a number based on how often you felt it by choosing a number between 1 and 6 that best describes how frequently you feel that way.

Never	Almost never	Rarely	Sometimes	Often	Very often	Always
0	1	2	3	4	5	6
Never	A few times a year or less	Once a month or less	A few times a month	Once a week	A few times a week	Every day

11. When I am at the health center, I feel bursting with energy.

12. I find the work with MDR-TB patients full of meaning and purpose.

13. Time flies when I am at work.

14. At my job, I feel strong and vigorous.

15. I am enthusiastic about my job.

16. When I am working, I forget everything else around me.

17. My job inspires me.

18. When I get up in the morning, I feel like going to work.

19. I feel happy when I am working intensely.

20. I am proud of the work that I do.

21. I am immersed in my work.

22. I can continue working for very long periods at a time.

23. To me, my job at the health center is challenging.

24. I get carried away when I am working.

25. At my job, I am very resilient, mentally.

26. It is difficult to detach myself from my job.

27. At my work, I always persevere, even when things do not go well.

Section D: Interactions With Patients

Healthcare workers in TB units, such as yourself, see most MDR-TB patients daily. The next set of questions are about the interactions you and your colleagues have with patients when they come to the health center to take their medications.

28. Thinking about the last seven days, how frequently did MDR-TB patients talk to you about personal (non-medical) issues when they came to the health center to take their medications?

Everyday / 5-7 days / 3-4 days / 1-2 days / 0 days / I do not remember

29. Thinking about the last seven days, how many MDR-TB patients did you notice were having a hard time with their treatment (either due to side effects or emotional problems)?

Number: [blank space] / I do not remember [→ Skip to 31 if answer is 0/don't remember]

30. When you saw a patient having a hard time in the last seven days, did you spend time encouraging him/her to adhere to their treatment?

Yes, for all of them / Yes, for some of them / No, I was very busy

31. Do you think patients' educational levels affect their ability to understand MDR-TB and/or how important it is to take their medications as prescribed?

Yes / No / I don't know

32. In this health center, at what points during treatment do patients receive information about MDR-TB and/or the importance of taking all of their medications when they are supposed to?

When they receive their diagnosis / At treatment initiation / At monthly check-ups / At special educational events (e.g. workshops, support groups) / During their daily visits / I don't know

33. How much more, if any, do you think you and/or your co-workers can do to help patients take all their medications when they are supposed to?

Nothing more / A little more / More / A lot more

34. On average, how much time do you think you spend asking each patient about their day and how they are feeling?

Not much / 1-2 minutes / 2-5 minutes / 5-10 minutes / more than 10 minutes

35. From all the MDR-TB patients treated at this clinic, in your opinion, how many of them understand the importance of taking their medication as prescribed.

1. Number: [blank space] / I don't know

36. In the past 3 months, have you organized any educational sessions, social events, or support groups for MDR-TB patients to help them cope with their illness?

Yes / No / I don't remember

37. For some patients, taking their treatment every day is very hard. What have you observed are the most common reasons for missing dosages among your MDR-TB patients?

Forgetfulness / Lack of understanding its importance / They have other priorities (e.g. work, school) / Severe side effects / Shame or stigma / They cannot afford the bus or taxi fee / Drugs and alcohol abuse / They don't understand the importance of adhering to their treatment / Other

Section E: Training and Guidelines

Caring for MDR-TB patients can be difficult and complicated. The following set of questions will be about the training you have received on MDR-TB case management and the practices at this health center.

