# UNDERSTANDING LOSS TO FOLLOW-UP FROM AND QUALITY OF LIFE DURING DRUG-RESISTANT TUBERCULOSIS TREATMENT IN PUNE, INDIA

by

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# Abstract

The treatment and prevention of multidrug resistant tuberculosis (MDR TB) is a significant public health challenge, particularly in India, which accounts for approximately one quarter of the global burden. First, an overview of MDR TB in India and its public sector treatment is provided, including special emphasis on the challenges of quality of life during and loss to follow-up from treatment (**Chapter 1**). Leveraging multiple sources of registry data in Pune, India, we identified several risk factors for loss to follow-up and mortality during public sector MDR TB treatment. Notably, any history of alcohol use, current treatment for extrapulmonary TB and no prior private treatment were associated with increased loss to follow-up. Mortality was associated with baseline low body mass index, anemia and any prior loss to follow-up from TB treatment (**Chapter 2**). A prospective cohort of individuals newly diagnosed with MDR TB and drug-susceptible TB (DS TB) as well as healthy controls testing negative for TB was established in order to compare quality of life across all three groups. Baseline quality of life (QOL) was impaired in TB and MDR TB patients compared to healthy controls with no significant QOL differences found between individuals with DS TB and MDR TB (**Chapter 3**). In a separate multi-site cross-sectional study, we assessed the willingness of household contacts (HHC) of MDR TB index cases to take preventive therapy to reduce their risk of TB. Overall, HHC willingness was high and notably associated with high TB-related knowledge, comfort telling others about taking preventive therapy and confidence in taking therapy (**Chapter 4**). This dissertation contributes to our understanding of patient-reported and traditional outcomes of public sector MDR TB treatment in India as well as the potential uptake of effective MDR TB preventive therapy when implemented.

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# Chapter I: Introduction

**The global tuberculosis epidemic and the challenge of drug resistance**

The widespread emergence of increasingly drug resistant forms of tuberculosis (TB) is a substantial challenge to current and future TB prevention and care efforts. Despite recent progress in addressing the epidemic, TB remains one of the leading causes of mortality globally with an estimated 10.4 million new cases and 1.7 million deaths in 2016 alone.[1] Multi-drug resistant TB (MDR TB), resistant to at least the two most effective 1st-line anti-TB drugs (rifampicin and isoniazid), and rifampicin-resistant TB (RR TB) were estimated to have caused 580,000 of these new cases and a disproportionately high number of deaths.[1] While drug susceptible TB (DS TB) is generally curable, treatment outcomes for MDR TB are often dismal with only 54% of individuals in 2016 estimated to have had a successful outcome (treatment completion or cure).[1] MDR TB with additional fluoroquinolone and aminoglycoside resistance (i.e. extensively drug-resistant TB, XDR TB) often results in even poorer treatment outcomes. The treatment of MDR and XDR TB although cost-effective[2,3] remains expensive with programmatic costs 10-200 times that of DS TB[4,5] and direct and indirect costs (e.g. lost wages) to patients often exceeding ≥20% of their annual household income.[6,7]

**Burden of tuberculosis and drug-resistant tuberculosis in India**

In 2016, India with the world's second largest population (1.3 billion people) accounted for approximately one quarter of the estimated global incidence of TB (2.8 million cases; 211 per 100,000 persons), 33% of global TB deaths among human immunodeficiency virus (HIV)-negative persons and 26% of overall global TB deaths (435,000; 33 per 100,000 persons).[1] Recent household surveys and studies of anti-TB drug sales[8] have been leveraged to improve these estimates; however, they remain limited by the lack of a national TB prevalence survey, which is scheduled for 2018 and 2019, as well as poor albeit improving TB notification rates from a complex and vast private healthcare sector.[1]

From the initial rollout of a nationwide DR TB plan in 2007, baseline TB drug sensitivity testing (DST) in India was performed only for individuals with a higher risk of resistance (e.g. failures of DS TB regimens

and contacts of known pulmonary MDR TB cases).[9] With increasing laboratory capacity, these eligibility criteria for DST have been expanded over time to include other high-risk groups with a policy of universal baseline DST currently being phased in.[10] As a result, nationwide prevalence estimates of MDR TB have been historically unavailable and instead informed by state-level anti-TB drug resistance surveys from 4 states.[11] Based on these data and public sector recording, there were an estimated 147,000 new MDR TB cases in India in 2016 (11 per 100,000 persons),[1] also accounting for approximately one quarter of global incidence.

The results of the highly anticipated first nationwide prevalence survey of TB drug resistance in India was published in early 2018.[11] This study was a cluster randomized cross-sectional survey of public sector TB diagnostic facilities with the goal of characterizing the prevalence of resistance to 13 anti-TB drugs for recently diagnosed individuals. Compared to previous state-level surveys, a similar prevalence of MDR TB was identified for new (2.8%) and previously treated individuals (11.6%). However, the identification of widespread and diverse resistance to at least one 1$^{st}$ or 2$^{nd}$ line drug (28% new patients; 37% previously treated) highlighted the importance of universal DST and personalized TB regimens.[11]

**Public sector TB diagnosis and treatment in India: The Revised National TB Control Programme**

The National TB Programme of India was founded in 1962 and based on a community-oriented approach of case finding and self-administered TB treatment at home.[12] Over the next three decades, the program was plagued by a wide range of challenges, including: inadequate funding, limited passive case finding, drug shortages, high rates of loss to follow-up from treatment and the development of anti-TB drug resistance. After several national and international review committees, the Revised National TB Control Programme (RNTCP) was launched in 1993 on the basis of the internationally recommended Directly Observed Treatment - Short Course (DOTS) strategy. Many of the observed challenges of NTP were addressed by the pillars of the DOTS strategy: diagnosis by quality ensured sputum smear microscopy, treatment by a recently developed and standardized six-month (short course) DS TB regimen, regular

supply of anti-TB drugs, standardized recording and monitoring and sustained political and financial commitment. Initially piloted in a few districts in India, RNTCP became a national program in 1997 and was expanded from 1998 to 2006.[13] With many successes, RNTCP continues to provide free of cost public sector TB diagnosis, treatment and hospitalization across the country.[14,15]

Due to the increasing global evidence and consequences of widespread MDR TB in the late 1990s and early 2000s, the World Health Organization and many key partners created guidelines for the programmatic management of drug-resistant TB (PMDT)[16] in an attempt to more proactively address the challenge of resistance. This approach was introduced in India through RNTCP in 2007 and successfully scaled up nationwide by 2013.[9,11]

**MDR TB diagnosis and pre-treatment evaluation in India through PMDT**

In accordance with RNTCP PMDT guidelines,[17] initial MDR TB diagnosis is performed using either culture-based or rapid molecular assay (line probe assay, LPA; cartridge-based nucleic acid amplification testing, CBNAAT) drug sensitivity testing (DST). Accredited DST laboratories include primarily National Reference Laboratories and Intermediate Reference Laboratories (IRL) as well as district-level RNTCP CBNAAT labs, government medical colleges and some private facilities. Since the rollout of CBNAAT in India starting in 2012, DST for presumptive MDR TB has been increasingly decentralized with the step-wise introduction of CBNAAT machines to high-burden anti-retroviral therapy (ART) centers in 2014, high-burden microscopy centers in 2015 and RNTCP district-level laboratories in 2016. Baseline DST eligibility criteria have expanded from only individuals failing DS TB treatment prior to 2013 to currently all patients diagnosed with TB except for new pulmonary cases without HIV co-infection (**Table 1.1**).[17] As RNTCP moves toward universal baseline DST, recent program guidelines have also included DST for other high-risk groups, including children, extrapulmonary TB cases (EP TB), and individuals with diabetes or malnutrition.[11,17]

MDR TB pre-treatment evaluation and care through RNTCP is coordinated at four progressively decentralized administrative levels: Drug-resistant TB Centers (DR TB Centers), District TB Offices (DTOs), the sub-district Tuberculosis Units (TUs) and peripheral health institutions (PHIs) or DOT centers.[17] Individuals diagnosed with MDR TB who plan to initiate public sector treatment are first referred for a 3 to 7-day hospitalization for pre-treatment evaluation at a DR TB Center. During this baseline assessment, socio-demographic information and clinical history are recorded and relevant imaging (e.g. chest radiograph) performed. Baseline laboratory tests include: complete blood count, random blood glucose, liver function tests, blood urea, serum creatinine, thyroid stimulating hormone, urinalysis and if relevant a pregnancy test. Fasting blood glucose and an oral glucose tolerance test are also performed for patients with potential or known diabetes. Patients with unknown HIV status or a negative HIV test that is more than 6 months old are referred for HIV counseling and testing at the nearest public sector testing center.[9,17]

At the DR TB Center, all clinical, laboratory and TB diagnostic data are recorded and compiled in patient medical records by physicians and staff. A committee of physicians, microbiologists and other clinical experts review cases of all individuals eligible for MDR TB treatment and recommend initiation when appropriate.[9,17] Diagnostic and pre-treatment evaluation data are also abstracted at some DR TB Centers onto a single page form by a medical officer and the site's statistical assistant in preparation for committee meetings. After treatment initiation, each individual is assigned an RNTCP PMDT identification number, PMDT cards for each administrative level are created for treatment monitoring and patients are registered in the PMDT register maintained at the DR TB Center as both a hard copy and also often a soft copy in Microsoft Excel. Not all patients are able or willing to present for pre-treatment evaluation at DR TB Centers. These individuals, are most often evaluated and initiated on treatment at the district level. Although basic patient data is communicated to the DR TB Center to facilitate the assignment of a unique TB identification number, complete pre-treatment evaluation data for these individuals is not always readily available.

**MDR TB treatment in India through PMDT**

Upon discharge from the DR TB Center, all patients are given a 7-day supply of medication and referred to the District TB Office (DTO) corresponding to their place of residence. The DOTS-Plus Supervisor (DPS) for each district works with the patient to identify the most convenient location for treatment continuation first at the TU-level and then a specific PHI or DOT center. Since the initiation of PMDT in India, standardized MDR TB treatments have been administered, consisting of a 6 to 9-month intensive phase of 6 drugs (kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol and cycloserine) followed by an 18-month continuation phase of 4 drugs (levofloxacin, ethionamide, ethambutol and cycloserine) with weight-based dosing. This treatment regimen can be modified to account for demonstrated drug intolerance during pre-treatment evaluation or baseline resistance. Monitoring of therapy occurs theoretically through direct observation 6 out of 7 days a week for 24-27 months by a program-approved DOT provider at a DOT center.[9] In practice, however, some patients or their family members may be given several days of medication at intervals ranging from a few days to a month.[18] For pulmonary TB cases, microbiological treatment response is assessed by sputum smear and culture at 3, 4, 5, 6, 7, 9, 12, 15, 18, 21, and 24 months of treatment with samples analyzed most often at IRLs. Treatment response for extrapulmonary TB cases is monitored clinically.

**Recording and monitoring of MDR TB treatment in India through PMDT**

MDR TB treatment status is recorded and monitored at each of the four RNTCP PMDT administrative levels (**Figure 1.1**). Separate copies of PMDT treatment cards are maintained at each level for all individuals on MDR TB treatment. These treatment cards contain: basic demographic information, HIV status, diagnostic DST results, records of the directly observed administration of drugs, follow-up sputum culture and chest radiograph results, adverse drug reactions, information on attempts to trace patients during treatment interruptions and the final treatment outcome and date. The treatment cards of all levels are updated by hand at a series of monthly meetings between the supervisors of each level and the level below. For example, DOT Providers at the PHI / DOT center level update treatment cards daily after the

administration of drugs. Senior TB Treatment Supervisors (STS) overseeing RNTCP activities at the TU-level meet with all DOT Providers monthly and update their TU-level treatment cards based on the PHI-level cards. Similarly, district-level DPSs meet with all STSs at least once per month, and the DPSs in turn meet with the DR TB Center's Data Coordinator monthly.

As a result of the large number of patients and consequently number of treatment cards, PMDT treatment registers are also maintained at the district and DR TB Center-levels. These registers provide a summary of treatment card information but do not include records of the directly observed administration of drugs, chest radiograph results, adverse drug reactions and tracing attempts during treatment interruptions. Data quality can be highly variable across all administrative units for patient information in general and specifically for data not required for reporting activities or frequently reviewed by supervisors.

**Loss to follow-up from MDR TB treatment: a key outcome for patients and programs**

Due to prolonged, costly treatment regimens with less effective and more toxic medications, MDR TB treatment is particularly challenging to patients, their families and TB programs. Quality of life is substantially impaired by both tuberculosis as well as its treatment through adverse drug events, stigma and depression among other mechanisms.[19-21] These negative effects, in addition to being important patient outcomes on their own, can also lead to poor treatment adherence and loss to follow-up.[20,21] Reported public sector treatment outcomes in India through RNTCP are poor and similar to global averages: 47% success (completion or cure), 20% death and 19% loss to follow-up.[10] Loss to follow-up from treatment, most often defined for TB as a treatment interruption ≥2 months for any reason has been associated with substantially higher mortality,[22,23] development of additional drug resistance,[24] and the potential for community transmission of drug-resistant TB.

**Health-related quality of life during MDR TB treatment**

Traditionally, the focus of TB treatment has been on achieving microbiological cure with less emphasis on morbidity and patient-reported outcomes, such as quality of life (QOL). Health-related quality of life is a multi-dimensional construct that emphasizes the patient's perspective and defines health as physical, mental and social well-being rather than strictly the absence of illness.[25] Despite the well-documented negative impacts of TB and TB treatment on quality of life, prior studies have several limitations: study populations composed predominantly of young to middle-aged adult males, limited socioeconomic data, a wide range of survey instruments utilized, lack of comparison groups and individuals with MDR TB.[26-28]

**Research objectives and conceptual framework**

Strategies aimed at addressing drug-resistant TB have historically focused on preventing acquired drug resistance by optimizing DS TB treatment completion and cure rates.[9] Recent research has however suggested that the primary driver of MDR TB epidemics in high-burden settings may actually be transmission, highlighting the fundamental importance of improving MDR TB diagnosis, treatment and cure rates.[29-31] Achieving the 2015 WHO *End TB Strategy*[32] and the recent Government of India target of TB elimination by 2025[12] will require substantial efforts and funding to continue to improve MDR TB care in India. Critical to meeting these targets is a more systematic and granular understanding of the extent and severity of TB patient needs and the barriers to treatment retention. The flexible application of this knowledge to broad or local implementation challenges will substantially inform both the development of treatment support programs and efforts to improve outcomes.[33]

As patient quality of life and treatment retention are key drivers of treatment success, and loss to follow-up an opportunity for intervention, the present research has two primary aims:

(1) Examine the timing and risk factors for loss to follow-up among public sector MDR TB patients by integrating pre-treatment evaluation, laboratory and treatment data in Western Maharashtra, India

(2) Compare baseline quality of life for newly diagnosed MDR TB and DS TB patients initiating public sector treatment to TB-negative healthy controls undergoing sputum microscopy through RNTCP in Pune, India

Risk factors of loss to follow-up and challenges during MDR TB treatment were categorized based on recent systematic reviews and WHO guideline documents (**Figure 1.2**).[20,34,35] The causal relationships between these factors are likely complex and were not investigated.

**References**


1) Global Tuberculosis Report, 2017. WHO/HTM/TB/2017.23. Geneva, Switzerland: World Health Organization, **2017**.

2) Fitzpatrick MC, Floyd K. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis. PharmacoEconomics **2012**; 30:63–80.

3) Resch SC, Salomon JA, Murray M, Weinstein MC. Cost-effectiveness of treating multidrug-resistant tuberculosis. PLoS Med **2006**; 3:e241.

4) TB India 2015 Annual Status Report. Revised National Tuberculosis Control Program. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, **2015**.

5) TB Drug Resistance in the US – Factsheet. Centers for Disease Control and Prevention (CDC), **2015**.

6) Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. Eur Respir J **2014**; 43:1763–1775.

7) Wingfield T, Boccia D, Tovar M, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. PLoS Med **2014**; 11.

8) Arinaminpathy N, Batra D, Khaparde S, et al. The number of privately treated tuberculosis cases in India: an estimation from drug sales data. Lancet Inf Dis **2016**; 16:1255-1260.

9) Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, **2012**.

10) India TB Report 2018. Revised National Tuberculosis Control Programme Annual Status Report. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, **2018**.

11) Report of the First National Anti-Tuberculosis Drug Resistance Survey India 2014-16. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, **2018**.

12) National Strategic Plan for Tuberculosis Elimination 2017-2025. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, **2017**.

13) Brimnes N. Languished Hopes: Tuberculosis, the State, and International Assistance in Twentieth-century India. Orient Blackswan, **2016**, 249-269.

14) Khatri GR, Frieden TR. Controlling tuberculosis in India. New Engl J Med **2002**; 347:1420–1425.

15) Khatri GR, Frieden TR. Rapid DOTS expansion in India. Bull World Health Organ **2002**; 80:457–463.

16) Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2006.361. Geneva, Switzerland: World Health Organization, **2006**.

17) Guidelines on Programmatic Management of Drug-Resistant Tuberculosis in India, 2017. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, **2017**.

18) 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.

19) Rajeswari R, Balasubramanian R, Muniyandi M, Geetharamani S, Thresa X, Venkatesan P. Socio-economic impact of tuberculosis on patients and family in India. Int J Tuberc Lung Dis **1999**; 3:869–877.

20) Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med **2007**; 4.

21) Thomas BE, Shanmugam P, Malaisamy M, et al. Psycho-socio-economic issues challenging multidrug resistant tuberculosis patients: a systematic review. PLoS One **2016**; 11:e0147397.

22) Franke MF, Appleton SC, Bayona J, et al. Risk factors and mortality associated with default from multidrug-resistant tuberculosis treatment. Clin Infect Dis **2008**; 46:1844–1851.

23) Moyo S, Cox HS, Hughes J, et al. Loss from treatment for drug resistant tuberculosis: risk factors and patient outcomes in a community-based program in Khayelitsha, South Africa. PLoS One **2015**; 10:e0118919.

24) Caminero, JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. Int J Tuberc Dis **2010**; 14:382–390.

25) WHOQOL User Manual. Geneva, Switzerland: World Health Organization, Division of Mental Health and Prevention of Substance Abuse, **1998**.

26) Bauer M, Leavens A, Schwartzman K. A systematic review and meta-analysis of the impact of tuberculosis on health-related quality of life. Qual Life Res **2013**; 22:2213–35.

27) Brown J, Capocci S, Smith C, Morris S, Abubakar I, Lipman M. Health status and quality of life in tuberculosis. Int J Inf Dis **2015**; 32:68–75.

28) Guo N, Marra F, Marra CA. Measuring health-related quality of life in tuberculosis: a systematic review. Health Qual Life Outcomes **2009**; 7:14.

29) Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. Lancet Respir Med **2015**; 3:963–972.

30) Van Rie A, Warren RM. MDR tuberculosis control: time to change the dogma? Lancet Respir Med **2015**; 3:907–909.

31) Sharma A, Hill A, Kurbatova E, et al. Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study. Lancet Inf Dis **2017**; 17:707–715.

32) The End TB Strategy: Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015. Geneva, Switzerland: World Health Organization, **2015**.

33) Report of the Joint Monitoring Mission Revised National Tuberculosis Control Programme, April 2015. New Delhi, India: World Health Organization Country Office for India, **2016**.

34) Sabaté E. Adherence to long-term therapies: evidence for action. Geneva, Switzerland: World Health Organization, **2003**.

35) Ogundele OA, Moodley D, Pillay AW, Seebregts CJ. An ontology for factors affecting tuberculosis treatment adherence behavior in sub-Saharan Africa. Patient Prefer Adherence **2016**; 10:669–681.

**Table 1.1:** Change in presumptive MDR TB criteria and availability of cartridge-based nucleic acid amplification testing (CBNAAT) during CBNAAT rollout within the Drug-resistant Tuberculosis Center – Pune catchment area between 2012-2017[9]

| Year | Presumptive MDR criteria* | CBNAAT |
|---|---|---|
| 2012 | A | None |
| 2013 | A + B | IRL Pune |
| 2014 | A B C | High-burden ART centers |
| 2015 | A B C | High-burden microscopy centers |
| 2016 | A B C | Each district |
| 2017 | A B C | >1 in some districts + medical colleges |
| ***Criteria A –**<br>• All failures of new TB cases<br>• Smear positive previously treated cases who remain smear positive at 4th month onwards<br>• All pulmonary TB cases who are contacts of known MDR TB case | | |
| ***Criteria B –** in addition to Criteria A<br>• All smear positive previously treated pulmonary TB cases at diagnosis<br>• Any smear positive follow up result in new or previously treated cases | | |
| ***Criteria C –** in addition to Criteria B<br>• All sputum smear negative previously treated pulmonary TB cases at diagnosis,<br>• HIV TB co-infected cases at diagnosis | | |

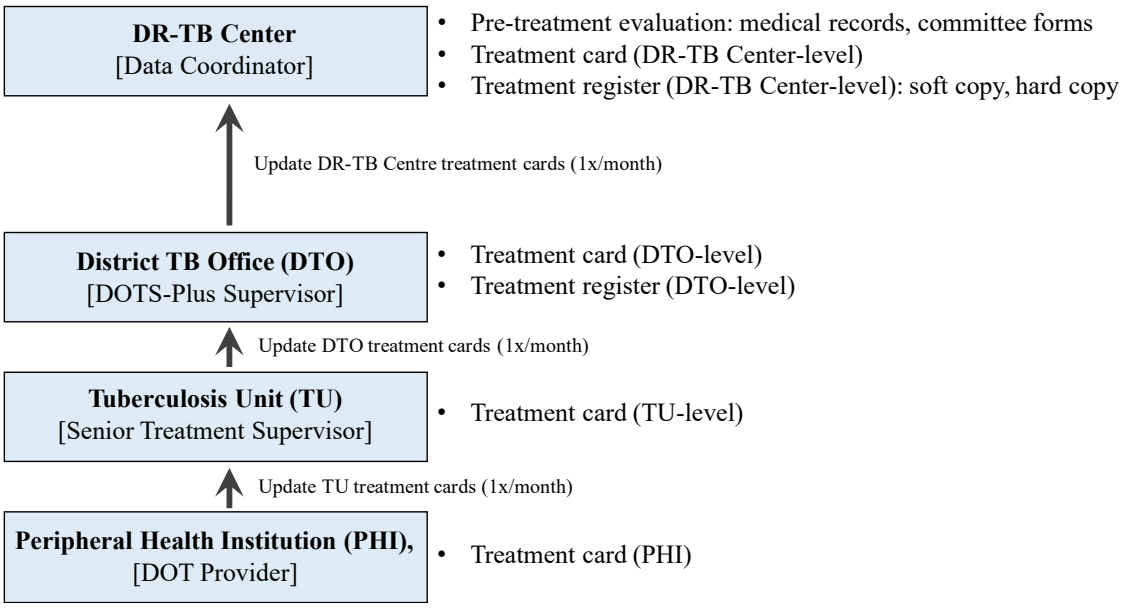


**Figure 1.1:** Administrative levels of programmatic management of drug-resistant tuberculosis in India (left), records maintained for pre-treatment evaluation and treatment monitoring (right) as well as the flow and timing of treatment data from decentralized to centralized levels in the hierarchy[9,17]

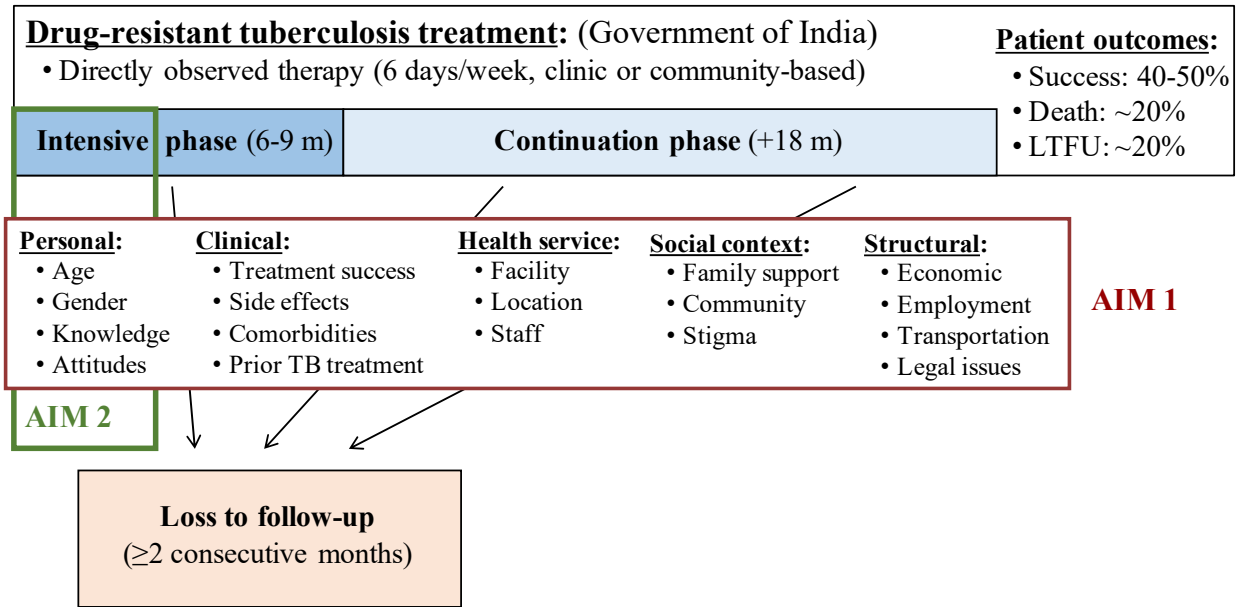


**Figure 1.2:** Conceptual framework for factors influencing loss to follow-up (LTFU) from public sector MDR TB treatment in India

# Chapter II: Factors Associated with Loss to Follow-up and Mortality during Public Sector Multidrug-Resistant Tuberculosis Treatment in Western Maharashtra, India

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**Abstract:**

**Background:** Poor treatment outcomes for multidrug-resistant tuberculosis (MDR TB) are a continued challenge for patients, clinicians, communities and TB programs. Leveraging programmatic data provides an opportunity to identify local challenges and barriers to TB care. In the present analysis, factors associated with mortality and loss to follow-up (LTFU) from MDR TB treatment in Western Maharashtra, India were examined.

**Methods:** For this registry analysis, individuals starting public sector MDR TB treatment in 5 districts of Western Maharashtra between 2015-2016 were included. LTFU was defined as a treatment interruption ≥2 months, and mortality defined as death from any cause. Baseline factors associated with LTFU and mortality were assessed using cause-specific hazards models. Kaplan-Meier estimates of the cumulative incidence of LTFU were corrected for the competing risk of death. The impact of missing values on final model parameter estimates was examined by comparing estimates from complete case analyses and after multiple imputation to fill in missing values.

**Results:** In total, 921 individuals on MDR TB treatment were included with 1127 person-years (PY) of follow-up after treatment initiation. During follow-up, 130 patients were lost to follow-up and 194 died. After adjusting for district, year of treatment registration and baseline covariates, factors significantly associated with LTFU after multiple imputation of missing values were history of alcohol use (aHR 1.62, 95%CI 1.01-2.61), extrapulmonary TB (vs. pulmonary TB, aHR 2.14, 95%CI 1.04-4.41) and any history of prior private TB treatment (aHR 0.56, 95%CI 0.34-0.91). Mortality during MDR TB treatment was associated with baseline severe underweight (BMI <16 kg/$m^2$; aHR 2.78, 95%CI 1.68-4.59) and moderate underweight (<17 & ≥16 kg/$m^2$; aHR 1.94, 95%CI 1.01-3.70) vs. normal BMI or overweight (≥18.5 kg/$m^2$), baseline severe anemia (aHR 3.44, 95%CI 1.58-7.52) and moderate anemia (aHR 2.04, 95%CI 1.01-4.12) vs. no anemia, any prior LTFU from TB treatment (aHR 2.17, 95%CI 1.56-3.03) and treatment initiation in 2016 vs. 2015 (aHR 0.73, 95%CI 0.54-0.99).

**Conclusion:** An understanding of the factors associated with mortality and LTFU from treatment has the potential to inform the development and implementation of patient-centered support programs. Efforts to address several of the identified risk factors are underway through the public sector TB program in India, including: decentralized drug susceptibility testing and integrating TB counseling activities with de-addiction services.

**Introduction:**

Poor treatment outcomes for multidrug-resistant tuberculosis (MDR TB) remain a challenge with substantial ramifications for patients, clinicians, communities and TB programs. An understanding of the determinants of poor outcomes has the potential to inform efforts to improve TB care and has been continually prioritized in national and international TB research agendas.[1-3] Significant research has been conducted characterizing factors associated with MDR TB treatment outcomes, including: TB resistance profiles and treatment characteristics,[4-6] directly observed therapy[7] and comorbidities.[8-10] Although significant research on drug susceptible TB treatment outcomes has also been conducted, factors associated with poor outcomes may differ from MDR TB due to prior patient treatment experiences as well as a longer, more difficult regimen.[11] Furthermore, recent studies on MDR TB loss to follow-up and mortality have described disparate sets of risk factors in different settings, emphasizing the need to understand local context in order to develop effective support programs.[12-15]

India accounts for approximately one quarter of the global burden of MDR TB.[16] Quantitative studies of risk factors of loss to follow-up and mortality during MDR TB treatment in India's large public sector program have been predominantly small (~100 patients or less) and often confined to single treatment facilities.[17-26] Notable retrospective studies of public sector treatment data at district and even national levels[27-31] have been published primarily for patients initiating treatment between 2007 and 2013. These studies have observed that approximately half of treatment loss to follow-up occurred within 6 months of initiation, and loss to follow-up was consistently associated with male sex and low BMI as well as in some settings migration, provider change during treatment and poor treatment response. Qualitative studies examining reported barriers to retention among successfully traced patients lost to follow-up in the Indian states of Maharashtra and Gujarat have revealed diverse and multifaceted barriers, including: adverse drug effects, stigma, lack of family support, poor relationships with medical providers and competing employment demands.[32,33] For mortality during MDR TB treatment, prior research has identified

associations between higher mortality and low BMI, HIV infection, pulmonary TB and second-line drug resistance.[29-31,34]

This and related prior research, however, has generally had four primary limitations: (1) lack of inclusion of likely relevant risk factors (e.g. alcohol and tobacco use),[29-31] (2) analysis of composite unfavorable treatment outcomes (e.g. death, failure and loss to follow-up) that may have different risk factor patterns if outcomes were analyzed individually,[24,29] (3) reliance on complete case analyses or a lack of explicit description of approaches taken to address missing data[30] and (4) survival analyses conducted without taking into account competing risks,[27,31] such as death for the outcome of loss to follow-up.[35,36] Attempting to address these limitations, the present research aimed to leverage programmatic public sector MDR TB diagnosis, pre-treatment evaluation and treatment data through the DR TB Center – Pune in order to identify factors associated with loss to follow-up (LTFU) and mortality during MDR TB treatment.

**Methods:**

*Study setting:*

Through collaboration with the State TB Office – Maharashtra, the Drug Resistant TB Center – Pune at Aundh Chest Hospital (ACH), and the State TB Training and Demonstration Center, Pune (STDC), a retrospective cohort of MDR TB patients initiating public sector treatment from 2015 to 2016 was created. Established in 2011, the DR TB Center – Pune and STDC coordinate the diagnostic testing, pre-treatment evaluation and DR TB treatment for 5 districts in Western Maharashtra, India. Due to the continued decentralization of TB care, the districts included within its catchment area have changed over time. Kolhapur, Sangli and Sindhudurg Districts were transferred to other centers in 2013, and Raigad District was added in July 2015 (**Figure 2.1**). At present, ACH serves as the DR TB Center for Pune, Solapur, Satara, Ahmednagar and Raigad districts that have a combined population greater than 23 million[37] and an average of approximately 600 individuals initiating public sector MDR TB treatment per year between 2015 and 2017.

*Study population:*

This study included individuals starting public sector MDR TB treatment through RNTCP who registered for treatment within the catchment area of the DR TB Center – Pune between January 1, 2015 and December 31, 2016 with follow-up through April 10, 2018. Exclusion criteria for treatment registrations included: (1) XDR TB treatment initiation; (2) previous treatment registration in 2015 and 2016 following transfer out or loss to follow-up; (3) missing pre-treatment evaluation data; and, (4) unknown patient treatment status and/or treatment outcome date following review of follow-up sputum culture data, PMDT cards, PMDT registers and adjudication discussions with district-level DPSs.

*Data collection and adjudication:*

For pre-treatment evaluation data, a codebook of potential variables of interest was created based on India's Revised National TB Control Programme (RNTCP) programmatic management of drug-resistant TB (PMDT) guidelines[38,39] and an initial data review of 2 months of medical records and DR TB Center committee forms at ACH. Using this codebook, a standardized Microsoft Excel sheet for data abstraction was developed with data validation to minimize entry errors. For all individuals starting treatment at ACH between January 1, 2015 and December 31, 2016, relevant data were abstracted from all available case papers and DR TB Center committee forms. Any discrepancies between medical records and the committee forms were adjudicated with the DR TB Center Statistical Assistant.

For corresponding MDR TB treatment data, an updated version of the soft copy PMDT register was obtained from the DR TB Center Statistical Assistant two months prior to study administrative censoring on April 10, 2018. All variables were cross-checked with the hard copy PMDT register at the DR TB Center and any discrepancies adjudicated with the Statistical Assistant. To obtain the most accurate outcome information available, treatment outcomes and dates were also abstracted from DR TB Center PMDT cards. Discrepancies, including missingness, between the soft copy PMDT register, hard copy PMDT register and

DR TB Center PMDT cards were adjudicated through comparisons with the district-level PMDT registers as well as discussions with the DOTS-Plus supervisors (DPS) from each district during their April 10-11, 2018 monthly data review meeting at ACH. The current treatment status for individuals without any recorded treatment outcome was ascertained through discussion with each DPS based on their personal knowledge of the individual's treatment and recent discussions with staff at more decentralized levels. Individuals known to be on treatment were administratively censored on April 10, 2018 and a treatment outcome of "on treatment" was recorded. Individuals not known to be on treatment or with an unknown outcome date were administratively censored as "on treatment" at the last known date of sample collection for culture follow-up.