38. Have you had any formal training by the Ministry of Health on how to care for MDR-TB patients?

Yes / No / Cannot remember [→ Skip to 41 if answer is no]

39. How many times have you attended trainings since you started caring for MDR-TB patients?

Once / Twice / Three or more times

40. How long ago was your last training?

In the past month / In the past 6 months / In the past year / More than 1 year ago / NA

41. Who is in charge of making sure patients are adhering to treatment at this healthcare center?

I am / My supervisor / The physician / The whole team / The patients / I am not sure

42. Do you know where to find a copy of the Technical Norms (guidelines) for Caring for MDR-TB Patients?

Yes / No / What is that? [→ skip to 44 if they do not know what Technical Norms are]

43. Have you read the Technical Norms for Caring for MDR-TB Patients?

Yes / No / NA

44. What have you been trained to do if you notice a patient is missing several dosages of treatment?

Do a home-visit myself during work hours / Do a home-visit myself after work hours / Send a CHW or someone else to find the patient / I don't know what to do / I haven't been trained about that / Other

45. Given your resource restrictions, what do you actually do if a patient misses several dosages of treatment?

Nothing in particular, no resources to follow-up / Do a home-visit / Call them / Send a CHW or another person to do a home-visit / Tell my supervisor / Other

46. Do you or the healthcare center you work for implement interventions to help patients take their medications as prescribed? [explain "implement interventions" as needed]

Yes / No / I don't know

47. Do external NGOs, churches, researchers, or the government implement interventions to help patients adhere to their medications? [describe "NGOs" as needed]

Yes / No / I don't know

Section F: Community Health Workers

Many health centers count on CHWs to help with delivering medications for patients outside working hours, at their homes, and/or at their worksites. The following few questions are about how they support you and the patients to ensure completion of treatment.

48. How well do you know the CHWs who volunteer at this healthcare center with MDR-TB patients, if at all?

Very well / fairly Well / Not very well / Not at all / NA

49. How many CHWs does this health center count on to help with delivering medications to MDR-TB patients?

Number: [blank space] / I do not know [→ Skip to 53 if answer is none]

50. Out of all the CHWs who volunteer at this health center, how many consistently deliver all prescribed medications and watch patients take them.

Number: [blank space] / I do not know

51. Out of all the CHWs who volunteer at this health center, how many consistently log (or tell you to log) dosages taken or missed by patients.

Number: [blank space] / I do not know

52. Out of all the CHWs who volunteer at this health center, how many are well-trained to support patients to take their medications throughout their MDR-TB treatment.

Number: [blank space] / I do not know

Section G: Demographics

I only have a few more questions about you. Please remember that your personal information will not be linked to your answers and only I have access to this data.

53. How old are you?

[Blank space] years old.

54. How many children do you have? Biological and live children only.

[Blank space] children.

55. How many people live in your household, including yourself?

[Blank space] people

56. Are there any children (18 years old or younger) living in your household?

Yes / No / Sometimes

Thank you for your time!

APPENDIX K. ADMINISTRATIVE DATA

Section A: Clinic Information

Clinic Name: _____

Clinic Address: _____

Length of time serving MDR-TB patients: _____

Section A: Patient Level Data [see end of document for more details]

Patient ID	Dosages Taken	Dosages Prescribed	Regimen (past+current)	Sputum Smear Conversion Date

Section B: Clinic Level Data

1. MDR-TB patient care team composition: [Blank space]
2. Number of MDR-TB healthcare provides: [Blank space]
3. Number of supporting staff (nutritionist, psychiatrist, etc.): [Blank space]
4. Number of CHWs supporting MDR-TB patients: [Blank space]
5. Number of TB patients registered: [Blank space]
6. Number of MDR-TB patients registered: [Blank space]
7. Number of MDR-TB patients with recorded outcomes in the past 36 months: [Blank space]

Out of the recorded outcomes for MDR-TB patients, how many…

8. Completed Treatment: [Blank space]
9. Defaulted: [Blank space]
10. Dead: [Blank space]
11. Failed: [Blank space]
12. TB entrance separate from general clinic's: Yes / No
13. The space for treatment intake for TB and MDR-TB patients is separated: Yes / No
14. In the past 12 months, has the TB clinic been visited by a delegate from the Ministry of Health? Yes / No
15. If yes, what was the purpose of this visit? [Blank space]

16. In the past 12 months, has the TB clinic been visited by a politician? Yes / No
17. If yes, what was the purpose of this visit? [Blank space]
18. In the past 3 months, has the TB clinic implemented any interventions to help MDR-TB patients adhere to treatment? (e.g. food bags, support groups, transportation costs reimbursement) Yes / No
19. If yes, which interventions have been implemented in the past 3 months? [Blank space]
20. If yes, which interventions have been implemented in the past 12 months? [Blank space]

For each intervention mentioned, please answer the following questions:

21. Intervention 1: [Blank space]
22. Who or what entity is financing this intervention?

MINSA / NGO / Private organization / No one / Other [blank space]

23. How many MDR-TB patients have benefited from this intervention in this TB clinic? [Blank space]
24. How many times does a MDR-TB patient benefit from this intervention throughout their treatment?