Individual pre-treatment evaluation and MDR TB treatment data were matched using PMDT numbers, name, age, sex and district of residence. Data available in both sources (**Table 2.1**) were compared and discrepancies resolved by reviewing both data sources and through discussions with the Statistical Assistant. A list of all individuals registered in treatment in 2015 or 2016 but without identified pre-treatment evaluation data at ACH was compared to records of patients known to have started treatment at the district level (i.e. start at district), referred to ACH after pre-treatment evaluation (i.e. refer in) or transferred into the DR TB Center – Pune catchment area after public sector treatment initiation elsewhere (i.e. transfer in). Remaining individuals with unexplained missing pre-treatment evaluation data were discussed with the DR TB Center Statistical Assistant and district DPSs to identify other reasons for missingness, including treatment initiation in the outpatient department at ACH or other surrounding hospitals. Successful merger of data sources for each individual was verified by manually by comparing names and demographic information. Multiple registrations were identified for individuals who were lost to follow-up or transferred out and later returned to initiate treatment again. In these cases, the first registration was retained and subsequent registrations were excluded from the study.

*Study variables:*

The primary treatment outcomes for this analysis were loss to follow-up and death, which were defined according to World Health Organization (WHO) and RNTCP definitions as a treatment interruption ≥2 months for any reason and death during MDR TB treatment for any reason, respectively.[38-40] Other treatment outcomes were censored for this analysis and included: cure, treatment completion, treatment failure, switch to XDR TB regimen, transfer out and still on treatment. Analyzed baseline risk factors of loss to follow-up and mortality during treatment included demographic, clinical, health service and social variables routinely collected during pre-treatment evaluation or treatment through RNTCP (**Table 2.1**). For each patient, information about each period of prior TB treatment was abstracted from the medical record into the following variables: type of treatment, location (public vs. private), year of initiation, duration and outcome. Loss to follow-up from either public or private treatment and any prior treatment in the private sector were treated as binary variables.

Baseline clinical factors included: malnutrition, HIV infection, anemia, and diabetes. Nutritional status was assessed using body mass index (BMI), which was categorized according to WHO cut-offs: <16 kg/$m^2$ (severe underweight), 16.0–16.9 kg/$m^2$ (moderate underweight), 17.0–18.49 kg/$m^2$ (mild underweight), 18.5–24.9 kg/$m^2$ (normal range), ≥25 kg/$m^2$ (overweight).[41] The categories of normal and overweight BMI were combined due to the small number of individuals in the latter category. HIV status was ascertained from HIV test reports at or within 6 months of pre-treatment evaluation or evidence of current anti-retroviral treatment in the medical record. Hemoglobin concentrations for the diagnosis of anemia severity were based on WHO recommendations,[42] which include separate cutoffs for children 6-59 months of age, children 5-11 years of age, children 12-14 years of age, non-pregnant women 15 years of age and above, pregnant women and men 15 years of age and above. Adjustments of hemoglobin concentrations for residential elevation above sea level were not required due to the <1000-meter elevation of the study area. Hemoglobin adjustments for current smoking status were not possible due to a lack of data. Diabetes was defined as

either (1) self-reported diagnosis or diabetes treatment by the patient or (2) fasting plasma glucose ≥126mg/dL or oral glucose tolerance test at 2 hours of ≥200mg/dL at the time of pre-treatment evaluation.

Health service and social factors included delay in treatment initiation, RNTCP district coordinating treatment, year of treatment registration and any history of alcohol or tobacco use. Delay in treatment initiation was defined as the days between DST diagnostic sample collection and admission at ACH for pre-treatment evaluation. For analysis, delay was categorized as 0-7 days, 8-14 days, 15-30 days and >30 days. Evidence of either a history of alcohol use or smoking/smokeless tobacco use in the medical record were categorized as binary variables.

*Statistical analysis:*

Baseline factors associated with loss to follow-up and mortality during public sector MDR TB treatment were assessed using survival analysis methods. Person-time contributing to the study was calculated from MDR TB treatment initiation to treatment outcomes of interest (loss to follow-up, death) or censoring. Individuals were censored on the outcome date for cure, completion, failure, switch to XDR TB treatment and transfer out, or on the last known follow-up sputum sample collection date for patients without complete outcome information. All individuals still on treatment through April 10, 2018 were administratively censored. Covariates of interest were chosen prior to statistical analysis based on literature review and conversations with RNTCP staff. Crude loss to follow-up and mortality rates were calculated for levels of each covariate included in the analysis.

In survival analysis, the presence of competing events, which preclude the event of interest from occurring, may result in informative censoring and biased Kaplan-Meier estimates of the survival function. Two approaches have become widely used for these analyses: cause-specific and subdistribution hazards models,[43] both of which model variations in the standard hazard function used in Cox proportional hazards models. The cause-specific hazard is defined as the hazard of experiencing a specific event in the presence

of competing events. Similar to the standard hazard function, individuals experiencing either the event of interest or a competing event are censored and removed from subsequent risk sets. As a result, the modeling of covariate effects on cause-specific hazards can be accomplished using Cox proportional hazards models. Although, cause-specific hazard ratios (csHR) are a useful measure of association they are not a direct measure of association with the risk or cumulative incidence of the event of interest.[44,45] The subdistribution hazard function redefines the risk sets in a survival analysis by including all individuals who have experienced a competing event at a prior time. Although less frequently used, subdistribution hazards models (i.e. Fine and Gray models), allow for the estimation of measures of association, the subdistribution hazards ratio (sdHR), that are directly related to the risk of the event of interest.[44]

In the present analysis of factors associated with loss to follow-up from treatment, mortality is a competing event. Cumulative incidence curves, produced using Kaplan-Meier estimators corrected for competing events if any (Stata –stcompet), were used to visualize the risk of loss to follow-up and mortality during treatment. Factors associated with loss to follow-up during MDR TB treatment were examined using both univariate and multivariable cause-specific hazards models.

Prior to fitting the final multivariable models, multiple imputation by chained equations (MICE) was used to fill in values[46] for the following variables: tobacco use (11.1%), alcohol use (11.0%), diabetes (9.0%), anemia (1.3%), nutrition status (categorized BMI, 1.1%), pre-treatment delay (0.5%), HIV status (0.4%) and site of TB disease (0.1%). Assuming missingness at random, multiple imputation uses a conditional regression-based approach to create multiple imputed data sets where missing values are estimated for each imputed variable from distributions conditional on specified covariates. Multinomial and standard logistic imputation models were fit for categorical and binary variables, respectively, using the –augment option in Stata to account for the presence of perfect prediction of categorical variables.[47] Imputation models contained the 14 covariates included in the cause-specific hazards models as well as the auxiliary variables of the outcome of interest (loss to follow-up or death) and month of treatment registration. MICE was used

to generate 20 imputed data sets (Stata v13.1 -mi impute chained), and the distribution of imputed values for all variables was compared to the observed values to assess for any systematic differences.[48] Exploratory data analysis of the mean and standard deviation of imputed values for each covariate suggested that ~10 iterations prior to saving the imputed data set was adequate to ensure convergence of the algorithm (**Supplementary Figures 2.1 and 2.2**).

Using the 20 imputed datasets, multivariable cause-specific hazards models were fit and the parameter estimates and standard errors were combined using Rubin's formulas.[49] Results from the complete-case analyses and the analyses following multiple imputation were compared qualitatively. The proportional hazards assumption for each model was assessed using log-log plots of the survival function and the inclusion of interactions between specific covariates and time. Goodness of final model fit was assessed using Cox-Snell residuals plotted against the observed cumulative hazard function. All analyses were conducted in Stata v13.1 (StataCorp, College Station, TX, USA).

*Ethical considerations:*

Ethical approval was obtained from the State Public Health Research Ethics Committee – STDC, Pune and Johns Hopkins School of Medicine Institutional Review Board.

**Results:**

*Eligibility for study inclusion of public sector DR TB treatment registrations at DR TB Center – Pune*

Between January 1, 2015 and December 31, 2016, there were 1246 registrations for public sector DR TB treatment at the DR TB Center – Pune (**Figure 2.2**). XDR TB registrations (n = 99, 7.9% of all registrations), second MDR TB registrations during 2015 and 2016 (n = 8, 0.7% of all MDR TB registrations) and patients transferring in from other public sector DR TB centers after treatment initiation (n = 97, 8.5% of new MDR TB registrations 2015-16) were ineligible for study inclusion. Among individuals registering for a new course of MDR TB treatment at the DR TB Center – Pune, 101 (8.9% of new MDR TB registrations from

2015-16) were excluded due to unavailable pre-treatment evaluation data. The primary reason for unavailable data was pre-treatment evaluation conducted at a district-level public sector hospital and not at the DR TB Center (n = 94, 93% of unavailable pre-treatment data) with additional minor reasons being referrals from unspecified hospitals (n = 2), evaluation at a nearby local hospital (n = 1), and no reason identified (n = 4). Of the 941 individuals registered for new MDR TB treatment in 2015-16 with available pre-treatment evaluation data, 20 (2.1%) had unknown treatment status after PMDT registration with no clarifying information identified following review of follow-up sputum culture data, PMDT cards, PMDT registers and adjudication discussions with district-level DPSs.

*Characteristics of included MDR TB patients initiating public sector in 2015-2016*

For all covariates of interest, complete data was available for 740 MDR TB patients (80.3%) in the cohort (n = 921) with no missing values for patient age, sex and TB treatment history. Observed missingness for the other covariates ranged from 0.1 to 11% (102/921) (**Table 2.2**) with tobacco history (11%), alcohol history (11%) and diabetes (9%) having the highest proportion of missing values and all other covariates with 1.3% missingness or less.

The median cohort age was 30 years (interquartile range; IQR 24-42) and 36% of included MDR TB patients were female. For prior TB treatment history, 28% had previously taken TB treatment in the private sector and 21% had been lost to follow-up from either public or private treatment. Alcohol and tobacco use, either current or in the past, were reported by 20% and 15% of patients, respectively. For the present diagnosis of MDR TB, median pre-treatment delay was 13 days (IQR 7-21, max 154) and 4.7% of patients had extrapulmonary TB (EP TB). Among the included EP TB cases (n = 43), 36 (84%) had available information on EPTB site: 20 (56%) isolated TB lymphadenitis, 6 (17%) isolated cold abscess, 4 (11%) pleural effusion, 4 (11%) abdominal TB and 2 (6%) TB arthritis. Of recorded comorbidities, 7% had a recent HIV positive test result or were on antiretroviral therapy (ART), 12% had diabetes, 77% had a body mass index (BMI) categorized as underweight (<18.5 $kg/m^2$) with 49% severely underweight (<16 $kg/m^2$);

and 91% had a baseline hemoglobin diagnostic of anemia with 27% mild anemia, 55% moderate and 9% severe.

*Loss to follow-up and mortality during public sector MDR TB treatment and associated factors*

The median duration of follow-up after initiating public sector MDR TB treatment was 16.6 months (IQR 5.9-23.7) with 1127 person-years (PY) of follow-up in the cohort. Among the included individuals who had an official final treatment outcome declared (n = 299, i.e. enrolling in treatment before October 2015), 39% completed treatment or were cured, 27% died, 15% loss to follow-up, 11% transferred out, 4% switched to XDR TB treatment and 4% failed treatment. Among all included individuals (n = 921), 20% completed treatment or were cured, 21% died, 14% loss to follow-up, 8% transferred out, 7% switched to XDR TB treatment, 1% failed treatment and 29% were still on treatment at the time of administrative censoring. During follow-up for all included individuals starting treatment during 2015 and 2016, 130 were lost to follow-up with a median time to LTFU of 6.2 months (IQR 3.0-11.7) and a crude incidence rate of 11.5 events per 100PY (95%CI 9.7-13.7). Regarding mortality, 194 individuals died of any cause during treatment with a median time to death of 5.1 months (IQR 1.7-12.0) and a crude mortality rate of 17.2 deaths per 100PY (95%CI 15.0-19.8) (**Figure 2.3**).

Crude loss to follow-up rates and the results of univariate and multivariable cause-specific hazards models for loss to follow-up are summarized in **Table 2.2**. The highest crude loss to follow-up rates occurred among the following groups in decreasing order: individuals age >55y (24.0 events per 100PY), history of alcohol use (23.2), history of tobacco use (20.0), any prior LTFU from TB treatment (19.2) and HIV (17.1). In the multivariable complete case analysis (n = 740), history of alcohol use (aHR 1.66, 95%CI 1.01-2.74) and HIV (aHR 2.44, 95%CI 1.21-4.91) were associated with higher loss to follow-up; female sex (aHR 0.57, 95% CI 0.33-0.98) and any prior private TB treatment (aHR 0.56, 95%CI 0.3-0.96) were associated with lower loss to follow-up. Missing values for all covariates of interest were estimated in 20 imputed datasets using MICE. Similar adjusted relative cause-specific hazards for loss to follow-up were observed following

multiple imputation (n = 921 patients included) for history of alcohol use (aHR 1.62, 95%CI 1.01-2.67) and any prior private treatment (aHR 0.56, 95%CI 0.34-0.91). However, female sex and HIV were not found to be associated with loss to follow-up. Extrapulmonary TB, not associated with higher loss to follow-up in the complete case analysis, was significantly associated with higher loss to follow-up in the multivariable model after multiple imputation (aHR 2.14, 95%CI 1.04-4.41).

Crude mortality rates and the results of univariate and multivariable cause-specific hazards models for mortality are summarized in **Table 2.3**. The highest crude mortality rates were observed among the following groups in decreasing order: any prior loss to follow-up from TB treatment (38.4 deaths per 100PY), severe anemia (37.5), history of alcohol use (32.1), HIV (31.4) and severe underweight (25.5). In the multivariable complete case analysis (n = 740), prior loss to follow-up (aHR 2.27, 95%CI 1.56-3.32), moderate underweight (aHR 2.11, 95%CI 1.01-4.39) or severe underweight (aHR 3.23, 95%CI 1.78-5.87) vs. normal BMI or above as well as severe anemia (aHR 3.55, 95%CI 1.42-8.91) vs. no anemia were all associated with higher relative hazards of mortality. Treatment registration in 2016 vs. 2015 was associated with lower mortality (aHR 0.70, 95%CI 0.50, 0.99). Missing values for all covariates of interest were estimated in 20 imputed datasets using MICE separately for the mortality analysis due to the inclusion of death as an auxiliary variable in the imputation models. Similar adjusted relative cause-specific hazards for mortality were observed following multiple imputation (n = 921 patients included) with moderate anemia vs. no anemia also significantly associated with mortality (aHR 2.04, 95%CI 1.01-4.12).

**Discussion:**

In this cohort of MDR TB patients initiating public sector treatment during 2015 to 2016 in Western Maharashtra, overall loss to follow-up (15%) for patients with a final treatment outcome (i.e. enrolling before October 2015) was similar to global (16%)[16] and slightly lower than national averages (20%);[50] however, mortality was found to be higher (27%) than both (16% global; 22% national). The integration of pre-treatment evaluation and PMDT data at the DR TB Center-level[28,33] provides an opportunity to examine

factors not available in larger aggregate patient-level PMDT datasets.[29-31] These factors include: alcohol and tobacco use, diabetes, anemia and a more detailed prior TB treatment history.

In the present study, a history of alcohol use was consistently associated with higher loss to follow-up across all models (univariate, complete case - multivariable, multiple imputation - multivariable). This finding is similar to previously published MDR TB cohort studies.[8,10,11,23,34,51] Alcohol treatment interventions integrated into TB care have previously been demonstrated to improve outcomes[52-54] and their more routine incorporation into RNTCP activities provides an important opportunity to improve treatment retention and care in India. The association of any prior private treatment with lower loss to follow-up among those presenting for public sector treatment could be due to many factors, including catastrophic costs incurred during private treatment[55-57] or a preference shift toward the public sector over the course of private treatment.[58] Higher relative hazards of loss of follow-up among EP TB cases compared to pulmonary TB cases could have been confounded by site of EP TB or due to fewer symptoms or lower perceived severity of TB.

The lower relative hazard of mortality for patients starting MDR TB treatment in 2016 compared to 2015 suggests programmatic improvement in this crucial outcome. Trends in mortality since the inception of PMDT in India in 2007 to present would provide further insights into program progress.[31] The trend of higher mortality with decreasing categories of BMI has been consistently described in prior MDR TB treatment outcome studies from multiple countries.[8,10,31] This finding, similar to the observation of higher mortality with increasing anemia severity, highlight the importance of early intensive treatment interventions for individuals presenting with symptoms of severe disease.[8]

The present study had several notable strengths. The integration of pre-treatment evaluation and outcome data[27] allowed for the investigation of additional variables not frequently analyzed previously for PMDT data. Furthermore, through proactive discussions with program staff and DPSs regarding patient treatment

status, this study provided an opportunity to analyze more recent and potentially relevant PMDT data than previous studies that often wait until RNTCP has officially declared final treatment outcomes. Efforts to identify missing data by reviewing multiple sources as well as efforts to adjudicate discrepancies strengthened data quality and reduced missingness. When present, the impact of missing data on conclusions was evaluated by comparing complete case analyses and analyses after multiple imputation. Survival analysis models and Kaplan-Meier estimates of the survival function for loss to follow-up took into account the competing risk of death.

This study also had several limitations. Information routinely recorded during pre-treatment evaluation was consistent for the vast majority variables but not standardized. Alcohol and tobacco use history as well as diabetes for example were more routinely collected after July 2015. Treatment and outcome data are consistently monitored and validated by RNTCP staff at multiple levels in an attempt to ensure accuracy and timely reporting. Treatment outcomes, although updated monthly at data review meetings, are more rigorously evaluated at the time of final treatment outcome declaration, 31-33 months following treatment initiation.[38] Efforts to identify these outcomes prior to their finalization was at times challenging due to the decentralization of treatment and also knowledge of patient treatment status.

Regarding outcome status following loss to follow-up, there is the possibility of conflating loss to follow-up from the public sector program with an individual being off treatment entirely. In reality, individuals lost to follow-up at any treatment stage may be linked into other care programs (e.g. private sector) or have silently transferred to another public sector facility.[59] Additionally, the outcomes of individuals who transferred out or switched to XDR TB regimens should be ascertained through conversations with other DR TB centers, linkage of MDR TB and XDR TB registrations of the same individuals and if necessary tracing efforts. The incorporation of the true outcomes (completion, cure, death, not on treatment or failure) of these individuals would provide more accurate epidemiologic data to guide TB programs and funding

allocation. Lastly, the present study was entirely limited to the public sector and conclusions may or may or not be generalizable to private sector care in India.

Recent RNTCP changes have attempted to address several of the identified gaps in care. Pilot projects in India have demonstrated the potential of scaling-up molecular diagnostics,[60] public-private partnerships,[61] and directly observed therapy by family members.[62] Additional ongoing efforts include the expanded use of more diverse and likely effective MDR TB treatment regimens, such as: bedaquiline-containing regimens, shorter 9-11 month MDR TB regimens (i.e. Bangladesh regimen) and more personally tailored regimens based on expanded 1st and 2nd-line DST (i.e. DST-guided treatment).[39] Although their use has been somewhat limited as of 2018, their expanded use in the near future has great potential to improve patient outcomes and quality of life. Nikshay, an online governmental platform for TB notification and monitoring in India,[63,64] shows promise in facilitating reporting, data standardization,[65] and research from the Tuberculosis Unit to the national-level. Increased funding and leadership at all levels from local peripheral health institutions to the central research institutions[66] will, however, be essential for demonstration projects to be brought to scale.

The investigation of the timing, extent and factors of poor treatment outcomes during public sector MDR TB care provides significant opportunities to guide program development and interventions to specific gaps in order to maximize the impact of available resources. However, undue emphasis on single components of the care cascade may "shift attrition downstream"[67] due to weak linkages in care, implementation challenges and previously unidentified barriers.[68] Patient-centered and integrated approaches to addressing access to high-quality TB diagnosis, treatment and care offer the greatest probability of reducing transmission and improving patient outcomes.[69-71]

**References:**


1) Operational Research in India for TB Care and Control: Continuity and Change. International Union Against Tuberculosis and Lung Disease (IUATLD) South-East Asia Region, New Delhi. Aug 26-27, **2013**.

2) Research Agenda: Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis. National Institute of Allergy and Infectious Diseases (NIAID). Bethesda, United States: National Institutes of Health. **2007**.

3) National Action Plan for Combatting Multidrug-Resistant Tuberculosis. Washington D.C., United States: White House, **2015**.

4) Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med **2012**; 9:e1001300.

5) Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Inf Dis **2009**; 9:153–161.

6) Kibret KT, Moges Y, Memiah P, Biadgilign S. Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: a systematic review and meta-analysis of published studies. Infect Dis Poverty **2017**; 6:7.

7) 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.

8) Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One **2009**; 4:e6914.

9) Isaakidis P, Casas EC, Das M, Tseretopoulou X, Ntzani EE, Ford N. Treatment outcomes for HIV and MDR-TB co-infected adults and children: systematic review and meta-analysis. Int J Tuberc Lung Dis **2015**; 19:969–978.

10) Samuels JP, Sood A, Campbell JR, Ahmad Khan F, Johnston JC. Comorbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. Sci Rep **2018**; 8:4980.

11) Kendall EA, Theron D, Franke MF, et al. Alcohol, hospital discharge, and socioeconomic risk factors for default from multidrug resistant tuberculosis treatment in rural South Africa: a retrospective cohort study. PLoS One **2013**; 8:e83480.

12) Gler MT, Podewils LJ, Munez N, Galipot M, Quelapio MID, Tupasi TE. Impact of patient and program factors on default during treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis **2012**; 16:955–960.

13) Lalor MK, Greig J, Allamuratova S, et al. Risk factors associated with default from multi- and extensively drug-resistant tuberculosis treatment, Uzbekistan: a retrospective cohort analysis. PLoS One **2013**; 8:e78364.

14) Kuchukhidze G, Kumar AMV, de Colombani P, et al. Risk factors associated with loss to follow-up among multidrug-resistant tuberculosis patients in Georgia. Public Health Action **2014**; 4:S41–S46.

15) Tupasi TE, Garfin AMCG, Kurbatova EV et al. Factors associated with loss to follow-up during treatment for multidrug-resistant tuberculosis, the Philippines, 2012–2014. Emerg Infect Dis **2016**: 22:491–502.

16) Global Tuberculosis Report, 2017. WHO/HTM/TB/2017.23. Geneva, Switzerland: World Health Organization, **2017**.

17) Arora VK, Sarin R, Singla R, et al. DOTS-Plus for patients with multidrug-resistant tuberculosis in India: early results after three years. Indian J Chest Dis **2006**; 49:6.

18) Dhingra VK, Rajpal S, Mittal A, Hanif M. Outcome of multi-drug resistant tuberculosis cases treated by individualized regimens at a tertiary level clinic. Indian J Tuberc **2008**; 55:15–21.

19) Singla R, Sarin R, Khalid UK, et al. Seven-year DOTS-Plus pilot experience in India: results, constraints and issues. Int J Tuberc Lung Dis **2009**; 13:976–981.

20) Datta BS, Hassan G, Kadri SM, et al. Multidrug-resistant and extensively drug resistant tuberculosis in Kashmir, India. J Infect Dev Ctries **2010**; 4:19–23.

21) Joseph P, Desai VBR, Mohan NS, et al. Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India. Indian J Med Res **2011**; 133:529–534.

22) Dholakia Y, Shah D. Clinical profile and treatment outcomes of drug-resistant tuberculosis before directly observed treatment strategy plus: Lessons for the program. Lung India **2013**; 30:316–320.1.

23) Duraisamy K, Mrithyunjayan S, Ghosh S, et al. Does alcohol consumption during multidrug-resistant tuberculosis treatment affect outcome? Ann Am Thorac Soc **2014**; 11:712–718.

24) Jain K, Desai M, Solanki R, Dikshit RK. Treatment outcome of standardized regimen in patients with multidrug resistant tuberculosis. J Pharmacol Pharmacother **2014**; 5:145–149.

25) Akshata JS, Chakrabarthy A. Management of multidrug resistant tuberculosis (MDR-TB) – Monitoring is the key to successful outcome. Egypt J Chest Dis Tuberc **2016**; 65:447–450.

26) Thomas A, Ramachandran R, Rehaman F, et al. Management of multi drug resistance tuberculosis in the field: Tuberculosis Research Centre experience. Indian J Tuberc **2007**; 54:117–124.

27) Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK. Loss-to-follow-up on multidrug resistant tuberculosis treatment in Gujarat, India: the WHEN and WHO of it. PLoS One **2015**; 10:e0132543.

28) Patel SV, Nimavat KB, Alpesh PB, et al. Treatment outcome among cases of multidrug-resistant tuberculosis (MDR TB) in Western India: A prospective study. J Infect Public Health **2016**; 9:478–484.

29) Nair D, Velayutham B, Kannan T, et al. Predictors of unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India. Public Health Action **2017**; 7:32–38.

30) Suryawanshi SL, Shewade HD, Nagaraja SB, Nair SA, Parmar M. Unfavourable outcomes among patients with MDR-TB on the standard 24-month regimen in Maharashtra, India. Public Health Action **2017**; 7:116–122.

31) Parmar MM, Sachdeva KS, Dewan PK, et al. Unacceptable treatment outcomes and associated factors among India's initial cohorts of multidrug-resistant tuberculosis (MDR-TB) patients under the revised national TB control programme (2007–2011): Evidence leading to policy enhancement. PLoS One **2018**; 13:e0193903.

32) Deshmukh RD, Dhande DJ, Sachdeva KS, 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.

33) Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK, Das M, Daftary A. "When treatment is more challenging than the disease": a qualitative study of MDR-TB patient retention. PLoS One **2016**; 11:e0150849.

34) Kurbatova EV, Taylor A, Gammino VM, et al. Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. Tuberculosis (Edinb) **2012**; 92:397–403.

35) Alene KA, Yi H, Viney K, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug resistant tuberculosis in Hunan Province, China. BMC Infect Dis **2017**; 17.

36) Farley JE, Ram M, Pan W, et al. Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. PLoS One **2011**; 6:e20436.

37) Population Enumeration Data (Final Population). 2011 Census Data. New Delhi, India: Office of the Registrar General & Census Commissioner India, Ministry of Home Affairs, Government of India. Available at http://www.censusindia.gov.in/2011census/population_enumeration.html. Accessed 19 May 2018.

38) Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, **2012**.

39) Guidelines on Programmatic Management of Drug-Resistant Tuberculosis in India, 2017. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, **2017**.

40) Companion Handbook to the 2011 WHO Guidelines for the Programmatic Management of Multidrug-resistant Tuberculosis. Geneva, Switzerland: World Health Organization, **2015**.

41) WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet **2004**; 363:157–163.

42) Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. WHO/NMH/NHD/MNM/11.1. Geneva, Switzerland: World Health Organization, **2011**.

43) Lau B, Cole SR, Gange SJ. Parametric mixture models to evaluate and summarize hazard ratios in the presence of competing risks with time-dependent hazards and delayed entry. Stat Med **2010**; 30:654–665.

44) Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med **2007**; 26:2389–2430.

45) Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol **2009**; 170:244–256.

46) White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med **2011**; 30:377–399.

47) White IR, Daniel R, Royston P. Avoiding bias due to perfect prediction in multiple imputation of incomplete categorical variables. Comput Stat Data Anal **2010**; 54:2267–2275.

48) Enders CK. Applied Missing Data Analysis. Guilford Press, 2010.

49) Rubin DB. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons, 2004.

50) TB India 2017: Revised National Tuberculosis Control Programme Annual Status Report. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, 2017.

51) Miller AC, Gelmanova IY, Keshavjee S, et al. Alcohol use and the management of multidrug-resistant tuberculosis in Tomsk, Russian Federation. Int J Tuberc Lung Dis **2012**; 16:891–896.

52) Shin S, Livchits V, Connery HS, et al. Effectiveness of alcohol treatment interventions integrated into routine tuberculosis care in Tomsk, Russia. Addiction **2013**; 108:1387–1396.

53) Gelmanova IY, Taran DV, Mishustin SP, Golubkov AA, Solovyova AV, Keshavjee S. 'Sputnik': a programmatic approach to improve tuberculosis treatment adherence and outcome among defaulters. Int J Tuberc Lung Dis **2011**; 15:1373–1379.

54) Mathew TA, Yanov SA, Mazitov R, et al. Integration of alcohol use disorders identification and management in the tuberculosis programme in Tomsk Oblast, Russia. Eur J Public Health **2009**; 19:16–18.

55) Furin J, Isaakidis P, Reid AJ, Kielmann K. 'I'm fed up'': experiences of prior anti-tuberculosis treatment in patients with drug-resistant tuberculosis and HIV'. Int J Tuberc Lung Dis **2014**; 18:1479–1484.

56) Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. Eur Respir J **2014**; 43:1763–1775.

57) Kundu D, Katre V, Singh K, et al. Innovative social protection mechanism for alleviating catastrophic expenses on multidrug-resistant tuberculosis patients in Chhattisgarh, India. WHO South East Asia J Public Health **2015**; 4:69.

58) Lobo E, Shah S, Rangan S, Dholakia Y, Mistry N. Pathway to care for drug resistant tuberculosis cases identified during a retrospective study conducted in high TB burden wards in Mumbai. Gates Open Res **2018**; 2:9.

59) Geng EH, Bangsberg DR, Musinguzi N, et al. Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. J Acquir Immune Defic Syndr **2010**; 53:405–411.

60) Raizada N, Sachdeva KS, Swaminathan S, et al. Piloting upfront Xpert MTB/RIF testing on various specimens under programmatic conditions for diagnosis of TB & DR-TB in paediatric population. PLoS One **2015**; 10:e0140375.

61) Wells WA, Uplekar M, Pai M. Achieving systemic and scalable private sector engagement in tuberculosis care and prevention in Asia. PLoS Med **2015**; 12:e1001842.

62) Dave PV, Shah AN, Nimavat PB, et al. Direct observation of treatment provided by a family member as compared to non-family member among children with new tuberculosis: a pragmatic, non-inferiority, cluster-randomized trial in Gujarat, India. PLoS One **2016**; 11:e0148488.

63) Chadha, SS. Nagaraja SB, Trivedi A, Satapathy S, Devendrappa NM, Sagili KD. Mandatory TB notification in Mysore city, India: Have we heard the private practitioner's plea? BMC Health Serv Res **2017**; 17:1.

64) Jitendra R. 'NIKSHAY' – Harnessing information technology for delivery of enhanced TB care. NTI Bulletin **2012**; 48:1-4.

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

66) Pai M, Arinaminpathy N. How can India overcome tuberculosis? BMJ Opinion, 3 Oct 2016. Available at http://blogs.bmj.com/bmj/2016/10/03/how-can-india-overcome-tuberculosis/. Accessed 20 Feb 2017.

67) Fox MP. Are we shifting attrition downstream in the HIV cascade? Lancet HIV **2016**; 3:e554-5.

68) Chawla KS, Kanyama C, Mbewe A, et al. Policy to practice: Impact of GeneXpert MTB/RIF implementation on the TB spectrum of care in Lilongwe, Malawi. Trans R Soc Trop Med Hyg **2016**; 110:305-11.

69) O'Donnell MR, Daftary A, Frick M, et al. Re-inventing adherence: toward a patient-centered model of care for drug-resistant tuberculosis and HIV. Int J Tuberc Lung Dis **2016**; 20:430-4.

70) Cazabon D, Alsdurf H, Satyanarayana S, et al. Quality of tuberculosis care in high burden countries: the urgent need to address gaps in the care cascade. Int J Infect Dis **2017**; 56:111-16.

71) Graham WJ, Varghese B. Quality, quality, quality: gaps in the continuum of care. Lancet **2012**; 379:e5-6.

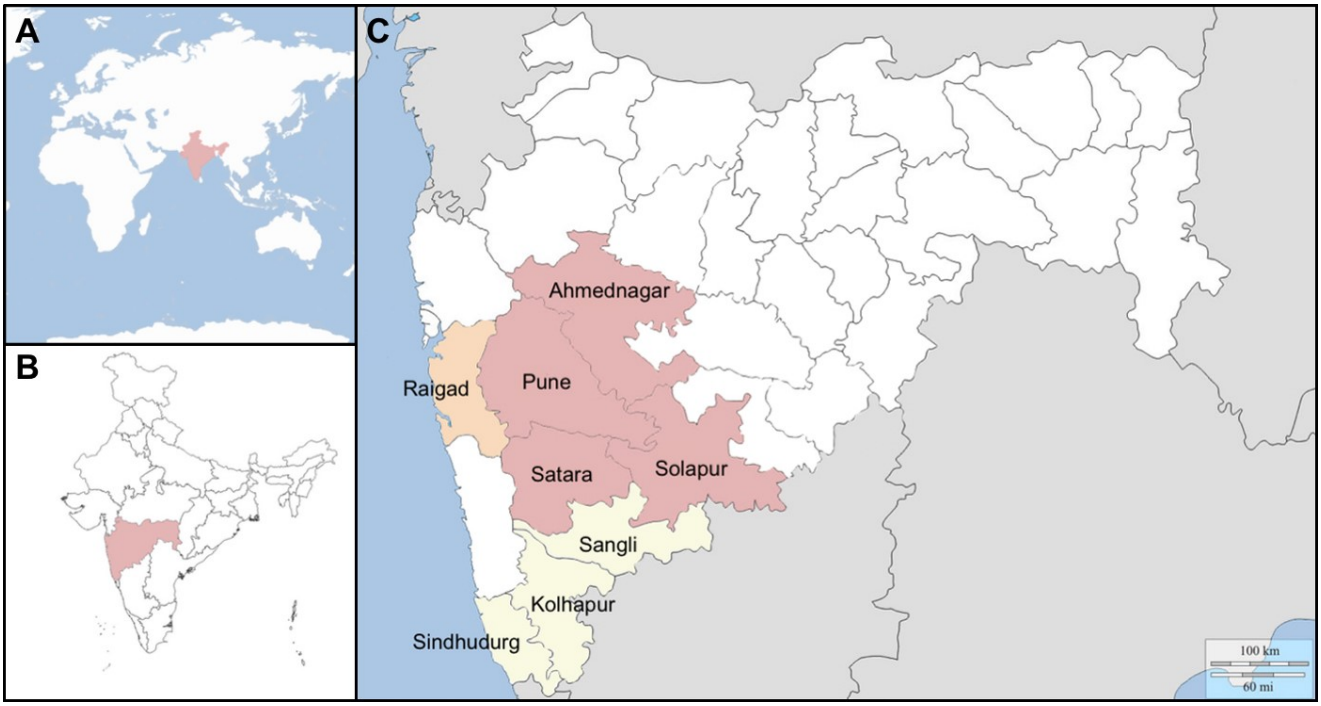



**Figure 2.1:** Location of study setting in Maharashtra (Panel B), India (Panel A). Individuals enrolling in public sector MDR TB treatment at DR TB Center – Pune from five administrative districts in Maharashtra (Panel C) were eligible for inclusion. All patients enrolling in treatment in 2015 and 2016 from four districts (red) were eligible. Individuals from Raigad District (orange) were only referred to DR TB Center – Pune for treatment initiation from July 2015. Individuals from other listed districts (yellow) were referred to DR TB Center – Pune before 2014 but not during the study period.