1 time / 2 times / 3-5 times / 5-10 times / Daily / Weekly / Monthly / Varies / I don't know

25. [For activities only] How long does each session of this activity last for a MDR-TB patient?

0-15 minutes / 15-30 minutes / 30-60 minutes / > 1 hour / A few hours / A day / Other

26. Intervention 2: [Blank space]
27. Who or what entity is financing this intervention?

MINSA / NGO / Private organization / No one / Other [blank space]

28. How many MDR-TB patients have benefited from this intervention in this TB clinic? [Blank space]
29. How many times does a MDR-TB patient benefit from this intervention throughout their treatment?

1 time / 2 times / 3-5 times / 5-10 times / Daily / Weekly / Monthly / Varies / I don't know

30. [For activities only] How long does each session of this activity last for a MDR-TB patient?

0-15 minutes / 15-30 minutes / 30-60 minutes / > 1 hour / A few hours / A day / Other

31. Intervention 3: [Blank space]
32. Who or what entity is financing this intervention?

MINSA / NGO / Private organization / No one / Other [blank space]

33. How many MDR-TB patients have benefited from this intervention in this TB clinic? [Blank space]
34. How many times does a MDR-TB patient benefit from this intervention throughout their treatment?

1 time / 2 times / 3-5 times / 5-10 times / Daily / Weekly / Monthly / Varies / I don't know

35. [For activities only] How long does each session of this activity last for a MDR-TB patient?

0-15 minutes / 15-30 minutes / 30-60 minutes / > 1 hour / A few hours / A day / Other

36. Intervention 4: [Blank space]
37. Who or what entity is financing this intervention?

MINSA / NGO / Private organization / No one / Other [blank space]

38. How many MDR-TB patients have benefited from this intervention in this TB clinic? [Blank space]
39. How many times does a MDR-TB patient benefit from this intervention throughout their treatment?

1 time / 2 times / 3-5 times / 5-10 times / Daily / Weekly / Monthly / Varies / I don't know

40. [For activities only] How long does each session of this activity last for a MDR-TB patient?

0-15 minutes / 15-30 minutes / 30-60 minutes / > 1 hour / A few hours / A day / Other

41. Intervention 5: [Blank space]
42. Who or what entity is financing this intervention?

MINSA / NGO / Private organization / No one / Other [blank space]

43. How many MDR-TB patients have benefited from this intervention in this TB clinic? [Blank space]
44. How many times does a MDR-TB patient benefit from this intervention throughout their treatment?

1 time / 2 times / 3-5 times / 5-10 times / Daily / Weekly / Monthly / Varies / I don't know

45. [For activities only] How long does each session of this activity last for a MDR-TB patient?

0-15 minutes / 15-30 minutes / 30-60 minutes / > 1 hour / A few hours / A day / Other

APPENDIX L. SEMI-STRUCTURED INTERVIEW GRUIDE

Introduction

Hello. My name is _____ (state your affiliation). We are conducting a study in order to understand the barriers to MDR-TB treatment adherence, and how to overcome them. I appreciate you taking the time to talk with me today.

Today, I will show you a model for MDR-TB treatment adherence that has been developed based on previous research. I will first explain the structure and components of the model. Then, I will ask how your experiences with MDR-TB matches or does not match this model. The goal is to improve the model based on your expertise on the subject. If you allow me, I will record the interview to make sure that I do not overlook any of your comments. All comments will be considered confidential: your name is not associated with any of them and you treatment and services will not be affected. You are free not to answer any questions you prefer not to answer.