**Table 2.1:** Data collected for DR TB patients by RNTCP at the time of pre-treatment evaluation

| Category | Variables | Pre-treatment | PMDT register and cards |
|---|---|---|---|
| Personal/ Demographic | Age (years) | **Yes** | **Yes** |
| | Gender (male, female) | **Yes** | **Yes** |
| Clinical | Tuberculosis diagnosis and treatment: | | |
| | Site of tuberculosis (pulmonary, extrapulmonary) | **Yes** | **Yes** |
| | Prior loss to follow-up from TB treatment (binary) | Yes | No |
| | Prior private treatment (binary) | Yes | No |
| | Culture follow-up data (result, date) | No | Yes |
| | Comorbidities: | Yes | No |
| | Malnutrition (body mass index) | **Yes** | **Yes** |
| | HIV (binary) | Yes | No |
| | Anemia (hemoglobin) | Yes | No |
| | Diabetes (self-report and blood glucose*) | | |
| Health service | Delay in treatment initiation (days between diagnostic sample collection to hospital admission for pre-treatment evaluation) | **Yes** | **Yes** |
| | RNTCP district coordinating treatment∞ | **Yes** | **Yes** |
| Social | Education (years) | Yes | No |
| | History of alcohol use (binary) | Yes | No |
| | History of tobacco use (binary, smoking/smokeless) | Yes | No |

*Diabetes: fasting blood glucose and postprandial blood glucose screen conducted if elevated random blood glucose or high clinical suspicion for diabetes at the time of pre-treatment evaluation

∞RNTCP districts: Pune Rural, Pune Corporation, Pimpri-Chinchwad, Solapur Rural, Solapur Corporation, Satara, Ahmednagar Rural, Ahmednagar Corporation, Raigad

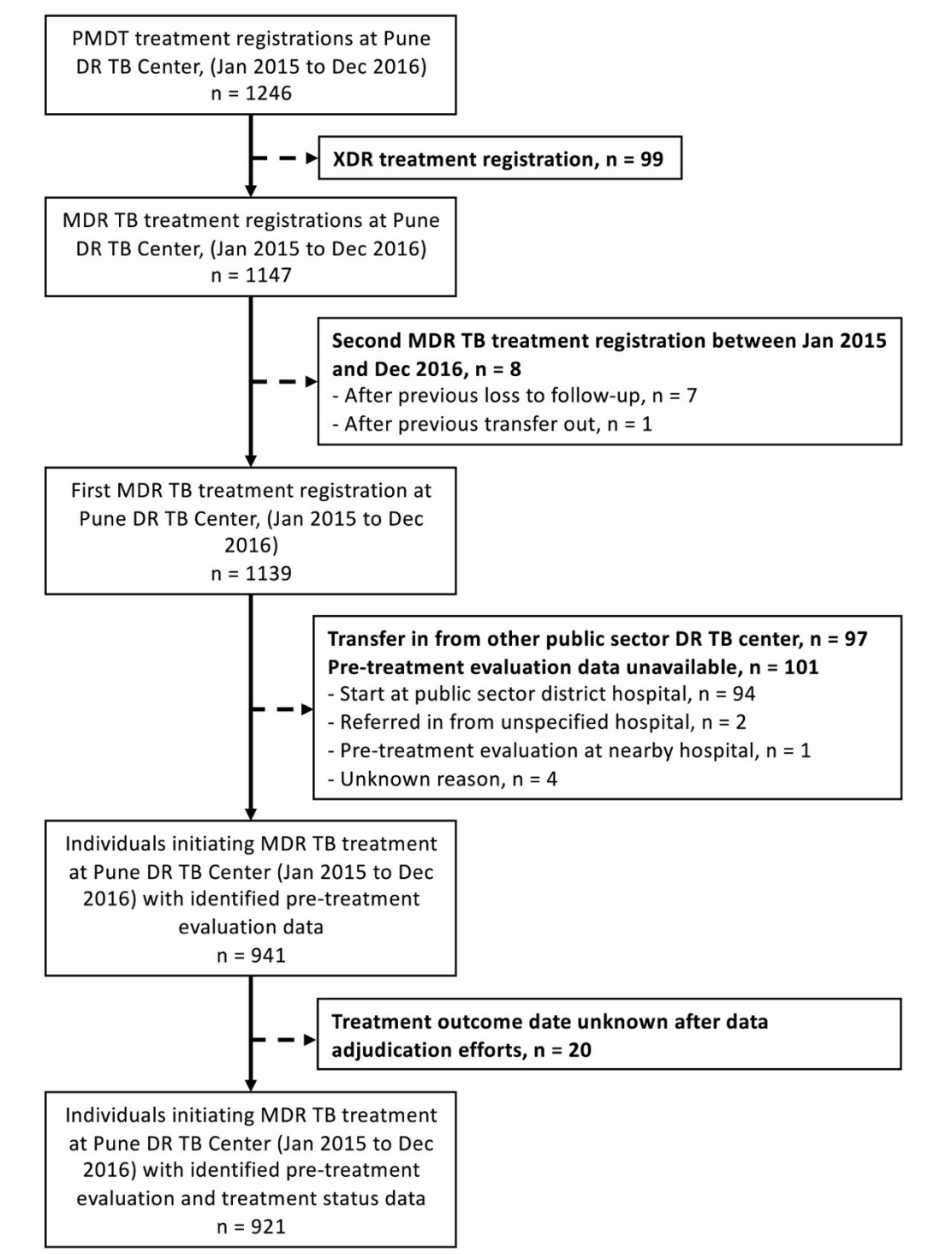



**Figure 2.2:** Eligibility and inclusion of 921 MDR TB patients enrolling in public sector treatment at DR TB Center – Pune in 2015 and 2016

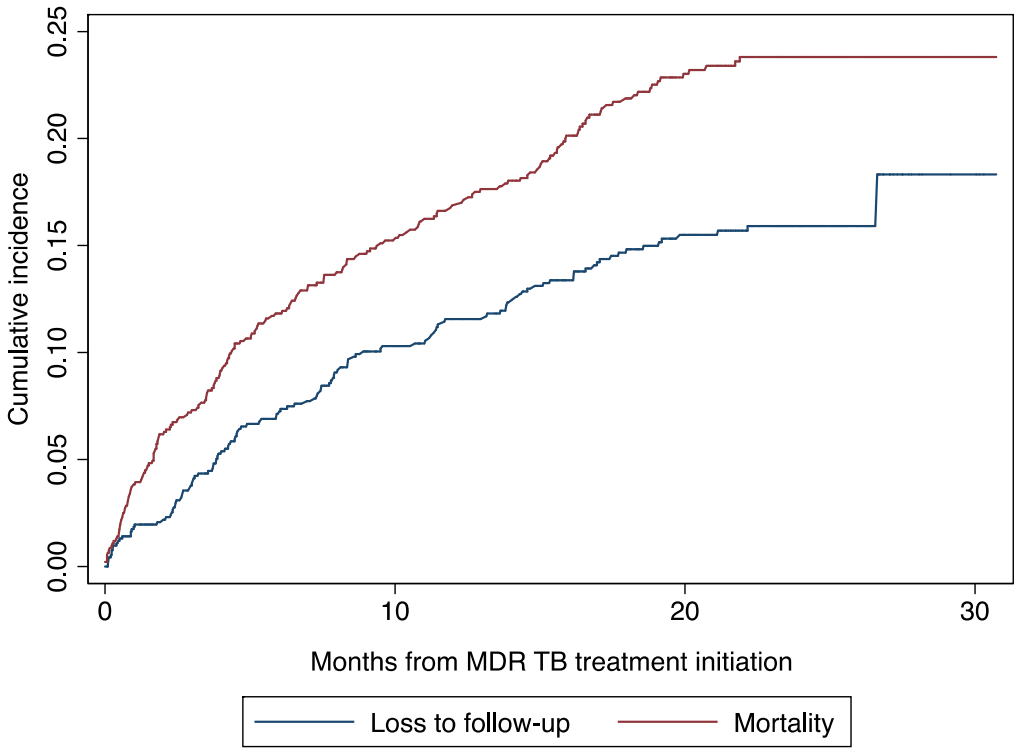



**Figure 2.3:** Cumulative incidence curves for loss to follow-up and mortality for patients enrolling in public sector MDR TB treatment at DR TB Center – Pune in 2015 and 2016. Cumulative incidence curves constructed using Kaplan-Meier estimates corrected for competing risk of mortality.

**Table 2.2:** Characteristics of MDR TB patients enrolling in public sector treatment through DR TB Center – Pune (n = 921), crude loss to follow-up rates and associated factors

| Baseline characteristics | Summary statistics (n = 921)^ | | | Univariate (Complete case) | | | Multivariable (Complete Case, n = 740)* | | | Multivariable (MI, n = 921)* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n (column %) | LTFU (n = 130) | Crude rate per 100PY (95%CI) | HR | 95%CI | p | aHR | 95%CI | p | aHR | 95%CI | p |
| **Demographics and social history** | | | | | | | | | | | | |
| Age | | | | | | | | | | | | |
| ≤25 years | 323 (35.1%) | 38 | 9.4 (6.8, 12.9) | Ref | - | - | Ref | - | - | Ref | - | - |
| >25 & ≤45 years | 262 (28.5%) | 33 | 9.9 (7.0, 13.9) | 1.05 | [0.66, 1.68] | 0.824 | 0.72 | [0.41, 1.28] | 0.260 | 0.80 | [0.49, 1.32] | 0.391 |
| >35 & ≤55 years | 263 (28.6%) | 40 | 13.0 (9.5, 17.7) | 1.35 | [0.87, 2.11] | 0.182 | 0.80 | [0.44, 1.43] | 0.443 | 0.85 | [0.50, 1.44] | 0.534 |
| >55 years | 73 (7.9%) | 19 | 24.0 (15.3, 37.6) | **2.49** | **[1.44, 4.33]** | **0.001** | 1.78 | [0.90, 3.52] | 0.095 | 1.66 | [0.87, 3.16] | 0.121 |
| Sex | | | | | | | | | | | | |
| Male | 546 (59.3%) | 94 | 14.2 (11.6, 17.3) | Ref | - | - | Ref | - | - | Ref | - | - |
| Female | 375 (40.7%) | 36 | 7.8 (5.6, 10.8) | **0.55** | **[0.38, 0.81]** | **0.003** | **0.57** | **[0.33, 0.98]** | **0.040** | 0.68 | [0.43, 1.09] | 0.111 |
| History of alcohol use | | | | | | | | | | | | |
| No | 635 (77.4%) | 76 | 9.5 (7.6, 11.9) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 185 (22.6%) | 42 | 23.2 (17.2, 31.5) | **2.31** | **[1.58, 3.37]** | **<0.001** | **1.66** | **[1.01, 2.74]** | **0.045** | **1.62** | **[1.01, 2.61]** | **0.047** |
| History of tobacco use | | | | | | | | | | | | |
| No | 680 (83.0%) | 87 | 10.5 (8.5, 13.0) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 139 (17.0%) | 31 | 20.0 (14.1, 28.4) | **1.84** | **[1.22, 2.78]** | **0.003** | 1.15 | [0.71, 1.89] | 0.567 | 1.17 | [0.74, 1.85] | 0.491 |
| **Tuberculosis history** | | | | | | | | | | | | |
| Site of current TB disease | | | | | | | | | | | | |
| Pulmonary | 877 (95.3%) | 121 | 11.3 (9.5, 13.6) | Ref | - | - | Ref | - | - | Ref | - | - |
| Extrapulmonary | 43 (4.7%) | 9 | 15.5 (8.1, 29.7) | 1.37 | [0.70, 2.70] | 0.364 | 1.92 | [0.73, 5.03] | 0.187 | **2.14** | **[1.04, 4.41]** | **0.038** |
| Pre-treatment delay, present diagnosis | | | | | | | | | | | | |
| <=7 days | 243 (26.5%) | 28 | 9.3 (6.4, 13.5) | Ref | - | - | Ref | - | - | Ref | - | - |
| >7 days and ≤14 days | 268 (29.3%) | 36 | 11.0 (7.9, 15.3) | 1.19 | [0.73, 1.94] | 0.498 | 1.01 | [0.57, 1.81] | 0.966 | 1.21 | [0.73, 2.03] | 0.459 |
| >14 days and ≤30 days | 279 (30.5%) | 45 | 12.9 (9.7, 17.3) | 1.42 | [0.88, 2.27] | 0.148 | 1.50 | [0.87, 2.60] | 0.144 | 1.34 | [0.81, 2.24] | 0.255 |
| >30 days | 126 (13.8%) | 21 | 14.4 (9.4, 22.1) | 1.58 | [0.89, 2.78] | 0.116 | 1.76 | [0.89, 3.45] | 0.103 | 1.34 | [0.72, 2.51] | 0.356 |
| Treatment registration year | | | | | | | | | | | | |
| 2015 | 404 (43.9%) | 63 | 12.3 (9.6, 15.8) | Ref | - | - | Ref | - | - | Ref | - | - |
| 2016 | 517 (56.1%) | 67 | 10.9 (8.5, 13.8) | 0.82 | [0.58, 1.16] | 0.267 | 0.94 | [0.62, 1.43] | 0.787 | 0.87 | [0.60, 1.25] | 0.449 |
| Prior LTFU from TB treatment | | | | | | | | | | | | |
| No | 731 (79.4%) | 95 | 10.1 (8.2, 12.3) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 190 (20.6%) | 35 | 19.2 (13.8, 26.7) | **1.82** | **[1.23, 2.68]** | **0.003** | 1.35 | [0.83, 2.18] | 0.224 | 1.35 | [0.87, 2.09] | 0.177 |
| Prior private treatment for TB | | | | | | | | | | | | |
| No | 660 (71.7%) | 109 | 13.6 (11.2, 16.4) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 261 (28.3%) | 21 | 6.5 (4.2, 10.0) | **0.48** | **[0.30, 0.77]** | **0.002** | **0.56** | **[0.32, 0.96]** | **0.037** | **0.56** | **[0.34, 0.91]** | **0.020** |
| **Clinical history** | | | | | | | | | | | | |
| Person living with HIV | | | | | | | | | | | | |
| No | 851 (92.8%) | 118 | 11.2 (9.4, 13.4) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 66 (7.2%) | 12 | 17.1 (9.7, 30.1) | 1.48 | [0.82, 2.68] | 0.196 | **2.44** | **[1.21, 4.91]** | **0.013** | 1.64 | [0.86, 3.13] | 0.130 |
| Diabetes | | | | | | | | | | | | |
| No | 725 (86.5%) | 95 | 10.7 (8.7, 13.1) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 113 (13.5%) | 22 | 16.8 (11.1, 25.5) | 1.56 | [0.98, 2.48] | 0.060 | 1.38 | [0.78, 2.44] | 0.265 | 1.31 | [0.76, 2.26] | 0.334 |
| Body mass index (BMI)** | | | | | | | | | | | | |
| Normal range or above (≥18.5) | 214 (23.5%) | 31 | 10.6 (7.4, 15.0) | Ref | - | - | Ref | - | - | Ref | - | - |
| Mild underweight (<18.5 & ≥17) | 136 (14.9%) | 20 | 11.3 (7.3, 17.5) | 1.04 | [0.59, 1.82] | 0.891 | 1.07 | [0.57, 2.00] | 0.837 | 1.14 | [0.63, 2.05] | 0.671 |
| Moderate underweight (<17 & ≥16) | 111 (12.2%) | 20 | 14.1 (9.1, 21.9) | 1.31 | [0.75, 2.30] | 0.343 | 1.42 | [0.73, 2.76] | 0.305 | 1.51 | [0.82, 2.78] | 0.188 |
| Severe underweight (<16) | 450 (49.4%) | 59 | 11.7 (9.0, 15.0) | 1.05 | [0.68, 1.62] | 0.834 | 0.93 | [0.52, 1.65] | 0.804 | 1.10 | [0.67, 1.82] | 0.709 |
| Anemia | | | | | | | | | | | | |
| No anemia | 85 (9.4%) | 11 | 9.4 (5.2, 17.0) | Ref | - | - | Ref | - | - | Ref | - | - |
| Mild anemia | 245 (27.0%) | 37 | 11.6 (8.4, 16.1) | 1.23 | [0.63, 2.41] | 0.548 | 1.18 | [0.53, 2.63] | 0.692 | 1.10 | [0.55, 2.19] | 0.793 |
| Moderate anemia | 499 (54.9%) | 71 | 12.0 (9.5, 15.2) | 1.26 | [0.67, 2.37] | 0.479 | 1.56 | [0.71, 3.42] | 0.267 | 1.35 | [0.69, 2.62] | 0.383 |
| Severe anemia | 80 (8.8%) | 11 | 13.3 (7.4, 24.0) | 1.40 | [0.60, 3.22] | 0.435 | 1.32 | [0.47, 3.68] | 0.596 | 1.32 | [0.54, 3.21] | 0.546 |

*Multivariable models also adjusted for RNTCP district of treatment registration; **Units for reported body mass index: kg/m2

^Summary statistics presented for available data for each covariate level; for variables with missing data, sum of sample size column will not equal total sample size of 921

Abbreviations: LTFU (loss to follow-up) PY (person years); CI (confidence intervals); aHR (adjusted hazard ratio); p (p-value); Ref (reference), MI (multiple imputation)

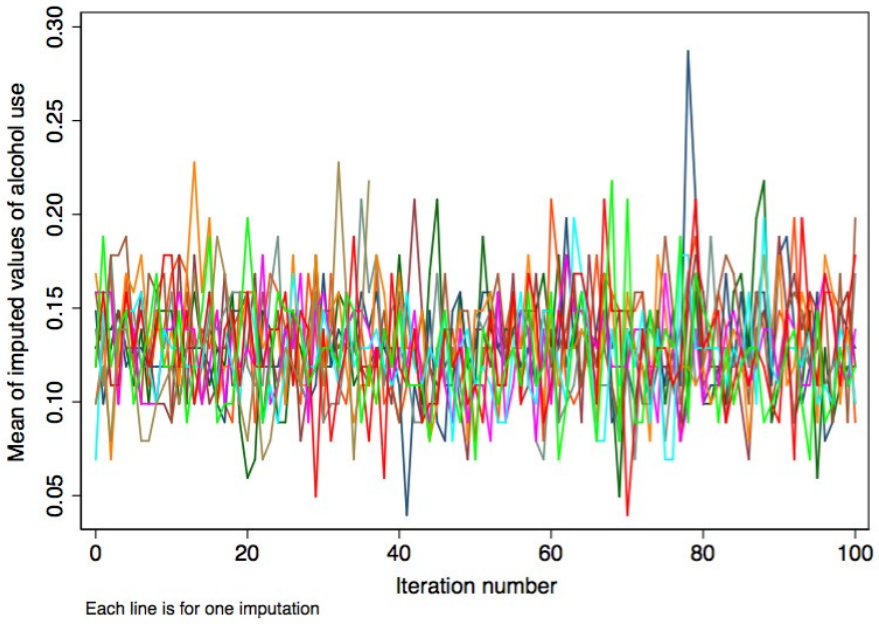
**Table 2.3:** Characteristics of MDR TB patients enrolling in public sector treatment through DR TB Center – Pune (n = 921), crude mortality rates and associated factors

| Baseline characteristics | Summary statistics (n = 921)^ | | | Univariate (Complete case) | | | Multivariable (Complete Case, n = 740)* | | | Multivariable (MI, n = 921)* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n (column %) | Mortality (n = 194) | Crude rate per 100PY (95%CI) | HR | 95%CI | p | aHR | 95%CI | p | aHR | 95%CI | p |
| **Demographics and social history** | | | | | | | | | | | | |
| Age | | | | | | | | | | | | |
| ≤25 years | 323 (35.1%) | 60 | 14.8 (11.5, 19.1) | Ref | - | - | Ref | - | - | Ref | - | - |
| >25 & ≤45 years | 262 (28.5%) | 54 | 16.1 (12.4, 21.1) | 1.10 | [0.76, 1.59] | 0.600 | 0.94 | [0.61, 1.46] | 0.796 | 0.91 | [0.62, 1.35] | 0.640 |
| >35 & ≤55 years | 263 (28.6%) | 64 | 20.7 (16.2, 26.5) | 1.37 | [0.96, 1.94] | 0.082 | 0.96 | [0.60, 1.53] | 0.857 | 0.97 | [0.64, 1.46] | 0.879 |
| >55 years | 73 (7.9%) | 16 | 20.2 (12.4, 33.0) | 1.33 | [0.77, 2.32] | 0.305 | 1.01 | [0.51, 1.99] | 0.986 | 1.08 | [0.59, 2.00] | 0.795 |
| Sex | | | | | | | | | | | | |
| Male | 546 (59.3%) | 121 | 18.2 (15.2, 21.8) | Ref | - | - | Ref | - | - | Ref | - | - |
| Female | 375 (40.7%) | 73 | 15.8 (12.5, 19.8) | 0.87 | [0.65, 1.16] | 0.352 | 1.15 | [0.75, 1.76] | 0.527 | 0.97 | [0.67, 1.41] | 0.867 |
| History of alcohol use | | | | | | | | | | | | |
| No | 635 (77.4%) | 116 | 14.5 (12.1, 17.4) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 185 (22.6%) | 58 | 32.1 (24.8, 41.5) | **2.07** | **[1.51, 2.84]** | **<0.001** | 1.37 | [0.87, 2.13] | 0.170 | 1.39 | [0.92, 2.12] | 0.121 |
| History of tobacco use | | | | | | | | | | | | |
| No | 680 (83.0%) | 135 | 16.4 (13.8, 19.4) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 139 (17.0%) | 38 | 24.5 (17.8, 33.7) | **1.46** | **[1.02, 2.10]** | **0.038** | 1.05 | [0.68, 1.62] | 0.819 | 1.03 | [0.68, 1.55] | 0.896 |
| **Tuberculosis history** | | | | | | | | | | | | |
| Site of current TB disease | | | | | | | | | | | | |
| Pulmonary | 877 (95.3%) | 190 | 17.8 (15.4, 20.5) | Ref | - | - | Ref | - | - | Ref | - | - |
| Extrapulmonary | 43 (4.7%) | 4 | 6.9 (2.6, 18.3) | 0.39 | [0.14, 1.05] | 0.062 | 0.25 | [0.03, 1.81] | 0.170 | 0.56 | [0.20, 1.54] | 0.259 |
| Pre-treatment delay, present diagnosis | | | | | | | | | | | | |
| <=7 days | 243 (26.5%) | 46 | 15.3 (11.5, 20.4) | Ref | - | - | Ref | - | - | Ref | - | - |
| >7 days and ≤14 days | 268 (29.3%) | 58 | 17.7 (13.7, 22.9) | 1.17 | [0.79, 1.72] | 0.432 | 1.21 | [0.76, 1.93] | 0.417 | 1.19 | [0.80, 1.78] | 0.393 |
| >14 days and ≤30 days | 279 (30.5%) | 58 | 16.7 (12.9, 21.6) | 1.12 | [0.76, 1.65] | 0.570 | 1.26 | [0.80, 1.99] | 0.315 | 1.12 | [0.74, 1.68] | 0.600 |
| >30 days | 126 (13.8%) | 31 | 21.3 (15.0, 30.3) | 1.41 | [0.90, 2.23] | 0.138 | 1.54 | [0.88, 2.69] | 0.128 | 1.33 | [0.82, 2.18] | 0.250 |
| Treatment registration year | | | | | | | | | | | | |
| 2015 | 404 (43.9%) | 147 | 18.3 (15.6, 21.5) | Ref | - | - | Ref | - | - | Ref | - | - |
| 2016 | 517 (56.1%) | 47 | 14.5 (10.9, 19.3) | **0.69** | **[0.52, 0.92]** | **0.011** | **0.70** | **[0.50, 0.99]** | **0.042** | **0.73** | **[0.54, 0.99]** | **0.043** |
| Prior LTFU from TB treatment | | | | | | | | | | | | |
| No | 731 (79.4%) | 124 | 13.1 (11.0, 15.7) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 190 (20.6%) | 70 | 38.4 (30.4, 48.5) | **2.73** | **[2.04, 3.67]** | **<0.001** | **2.27** | **[1.56, 3.32]** | **<0.001** | **2.17** | **[1.56, 3.03]** | **<0.001** |
| Prior private treatment for TB | | | | | | | | | | | | |
| No | 660 (71.7%) | 147 | 18.3 (15.6, 21.5) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 261 (28.3%) | 47 | 14.5 (10.9, 19.3) | 0.79 | [0.57, 1.10] | 0.170 | 0.98 | [0.66, 1.46] | 0.933 | 1.00 | [0.71, 1.41] | 0.988 |
| **Clinical history** | | | | | | | | | | | | |
| Person living with HIV | | | | | | | | | | | | |
| No | 851 (92.8%) | 172 | 16.4 (14.1, 19.0) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 66 (7.2%) | 22 | 31.4 (20.7, 47.7) | **1.84** | **[1.18, 2.87]** | **0.007** | 1.43 | [0.81, 2.51] | 0.215 | 1.48 | [0.91, 2.40] | 0.110 |
| Diabetes | | | | | | | | | | | | |
| No | 725 (86.5%) | 159 | 17.9 (15.3, 20.9) | Ref | - | - | Ref | - | - | Ref | - | - |
| Yes | 113 (13.5%) | 20 | 15.3 (9.9, 23.7) | 0.85 | [0.53, 1.35] | 0.494 | 1.09 | [0.61, 1.92] | 0.779 | 0.98 | [0.58, 1.65] | 0.931 |
| Body mass index (BMI)** | | | | | | | | | | | | |
| Normal range or above (≥18.5) | 214 (23.5%) | 21 | 7.2 (4.7, 11.0) | Ref | - | - | Ref | - | - | Ref | - | - |
| Mild underweight (<18.5 & ≥17) | 136 (14.9%) | 18 | 10.1 (6.4, 16.1) | 1.39 | [0.74, 2.61] | 0.307 | 1.57 | [0.76, 3.26] | 0.225 | 1.35 | [0.70, 2.59] | 0.366 |
| Moderate underweight (<17 & ≥16) | 111 (12.2%) | 19 | 13.4 (8.6, 21.0) | 1.84 | [0.99, 3.42] | 0.054 | **2.11** | **[1.01, 4.39]** | **0.047** | **1.94** | **[1.01, 3.70]** | **0.046** |
| Severe underweight (<16) | 450 (49.4%) | 129 | 25.5 (21.4, 30.3) | **3.37** | **[2.12, 5.34]** | **<0.001** | **3.23** | **[1.78, 5.87]** | **<0.001** | **2.78** | **[1.68, 4.59]** | **<0.001** |
| Anemia | | | | | | | | | | | | |
| No anemia | 85 (9.4%) | 9 | 7.7 (4.0, 14.8) | Ref | - | - | Ref | - | - | Ref | - | - |
| Mild anemia | 245 (27.0%) | 37 | 11.6 (8.4, 16.1) | 1.50 | [0.72, 3.11] | 0.276 | 1.68 | [0.69, 4.08] | 0.256 | 1.49 | [0.71, 3.14] | 0.288 |
| Moderate anemia | 499 (54.9%) | 115 | 19.5 (16.2, 23.4) | **2.49** | **[2.62, 4.90]** | **0.008** | 2.22 | [0.95, 5.17] | 0.066 | **2.04** | **[1.01, 4.12]** | **0.046** |
| Severe anemia | 80 (8.8%) | 31 | 37.5 (26.4, 53.3) | **4.73** | **[2.25, 9.94]** | **<0.001** | **3.55** | **[1.42, 8.91]** | **0.007** | **3.44** | **[1.58, 7.52]** | **0.002** |

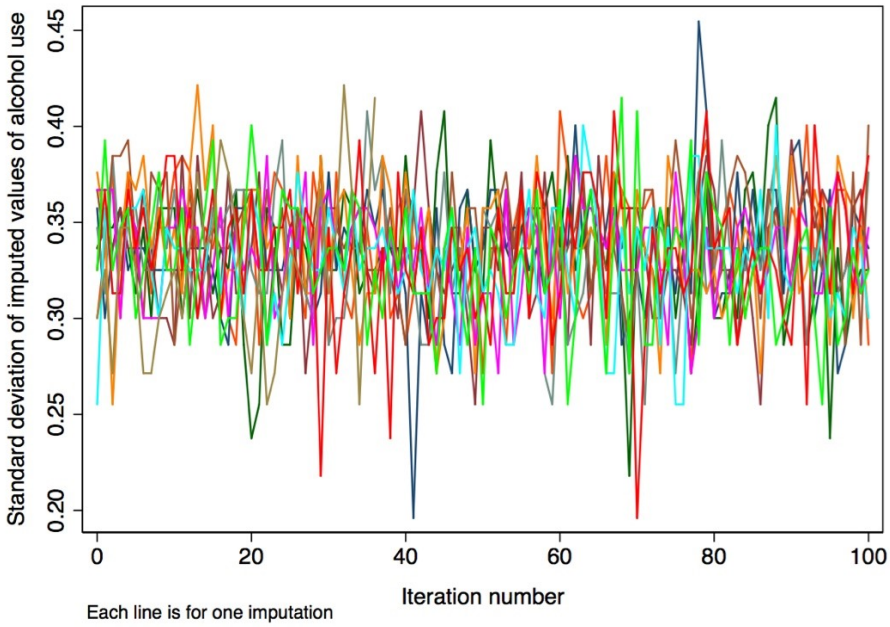
*Multivariable models also adjusted for RNTCP district of treatment registration; **Units for reported body mass index: kg/m2

^Summary statistics presented for available data for each covariate level; for variables with missing data, sum of sample size column will not equal total sample size of

Abbreviations: LTFU (loss to follow-up) PY (person years); CI (confidence intervals); aHR (adjusted hazard ratio); p (p-value); Ref (reference), MI (multiple imputation)




**Supplementary Figure 2.1:** Representative trace plot of mean estimated imputed values of missing variables (above: alcohol use) over 100 iterations. Evidence of imputation algorithm converging to a stationery state is seen in that traces of mean imputed values do not systematically increase or decrease with subsequent iterations




**Supplementary Figure 2.2:** Representative trace plot of the standard deviation of estimated imputed values of missing variables (above: alcohol use) over 100 iterations. Evidence of imputation algorithm converging to a stationery state is seen in that traces of mean imputed values do not systematically increase or decrease with subsequent iterations

# Chapter III: Assessment of Baseline Quality of Life in Patients Initiating Multidrug-Resistant and Drug-Susceptible Tuberculosis Treatment in Pune, India

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**Abstract:**

**Background:** Tuberculosis and its treatment have frequent and often severe consequences for patient quality of life. There is limited evidence however on the quality of life of individuals with multidrug-resistant TB (MDR TB) and its comparison with drug-susceptible TB (DS TB) patients and healthy controls.

**Methods:** Enrolled MDR TB, DS TB and healthy control participants from public sector diagnostic and treatment facilities in Pune, India were interviewed to compare quality of life using the WHOQOL-BREF questionnaire and other covariates of interest. Factors associated with quality of life were assessed using univariate and multivariable linear regression models.

**Results:** Overall, 236 participants were enrolled (80 MDR TB, 79 DS TB and 77 healthy controls). In multivariable linear regression models, quality of life was observed to be significantly lower for both TB groups compared to healthy controls in the physical (DS TB -18.4, 95%CI -24.7, -12.0; MDR TB -23.1, 95%CI -29.3, -16.9) and psychological (DS TB -15.7, 95%CI -22.7, -8.7; MDR TB -20.0, 95%CI -26.9, -13.1) domains and for MDR TB patients in the social domain (DS TB -4.9, 95%CI -10.6, 0.8; MDR TB -9.7, 95%CI -16.1, -3.3). MDR TB patient quality of life was consistently lower, although not statistically significant, than DS TB patient quality of life across all four domains except environmental. Broadly, lower quality of life scores were significantly associated with increased comorbidity severity and lower household assets. Lower social quality of life was also associated with lower education (-0.6 per year of less education, 95%CI -1.2, -0.1) as well as a marital status of separated, divorced or widowed vs. currently married (-16.0, 95%CI -26.2, -5.7). Lower environmental quality of life was associated with alcohol dependence (-9.5, 95%CI -15.6, -3.5) and lower education (-0.6 per year of less education, 95%CI -1.1, -0.1).

**Conclusions:** Quality of life is impaired in TB and MDR TB patients compared to healthy controls. Identified factors associated with quality of life highlight the importance of behavioral and social factors not included in many prior studies and suggest potential future directions of patient support programs.