[Explain consent procedures, collect signed consent form, and start tape recorder]

Can you tell me how you are associated with the fight against MDR-TB? I am a…

a. Patient
b. Healthcare Provider
c. Community Health Worker (CHW)
d. Ministry of Health decision-maker
e. Clinic decision-maker
f. Other: [blank space]

[Quick description of the MDR-TB treatment adherence model. Approximately 10 minutes]

Interview Questions [Approximately 20 minutes]

Now that you have a good understanding of the model, please answer the following questions:

1. Are there any components that need to be relabeled?
2. Are there any components that are missing or should not be in the model?
3. Are there any relationships between components that are missing or should not be in the model?
4. Would you make any changes to the direction of effects between components?
5. Would you make any changes to the feedback loops?
6. Are there any last changes you would make to this model?
7. As a [patient/healthcare provider/etc.], what are your assigned role(s) in terms of improving adherence? Please explain using the model.
8. What are the main barriers you face in trying to carry out this role and maintaining high levels of treatment adherence? [for decision-makers, inquire about costs]
9. Now that we have made some changes, does this model accurately represent your experience with the barriers to MDR-TB treatment adherence?

Thank you for your time!

[Give S/.10 in cash for his/her time and dismiss participant]

APPENDIX M. FOCUSED GROUP DISCUSSION GUIDE

Introduction

Hello. My name is _____ (state your affiliation) and this is _____ (introduce assistant). We are conducting a study to understand the barriers to MDR-TB treatment adherence, and how to overcome them. I appreciate you taking the time to talk with me today in this focus group discussion.

Before we begin, I would like to explain what a focus group is. A focus group is like a discussion group. It's a way of listening to people and learning from them. In a focus group, people are asked to talk with others about their thoughts and ideas about a subject. We are interested in hearing what you think and feel about this subject. There are no right or wrong answers. We expect that many you will have different points of view.

Today, I will show you a model for MDR-TB treatment adherence that has been developed based on previous research and individual interviews with stakeholders in your communities. I will first explain the structure and components of the model. Then, I will ask how your experiences with MDR-TB matches or does not match this model. The goal is to improve the model based on your expertise on the subject. If you allow me, I will record the interview to make sure that I do not overlook any of your comments. All comments will be considered confidential: your name is not associated with any of them and you treatment and services will not be affected. You are free not to answer any questions you prefer not to answer.

Our discussion today will last between 60 and 90 minutes. I would like the discussion to be informal, so there's no need to wait for me to call on you to respond. In fact, I encourage you to respond directly to the comments other people make. If you don't understand a question, please let me know. I am here to ask questions, listen to your answers, and make sure everyone has a chance to share their opinions. The only request I have for you is that only one person should speak at a time in order to show respect for everyone's opinions.

We are interested in hearing from each of you, so if we seem to be stuck on a topic, I may interrupt you to move the conversation along. If I do, please don't feel bad about it, it's only to make sure we get through all of the questions and everyone has a chance to share.

We will be tape recording the discussion, because we don't want to miss any of your comments. No one outside of this room will have access to these tapes. No names will be included in any reports. Your comments are confidential. We are also requesting that you make sure personal comments don't leave the room. What is said in this room stays in this room. I hope you'll feel free to speak openly and honestly.

[Explain consent procedures and obtain consent, serve refreshments, and start voice recording]

Can each of you tell me what your role is in relation to MDR-TB? (e.g. patient, healthcare provider, community health worker, Ministry of Health representative, clinic administrator)

[Description of the MDR-TB Treatment Adherence Model. Questions and Answers. Approximately 20 minutes]

Interview Questions [Approximately 40 minutes]

Now that you have a good understanding of the model, please answer the following questions. If there are disagreements, please voice them so that we can discuss and make compromises together:

10. Are there any components that need to be relabeled?

11. Are there any components that are missing?
12. Are there any components that should not be in the model?
13. Are there any relationships between components that are missing or should not be in the model?
14. Would you make any changes to the direction of effects between components?
15. Would you make any changes to the feedback loops?
16. Are there any last changes you would make to this model?
17. Are there any changes you would make to the assigned roles for each of the groups you represent in this model? Please explain using the model.
18. Are there any changes you would make in the model to the main barriers you face in trying to carry out your roles and maintaining high levels of treatment adherence? [probe decision-makers about costs]
19. Now that we have made some changes, does this model accurately represent your experiences with the barriers to MDR-TB treatment adherence?