**Introduction:**

Traditionally, the primary goal of tuberculosis (TB) treatment has been to achieve the important clinical and public health outcome of microbiological cure. Less emphasis, however, has been placed on morbidity and patient-reported outcomes.[1] It is well known that TB and its treatment have frequent and often severe physical, psychological and social ramifications for patients and their families with some sequelae extending long after treatment completion. The impact of drug susceptible TB (DS TB) on respiratory health impairment,[2] depression,[3] social stigma,[4] and high financial costs[5] among others have all been identified previously. Some of the substantial challenges of multidrug-resistant TB (MDR TB) and its more toxic and lengthy treatment regimens have also been documented with negative impacts on multiple domains of patients' lives.[6-8]

Health-related quality of life (QOL) is a multi-dimensional construct that defines health as physical, mental and social well-being rather than strictly the absence of disease.[9] Many generic (i.e. not focused on any specific disease or condition) and disease-specific instruments have been developed to measure an individual's perceived quality of life across a wide range of health-related domains. These patient-reported outcome measures are not a substitute for important clinical or microbiological outcomes, such as sputum conversion, but are rather complementary in that they provide a more nuanced understanding of the impact of disease and its treatment on patients. The utilization of these measures clinically or programmatically provide important opportunities to screen for and prioritize problems faced by patients, facilitate communication with health providers or program staff and monitor responses to treatments or interventions.[10,11] Additionally, patient-reported outcomes have also been found to be associated with poorer traditional outcomes, such as loss to follow-up and mortality.[12,13]

The World Health Organization QOL-BREF (WHOQOL-BREF) questionnaire and variations of the Medical Outcomes Study Short Form (SF) questionnaire (e.g. SF-36, SF-12) are two of the most frequently used generic instruments to examine quality of life, including among individuals with TB.[14,15] These

instruments have both been translated in multiple languages and validated in several settings and among diverse populations. The WHOQOL-BREF, compared to other generic quality of life instruments such as SF-36 and EuroQOL-5D, captures more subjective perceptions of health and well-being as opposed to more objective information regarding health-related functioning and disability.[16-18] Although TB-specific quality of life scales have been developed, such as FACIT-TB[19] and DR-12,[20] they have not been adequately examined and are to date not widely used. Additionally, as quality of life measures become more disease-specific, they are less useful in comparing health outcomes across different populations and groups, including healthy controls.[21] Other generic and disease-specific questionnaires focusing on specific dimensions of quality of life have also been examined among individuals with TB. These scales and the dimensions covered include but are not limited to: Patient Health Questionnaire-9 (PHQ-9),[22] Beck Depression Inventory (BDI), Center for Epidemiologic Studies Depression Scale (CES-D) for depressive symptoms; Explanatory Model Interview Catalogue [EMIC][23] and internalized social stigma scale[24] for stigma; and St. George Respiratory Questionnaire (SGRQ) for lung health.[2,25]

Prior systematic reviews and meta-analyses of quantitative quality of life studies for individuals with TB have identified that TB has a negative impact on quality of life compared to individuals with latent TB infection or healthy controls. In a limited number of longitudinal studies, significant improvements in quality of life have been observed over the course of treatment; however, residual impairment was common after treatment even among cured individuals.[2,26,27] These prior QOL studies have however been found to have several notable limitations: lack of comparison groups, limited descriptions of inclusion criteria and sampling mechanisms for healthy controls, little information about the recruitment process, limited data on key social and behavioral determinants of QOL and minimal inclusion of key groups likely to have more greatly impaired QOL such as individuals with MDR TB.[14,15,28]

The present cross-sectional study aimed to address several of these limitations by comparing baseline quality of life for newly diagnosed MDR TB and DS TB patients initiating public sector treatment to TB-

negative healthy controls in Pune, India. Given our objective of trying to understand the broad impact that TB has on QOL from the patient's perspective, the generic WHOQOL-BREF instrument was used for QOL assessments. Among the three included groups, it was hypothesized that quality of life among MDR TB patients would be lower than both DS TB patients and healthy controls.

**Methods:**

*Study setting:*

The study was conducted from August 11, 2017 to May 14, 2018 in Pune (PMC) and Pimpri-Chinchwad Municipal Corporations (PCMC) in Maharashtra, India. In 2017, these two municipal corporations had a population of approximately 6.8 million people with 5400 individuals initiating public sector DS TB treatment and 180 initiating public sector MDR TB treatment.[29]

*Study participant eligibility criteria and recruitment:*

Three main groups were included for comparison in the present quality of life study: MDR TB patients and DS TB patients initiating public sector treatment and healthy controls testing negative for TB by sputum smear at public sector microscopy centers. Inclusion and exclusion criteria for all study groups are summarized in **Table 3.1**.

MDR TB patients were eligible if the following inclusion criteria were met: (1) ≥18 years of age; (2) diagnosed with MDR or rifampicin resistant (RR) pulmonary or extrapulmonary TB by molecular or culture-based DST; (3) initiation of public sector MDR TB treatment (i.e. category IV) in PMC or PCMC between July 13, 2017 and April 21, 2018; (4) on treatment for <2 months before study interview; (5) ability to communicate in Marathi, Hindi or English; and (6) provision of written informed consent. In the study area, standardized MDR TB treatments were used in the public sector program and consisted of a 6 to 9-month intensive phase of 6 drugs (kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol and cycloserine) followed by an 18-month continuation phase of 4 drugs (levofloxacin, ethionamide,

ethambutol and cycloserine) with weight-based dosing (i.e. 6-9 Km Lfx Eto Cs ZEH + 18 Lfx Eto Cs E H). Consecutive individuals starting MDR TB treatment within the study period and area were approached for possible enrollment.

No centralized registries, either computer or paper-based, were available in the study area to facilitate the random sampling of potential DS TB or healthy control participants in PMC and PCMC. As a result, one DS TB patient and one healthy control were randomly selected for each enrolled MDR TB patient from the sub-district-level (i.e. Tuberculosis Unit, TU) DS TB treatment and designated microscopy center (DMC) registers, respectively. For the 2-week period after treatment initiation for each MDR TB patient, a list was made of potentially eligible DS TB patients starting treatment and individuals providing a sputum sample for TB screening. The screening order of enumerated individuals for each group was assigned using a random number generator. DS TB patient inclusion criteria were the same as for MDR TB patients with the following differences: (1) diagnosed with pulmonary or extrapulmonary TB without any documented evidence of rifampicin resistance, and (2) initiation of public sector DS TB treatment (i.e. either category I or II) in Pune and Pimpri-Chinchwad MCs within 2 weeks of the corresponding MDR TB patient. Category I treatment is given through the public sector program to newly diagnosed TB patients without a prior history of treatment. Category II treatment is administered to individuals with a prior treatment history of TB for any reason, including: treatment failure, sputum culture follow-up positive, treatment after loss to follow-up or prior private treatment. The duration of category I treatment is 6 months, consisting of a 2-month intensive phase of 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) followed by a 4-month continuation phase of 3 drugs (isoniazid, rifampicin and ethambutol) (i.e. 2HRZE + 4HRE). Category II treatment is similar with a 3-month intensive phase using the same drugs as category I but with the addition of the injectable drug streptomycin for the first two months; the category II continuation phase uses the same drugs as category I but is one month longer (i.e. 2HRZES + 1HRZE + 5HRE).

Healthy controls were identified by randomly screening adults (≥18 years of age) recorded in corresponding TU-level DMC registers to have two negative sputum smears for TB and an available telephone number. Due to the reliance on sputum smear microscopy for TB diagnosis in the study area, potentially eligible individuals were also screened prior to enrollment for self-reported TB treatment as well as TB symptoms in an attempt to minimize the possible inclusion of individuals with diagnosed or undiagnosed TB into the healthy control group. The symptom screen consisted of 5 self-reported TB-related symptoms: cough ≥2 weeks, fever, hemoptysis during the previous year, night sweats and unintentional weight loss. In a large study among HIV-negative individuals in Zimbabwe, a similar symptom screen (any cough instead of prolonged cough) had a sensitivity of 71.0% and specificity of 90.3% for active TB disease.[30] Prior to enrollment, potential healthy controls were also considered ineligible if they reported any of the following 14 additional medical conditions included in the self-administered comorbidity questionnaire (SCQ)[31] and often excluded in other QOL studies:[14,15] heart disease, high blood pressure, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer, depression or other psychiatric condition, osteoarthritis, chronic back pain, HIV and pregnancy.

*Data collection and variables:*

A semi-structured questionnaire was developed to examine the quality of life of and challenges faced by individuals initiating public sector MDR and DS TB treatment. Available Hindi and Marathi translations of the included quality of life (WHOQOL-BREF) scale were obtained with permission from the World Health Organization (WHO, http://www.who.int/substance_abuse/research_tools/whoqolbref/en/). The remaining sections of the questionnaire were translated into Marathi and Hindi by local translators with substantial experience in clinical research studies. Translations were revised based on reviews by study interviewers and a local anthropologist and then pilot tested among 5 eligible MDR TB and DS TB patients not included in the final study population. Pilot interviews demonstrated adequate clarity and feasibility of the instrument.

The final questionnaire consisted of four total sections: (1) demographic, (2) quality of life, (3) social and economic, (4) clinical and substance use. The primary outcomes in this analysis were the four separate domains of WHOQOL-BREF. This questionnaire is composed of a subset of questions from the larger WHOQOL-100 instrument, and it includes a total of 26 items, two separate general QOL questions and 24 items encompassing 4 health-related domains: physical, psychological, social, and environmental.

Information on gender identity, marital status, religion, education, employment status, as well as socioeconomic status of the participant and the participant's household were also collected. Questions on household assets were utilized to create an equally weighted index variable of participant living standards that included ownership of the following items: radio, refrigerator, television, phone or mobile, bicycle, motorcycle and car. This living standard index variable, with possible values ranging from 0 to 7, was then categorized at the $25^{th}$, $50^{th}$ and $75^{th}$ percentiles of all participants.

Information on prior TB diagnoses and treatment as well as HIV were recorded in the clinical history. Comorbidity information was collected using the Self-administered Comorbidity Questionnaire (SCQ) adapted for interviewer administration.[31] This questionnaire includes questions about the presence of 12 diseases and disease categories: heart disease, high blood pressure, lung disease, diabetes, ulcer / stomach disease, kidney disease, liver disease, anemia, cancer, depression, osteoarthritis, back pain, rheumatoid arthritis and also includes space to enter three additional conditions if applicable. For each reported comorbidity, two follow-up binary questions (0 = no, 1 = yes) are included regarding the limitation of activities due to the comorbidity and current treatment status, resulting in an overall score of 0-3 points for each condition. The overall score from the SCQ, summing responses for all 15 possible conditions, ranges from 0-45.

Information on study participant alcohol use was recorded using the Alcohol Use Disorders Identification Test, Consumption (AUDIT-C). This scale, developed by WHO, includes three questions on the frequency

of alcohol consumption and amount of alcohol consumed in terms of standard drinks (10g ethanol equivalents for India) in order to identify hazardous drinking or potential alcohol abuse or dependence.[32] Due to documented underestimation of alcohol consumption, a simplified photograph approach was used to capture information about volume consumed.[33] During pilot testing, interviewers noted difficulty translating alcoholic drinks consumed into standard drinks due to the variety of beverages. During the study for the AUDIT-C consumption question, participants were asked only about what alcoholic beverages they normally consumed and the volume. Conversions to standard drinks were made at the time of data entry using a review of alcoholic drinks and ethanol content in the three Indian states of Goa, Rajasthan and Delhi.[34] Each of the three AUDIT-C questions was coded from 0 to 4 with a possible scale range of 0 to 12. This scale has previously been demonstrated in India to have the highest combined sensitivity and specificity for alcohol use disorders when using a cutoff of $\geq 5$.[35] Additionally, tobacco smoking use was also measured as a categorical variable: current smoker, former smoker, and never smoked.

Interviewers were hired from the study area and trained for 1 month on the questionnaire, underlying scale constructs and interviewing skills. Preliminary work also included visits to each local participating TU to establish strong working relationships and to gain perspective on public sector program activities. Study staff had no involvement in clinical care and interviews were conducted at the public sector TB program hospital or dispensary considered most convenient for the participant. All interviews with TB patients were scheduled greater than 10 days after treatment initiation to minimize the risk of transmission to study staff. Prior to each interview, written informed consent was obtained, and after the interview participants were reimbursed a fixed amount for local travel to the clinic as well as lost wages based on local Institutional Review Board recommendations.

Data were entered into a Microsoft Access database using EpiInfo v7.0. All completed questionnaires were reviewed after data entry and any issues identified were cross-checked using the completed forms and discussed with the respective interviewers as required.

*Statistical analysis:*

WHOQOL-BREF domain scores were calculated as the average 5-point Likert response of questions within each respective domain (**Table 3.2**). Scores were then transformed to a 0-100 scale to allow for the comparison of domains with different numbers of questions.[18] The internal consistency of each domain was evaluated using Cronbach's alpha where >0.70 indicated was considered adequate. Internal convergent and discriminant construct validity were examined by comparing the polychoric correlation coefficients for ordinal variables of individual indicators to the four WHOQOL-BREF global quality of life questions.[9,36]

In the recruitment process, there were no attempts at frequency matching DS TB and healthy control participants on key covariates of interest, such as sex, age and site of TB disease (pulmonary vs. extrapulmonary). These variables and TB treatment category were available for all DS TB patients screened from public sector treatment registers. Sex and age information were available for all healthy controls screened from public sector microscopy center registers. To examine the potential for selection bias of participants, univariate and multivariable logistic regression models were fit using enrollment in the study as the outcome variable in order to identify factors associated with higher odds of participation.

In descriptive analyses, WHOQOL-BREF domain scores were summarized for MDR TB, DS TB and healthy control individuals using box plots. Covariates of interest were summarized by participant group and univariate comparisons performed using Fisher's exact test for categorical variables and Kruskal-Wallis rank test for continuous variables. Simple and multivariable linear regression models were used to compare WHOQOL-BREF domain scores across levels of each covariate of interest. Covariate selection was *a priori* and informed by the study's conceptual model (**Chapter 1, Figure 1.1**) and literature review. Due to potential selection bias in DS TB patient recruitment, a sensitivity analysis was performed by repeating the final multivariable models after restricting all participants with TB to only pulmonary cases and DS TB participants to only those undergoing category I treatment. Regression diagnostics for all multivariable linear models included: augmented component-plus-residual plots (linearity assumption), quantile-normal

and quantile-quantile plots of residuals (normality assumption), and plots of residuals vs. fitted values for each covariate of interest (homoscedasticity). Robust standard errors were used in all final multivariable models for each WHOQOL-BREF domain to account for heteroscedasticity. Multicollinearity was evaluated by checking for large variance inflation factors (>10) for each included covariate. All statistical analyses were conducted in Stata v13.1

*Human research ethics approvals:*

Ethics committee approval was obtained from the State Public Health Research Ethics Committee at Aundh Chest Hospital and Johns Hopkins University School of Medicine Institutional Review Board.

**Results:**

*Participant screening and recruitment:*

Screening and recruitment for all three study groups are summarized in **Figure 3.1**. Between July 2017 and April 2018, there were 177 registrations for public sector DR TB treatment in PMC and PCMC, of which 38% were not eligible for the study: 32 (18%) XDR-TB treatment initiations, 18 (10%) treatment initiations in a non-participating TU, 8 (5%) children or adolescents <18 years of age and 10 (6%) individuals either transferred out of the study area before screening or initiated treatment elsewhere and transferred in. Among the 109 (62%) individuals starting MDR TB treatment eligible for the study, nine (5%) declined to be interviewed with the most common reason being a lack of time. Sixteen eligible individuals (9%) were unable to be screened or interviewed due to the following: death (n = 6) or loss to follow-up (n = 2) before screening, illness or hospitalization (n = 4), lack of a suitable interview location (n = 3) and inability to give consent due to disability (n = 1). Overall, 80 individuals with MDR TB were recruited and interviewed within 2 months of starting treatment (median 22.5 days, IQR 18-28). In a multivariable logistic regression model including sex, age, TB site and TU of treatment registration, willingness to be interviewed was not

associated with sex or site of TB (pulmonary vs. extrapulmonary); however, lower recruitment was strongly associated with increasing age (aOR 0.46 for each 10 year increase in age, 95%CI 0.29-0.72).

For the DS TB patients, a total of 149 adult pulmonary and extrapulmonary TB patients were screened that had registered for public sector treatment within 2 weeks of each enrolled MDR TB patient. At the time of screening, five individuals did not meet the inclusion criteria for the following reasons: did not think they had TB (n = 2, 1% of screened), were participating in a TB clinical trial and not taking standard public sector treatment (n = 2, 1%) or did not speak Marathi, Hindi or English (n = 1, 1%). Among the 144 eligible individuals screened (97%) for willingness to participate in the study, 28 (19%) declined to be interviewed with the majority (n = 18) stating they did not have enough time. Additionally, 37 individuals were unable to be screened or interviewed due to death before screening (n = 1), illness or hospitalization (n = 14), travel outside of PMC or PCMC for an extended period of time (n = 9), inability to contact due to a change in phone number (n = 4) or not receiving phone calls from study staff (n = 9). Overall, 79 individuals with DS TB (53% overall, 55% of eligible) were recruited and interviewed within 2 months of starting treatment (median 21 days, IQR 16-31). Each completed interview required a median of 3 individuals screened (IQR 1-3). In a multivariable logistic model for enrollment that included gender, age, TB treatment category (I vs. II) site of TB (pulmonary vs. extrapulmonary), TU and month of treatment initiation, higher enrollment was strongly associated with treatment category II (aOR 4.3, 95%CI 1.3-14.4) and extrapulmonary TB (aOR 4.2, 95%CI 1.5-11.5).