Thank you for your time!

[Provide reimbursements for transportation and dismiss focus group participants]

APPENDIX N. CONSENT TO PARTICIPATE IN RESEARCH STUDY

STUDY:	***Complex systems: An innovative approach to improve treatment adherence for patients with multidrug-resistant tuberculosis***
INSTITUTIONS:	University of North Carolina at Chapel Hill (USA) Asociación Benéfica PRISMA (Lima, Peru)
INVESTIGATORS:	Kei Alegría-Flores, Dr. Carlton Evans, Dr. Marco Antonio Tovar

Objectives of the study:

This study is about the problems that make it difficult for patients to take their multidrug-resistant tuberculosis (MDR-TB) medications as prescribed. We are contacting 350 patients who have MDR-TB, 100 of their healthcare service providers, 4 community health workers, and 4 decision-makers from the clinic and the Ministry of Health to participate in this study. In the study we ask that you participate in the following activities: interviews and/or focus group discussions. The study is supported by the National Institutes of Health in the United States. Before deciding whether to participate or not, please take a moment to read this document and ask us any questions you may have. We thank you for taking the time to read this.

Procedures:

If you agree, we ask that you participate in one or more of the following activities:

- We will interview you to ask several questions about your experience with MDR-TB. This interview will take between 60 and 90 minutes to complete. If you are a patient, we would also like your permission to review your treatment card.
- We will interview you with questions about your experience with MDR-TB and will record the sound. This interview will take approximately 60 minutes to complete.
- We will ask you to join approximately 5 more persons in a group discussion to answer some questions regarding MDR-TB and share your experiences. Sound will be recorded during this discussion. The group discussion will take between 60 and 90 minutes to complete.

Exclusion criteria:

You will not be able to participate in the study unless you are between 18 and 65 years old, if you have been diagnosed with XDR-TB, or if you are not able to read or understand what is written in this consent form.

Benefits:

The results of this study are expected to improve patients' ability to adhere to MDR-TB treatment. The interviews and focus group discussions may serve as a safe place to express your concerns and satisfaction regarding the MDR-TB treatment process.

Compensation for transportation costs:

As compensation for any transportation costs that may be incurred in relation to participating in this study, participants will receive S/.10 once the questionnaire, interviews, or focus groups have been completed.

Risks/Discomfort:

It is possible that you will remember your experiences during the interviews and this may cause you anxiety or distress. For the discussion group, it is possible that some of what you say is remembered and repeated by other participants once the discussion is over.

Privacy:

Your answers during the interviews and/or group discussions will only be accessible to the investigators of this study. The investigators will keep everything you say anonymous and confidential. Since the group discussions will include other participants, it is possible that there may be a breach of confidentiality. However, each participant will sign an agreement to keep our discussion confidential as part of their consent process to participate in this study.

Questions:

Please ask us questions about anything that is unclear now or in the future. You can ask questions to the person who interviews you or leads the group discussions, or you can call 941914266 to speak with the investigators listed at the top of this consent form. If you would like to speak to someone about ethical issues or your rights as a participant, you could contact Dr. Salomón Zavala, president of the Institutional Review Board at the Asociación Benéfica PRISMA, phone number 2090 400 annex 246.

Voluntary participation:

The participation in this study is completely voluntary. You may stop participating at any moment without any consequences.

If you sign here, you agree to participate in this study. If you are participating in a group discussion today, with your signature you are also agreeing to keep the content of our discussion confidential.

Participant's signature: _____ Name:_____

Investigator's signature: _____ Name: _____

This consent form was fully completed on: ___/___/2015

You will receive a copy of this consent form for your records.