For the healthy control group, a total of 333 individuals were screened who had tested negative for TB by two sputum smears at public sector microscopy centers in the same TU as enrolled MDR TB participants. Among those screened for eligibility, 71 (21%) did not meet inclusion criteria: 28 (8%) had at least one TB-related symptom, 23 (7%) reported that they had been diagnosed with TB or were on TB treatment and 20 (6%) reported that they had at least one comorbidity. An inability to communicate with eligible healthy controls was one of the main challenges in recruitment. Of individuals randomly selected from microscopy

center registers, 74 (22% of enumerated) did not answer multiple phone call attempts from study staff and 40 individuals (12%) had an incorrect phone number recorded in the register. Four individuals (1%) had also died prior to screening. Of those that were successfully contacted, 53 declined to be interviewed due to primarily a lack of time (n = 34) but also due to travel outside of the study area (n = 12) or no reason provided (n = 19). Overall, 77 healthy controls were interviewed within two months of sputum collection for TB diagnosis. Each completed interview required a median of 6 individuals screened (IQR 3-8). In a similar model fit for DS TB enrollment, healthy control participation was not associated with sex or age. At the time of data review, two interviews were found to have occurred later than two months from sputum collection (64 and 88 days) and were dropped from the analysis.

*Characteristics of included MDR TB, DS TB and healthy control participants*

In total 80 MDR TB patients, 79 DS TB patients and 77 healthy controls were interviewed, and all participants had complete data (**Table 3.3**). Overall, the median age of participants was 30 years (IQR 24-41), 54% were female, the majority had a secondary education or lower (median 9 years, IQR 5-12 years) and 57% were primarily working either full or part-time over the last year. Education was found to be significantly different across the three groups ($p = 0.020$, Kruskal-Wallis rank test), lower among DS TB patients (median 8 years, IQR 3-11) compared to MDR TB patients (median 10 years, IQR 6-12) and healthy controls (median 9 years, IQR 7-13). Occupational status was also found to be different across the three groups ($p < 0.001$, Fisher's exact test) with MDR TB patients more likely to have reported an inability to work, due to illness or disability (16%) compared to DS TB patients (5%) and healthy controls (0%). In clinical history, MDR and DS TB patients had higher comorbidity scores than healthy controls as expected given study inclusion criteria. Participants with MDR TB also had significantly longer prior TB treatment histories (median 4.5 months, IQR 0-9) compared to DS TB patients (median 0 months, IQR 0-1) and healthy controls (median 0 months, IQR 0-0). Individual smoking tobacco use and alcohol dependence as well as household size and assets were not significantly different across groups. Due to lengthier screening efforts required for recruitment, days from baseline (i.e. treatment initiation or sputum collection) to study

interview were significantly longer for healthy controls (median 30 days, IQR 21-38) than MDR TB patients (median 22.5 days, IQR 18-28) and DS TB patients (median 21 days, IQR 16-31).

*Psychometric properties of WHOQOL-BREF in study population*

Each WHOQOL-BREF domain was found to have adequate internal consistency as assessed by a Cronbach's alpha score of >0.70: physical domain (0.886), psychological (0.875), social (0.789), environment (0.788). Internal construct validity was evaluated by comparing the polychoric correlations between individual indicator responses and domain scores. All indicators in the physical, psychological and social domains were most highly correlated with their respective domain scores. The environmental domain indicator on safety was more highly correlated with the psychological domain score, a finding that has been documented previously at some research sites.[9]

*Quality of life and associated factors among MDR TB, DS TB and healthy control participants*

Overall, WHOQOL-BREF domain scores were significantly higher for healthy controls than both MDR TB and DS TB participants (**Figure 3.2**). Univariate and multivariable linear regression models for each transformed WHOQOL-BREF domain score (scale 0-100) were fit to compare quality of life across MDR TB, DS TB and healthy control participants before and after adjusting for other covariates. In unadjusted analyses, quality of life for healthy controls was significantly higher than both MDR TB and DS TB participant groups for all domain scores (results not shown). Physical, psychological and social quality of life were lower for MDR TB patients than DS TB patients; however, this association was only significantly different for the physical domain score (β 5.9, 95%CI 0.03, 11.7).

In multivariable models, quality of life for both TB groups was significantly lower than healthy controls for the physical domain (DS TB vs. control β -18.4, 95%CI -24.7, -12.0; MDR TB vs control β -23.1, 95%CI -29.3, -16.9) and the psychological domain (DS TB vs. control β -15.7, 95%CI -22.7, -8.7; MDR

TB vs. control β -20.0, 95%CI -26.9, -13.1). Compared to controls, social quality of life was significantly lower for MDR TB (β -9.7, 95%CI -16.1, -3.3) but not DS TB patients (β -4.9, 95%CI -10.6, 0.8). Environmental quality of life was similar across all three groups in multivariable models. As the primary study hypothesis was that MDR TB quality of life would be lower than DS TB quality of life followed by healthy controls, coefficient estimates in **Table 3.4** are displayed with MDR TB participants as the reference group. Quality of life domain scores in adjusted models were lower for MDR TB patients compared to DS TB patients but not significantly different for the physical (β -4.7, 95%CI -11.6, 2.1), psychological (β -4.3, 95%CI -11.2, 2.6) and social domains (β -4.8, 95%CI -10.8, 1.3).

Regarding associations between quality of life and other included covariates, lower quality of life was consistently associated with increasing comorbidity scores (SCQ) for all domains: physical (β -2.1 per point on the SCQ scale, 95% CI -3.4, 0.8), psychological (β -1.7, 95%CI -2.6, -0.6), social (β -2.4, 95%CI -3.7, -1.2) and environmental (β -1.0, 95%CI -1.8, -0.2). Lower physical quality of life was not significantly associated with any other covariate examined but was marginally associated with female gender (vs. male β -5.9, 95%CI -12.3, 0.4). Lower psychological quality of life was marginally associated with alcohol dependence (AUDIT-C ≥5, β -6.9, 95%CI -14.6, 0.8) and an inability to work (vs. full or part-time work, β -10.5, 95%CI -22.7, 1.7). Lower social quality of life was associated with a marital status of separated, divorced or widowed (β -16.0, 95%CI -26.2, -5.7) compared to currently married. Higher education was associated with both higher social quality of life (β 0.6 per year of education, 95%CI 0.1, 1.2) and environmental quality of life (β 0.6, 95%CI 0.1, 1.1). Lower environmental quality of life was significantly associated with alcohol dependence (β -9.5, 95%CI -15.6, -3.5).

As a proxy of socioeconomic status, each participant was asked about seven household assets. Compared to participants with the lowest quartile of household assets (0-2 assets), those with the highest quartile (5-7) were observed to have higher psychological (β 9.9, 95%CI 2.9, 16.8), social (β 10.2, 95%CI 4.0, 16.5)

and environmental quality of life (β 9.7, 95%CI 4.2, 15.3). In a sensitivity analysis, the direction and magnitude of all multivariable linear regression parameter estimates were robust to the exclusion of all extrapulmonary TB patients and DS TB patients on category II treatment.

**Discussion:**

In this cross-sectional study of baseline quality of life among TB patients starting public sector treatment in Pune, India, quality of life was found to be broadly lower for participants with TB compared to healthy controls. Quality of life for MDR TB patients was lower than DS TB patients in the physical, psychological and social domains of the WHOQOL-BREF questionnaire but no differences were statistically significant. Prior systematic reviews and meta-analyses of quantitative quality of life studies among individuals with TB, have identified a significant negative impact of TB on quality of life compared to control groups measured by diverse generic and disease-specific questionnaires.[14,15] Multiple studies on DS TB patient quality of life in India have had similar findings.[26,37-42]

Few prior studies on MDR TB patient quality of life were identified. The majority of published research has focused on post-MDR TB treatment sequelae, identifying residual impairments in respiratory health and continued symptoms.[2,27,43,44] Identified cross-sectional studies that have included MDR TB patients have observed lower quality of life across multiple domains compared to DS TB patients or healthy controls. These studies however have been limited by the lack of a healthy control group[45,46], unclear inclusion criteria,[47] interviews over wide time periods during treatment[45,47] and observed associations unadjusted for potential confounders.[47] A recent longitudinal study of MDR TB patients on programmatic treatment in Pakistan, using the SF-36 quality of life questionnaire, identified impaired baseline physical and mental quality of life with improvements over the course of treatment.[48] This study thought to be the first longitudinal quality of life study including MDR TB patients did not include any control groups, either DS TB patients or healthy controls, but compared quality of life measures to population norms.

Prior quality of life studies among individuals with TB have been limited by a lack of social and behavioral determinant information, including alcohol use, smoking and socioeconomic status.[14] In the present study, alcohol dependence (AUDIT-C score ≥5) was associated with lower environmental quality of life. This finding further highlights the importance of potential alcohol treatment interventions in TB care where alcohol use reported at baseline or over the course of treatment has also been associated with poor treatment outcomes, such as loss to follow-up.[49-51] Higher numbers of household assets as a proxy for socioeconomic status, were found to be significantly associated with higher quality of life across all domains of WHOQOL-BREF except for the physical domain. A longitudinal study among DS TB patients in northern India[26] had a similar finding using a scale developed by Tiwari et al.[52] The most consistently significant factor associated with lower quality of life in the present study was increasing comorbidity severity as measured by the SCQ. Prior research among TB patients has demonstrated the added negative impact of single comorbid conditions, such as diabetes on quality of life[53] and HIV on quality of life as well as treatment outcomes.[6,50] Multimorbidity, often defined as the presence of two or more chronic conditions,[54] can substantially complicate TB care at levels ranging from pharmacokinetics and drug interactions[55,56] to healthcare seeking, psychological distress and socioeconomic disadvantage.[6,57] Vertical public sector TB program structures can complicate linkages with other services and programs. Continued efforts in India's TB program to link TB care with HIV diagnosis and treatment as well as other social services will likely improve treatment outcomes and quality of life.[29]

The present study aimed to address several previously identified limitations of prior TB quality of life studies. Both DS TB and healthy control comparison groups were included and methods of enumeration and sampling discussed. Data on the screening and recruitment process was documented and identified potential selection bias regarding significantly lower rates of participation for pulmonary DS TB patients and DS TB patients on Category I treatment. In a secondary analysis restricting the final multivariable models of WHOQOL-BREF domains to only pulmonary TB patients and DS TB patients on Category I treatment provided some evidence that the results were robust to this possible bias. Social and behavioral

determinants of quality of life, not frequently included in prior studies, were included in this study and found to be highly significant predictors of quality of life domains.

This study also had important limitations. Participants were recruited exclusively from the public sector TB program and did not include individuals from India's complex and vast private sector.[58] The overall sample size for each study group was small. Despite potential issues in lack of statistical power to detect differences between MDR TB and DS TB patients, large and highly significant differences were observed for physical, psychological and social quality of life domains comparing TB patients and healthy controls. Quality of life scales are also not without criticism, including: the individual nature of quality of life, the differential importance of domains depending on person and place as well as the potential for lack of inclusion of what participants find most important.[21,59,60] Observed associations in the present study may have also been confounded by important covariates not included in the present analysis and relevant only to individuals on TB, such as symptom severity, TB-related stigma, clinical experience and TB knowledge. Lastly, the study was cross-sectional in nature and longitudinal trends in quality of life, which have been identified previously,[26] were not examined. For enrolled participants in PMC, follow-up interviews at 2 and 6 months after treatment initiation or sputum collection are ongoing, and will provide important information on these quality of life trends.

**References:**


1) Aggarwal AN. Health-related quality of life: A neglected aspect of pulmonary tuberculosis. Lung India **2010**; 27:1–3.

2) Godoy MDP, Mello FCQ, Lopes AJ, et al. The functional assessment of patients with pulmonary multidrug-resistant tuberculosis. Respir Care **2012**; 57:1949–1954.

3) Ambaw F, Mayston R, Hanlon C, Alem A. Burden and presentation of depression among newly diagnosed individuals with TB in primary care settings in Ethiopia. BMC Psychiatry **2017**; 17.

4) Atre S, Kudale A, Morankar S, Gosoniu D, Weiss MG. Gender and community views of stigma and tuberculosis in rural Maharashtra, India. Glob Public Health **2011**; 6:56–71.

5) Wingfield T, Boccia D, Tovar M, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. PLoS Med **2014**; 11.

6) Furin J, Isaakidis P, Reid AJ, Kielmann K. 'I'm fed up'': experiences of prior anti-tuberculosis treatment in patients with drug-resistant tuberculosis and HIV'. Int J Tuberc Lung Dis **2014**; 18:1479–1484.

7) Furin JJ, Mitnick CD, Shin SS, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis **2001**; 5:648–655.

8) Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK, Das M, Daftary A. "When treatment is more challenging than the disease": a qualitative study of MDR-TB patient retention. PLoS One **2016**; 11:e0150849.

9) Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res **2004**; 13:299–310.

10) Higginson IJ, Carr AJ. Using quality of life measures in the clinical setting. BMJ **2001**; 322:1297–1300.

11) Kaplan RM, Bush JW. Health-related quality of life measurement for evaluation research and policy analysis. Health Psychol **1982**; 1:61.

12) Ambaw F, Mayston R, Hanlon C, Medhin G, Alem A. Untreated depression and tuberculosis treatment outcomes, quality of life and disability, Ethiopia. Bull World Health Organ **2018**; 96:243–255.

13) Thomas BE, Shanmugam P, Malaisamy M, et al. Psycho-socio-economic issues challenging multidrug resistant tuberculosis patients: a systematic review. PLoS One **2016**; 11:e0147397.

14) Bauer M, Leavens A, Schwartzman K. A systematic review and meta-analysis of the impact of tuberculosis on health-related quality of life. Qual Life Res **2013**; 22:2213–35.

15) Brown J, Capocci S, Smith C, Morris S, Abubakar I, Lipman M. Health status and quality of life in tuberculosis. Int J Infect Dis **2015**; 32:68–75.

16) Huang IC, Wu AW, Frangakis C. Do the SF-36 and WHOQOL-BREF measure the same constructs? Evidence from the Taiwan population. Qual Life Res **2006**; 15:15–24.

17) Hsiung PC, Fang CT, Chang YY, Chen MY, Wang JD. Comparison of WHOQOL-BREF and SF-36 in patients with HIV infection. Qual Life Res **2005**; 14:141–150.

18) WHOQOL User Manual. WHO/MNH/MHP/98.4.Rev.1. Geneva, Switzerland: World Health Organization, **1998**.

19) Dujaili JA, Sulaiman SAS, Hassali MA, Awaisu A, Blebil AQ, Bredle JM. Health-related quality of life as a predictor of tuberculosis treatment outcomes in Iraq. Int J Infect Dis **2015**; 31:4–8.

20) Dhingra VK, Rajpal S. Health related quality of life (HRQL) scoring (DR-12 score) in tuberculosis – additional evaluative tool under DOTS. J Commun Dis **2005**; 37:261–268.

21) Weis SE, Pasipanodya JG. Measuring health-related quality of life in tuberculosis: a systemic review - Response. Health Qual Life Outcomes **2010**; 8:7.

22) Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. J Gen Intern Med **2001**; 16:606–613.

23) Somma D, Thomas BE, Karim F, et al. Gender and socio-cultural determinants of TB-related stigma in Bangladesh, India, Malawi and Colombia. Int J Tuberc Lung Dis **2008**; 12:856–866.

24) Macq J, Solis A, Martinez G. Assessing the stigma of tuberculosis. Psychol Health Med **2006**; 11:346–352.

25) Pasipanodya JG, Miller TL, Vecino M, et al. Using the St. George Respiratory Questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis. Chest **2007**; 132:1591–1598.

26) Aggarwal AN, Gupta D, Janmeja AK, Jindal SK. Assessment of health-related quality of life in patients with pulmonary tuberculosis under programme conditions. Int J Tuberc Lung Dis **2013**; 17:947–953.

27) de Vallière S, Barker RD. Residual lung damage after completion of treatment for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis **2004**; 8:767–771.

28) Kastien-Hilka T, Abulfathi A, Rosenkranz B, Bennett B, Schwenkglenks M, Sinanovic E. Health-related quality of life and its association with medication adherence in active pulmonary tuberculosis– a systematic review of global literature with focus on South Africa. Health Qual Life Outcomes **2016**; 14:1.

29) India TB Report 2018. Revised National Tuberculosis Control Programme Annual Status Report. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, **2018**.

30) Corbett EL, Zezai A, Cheung YB, et al. Provider-initiated symptom screening for tuberculosis in Zimbabwe: diagnostic value and the effect of HIV status. Bull World Health Organ **2010**; 88:13–21.

31) Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The self-administered comorbidity questionnaire: A new method to assess comorbidity for clinical and health services research. Arthritis Rheum **2003**; 49:156–163.

32) AUDIT: The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Care 2nd Edition. WHO/MSD/MSB/01.6a. Geneva, Switzerland: World Health Organization, **2001**.

33) Kaskutas LA, Kerr WC. Accuracy of photographs to capture respondent-defined drink size. J Stud Alcohol Drugs **2008**; 69:605–610.

34) Nayak MB, Kerr W, Greenfield TK, Pillai A. Not all drinks are created equal: implications for alcohol assessment in India. Alcohol Alcohol **2008**; 43:713–718.

35) Nayak MB, Bond JC, Cherpitel C, Patel V, Greenfield TK. Detecting alcohol-related problems in developing countries: A comparison of two screening measures in India. Alcohol Clin Exp Res **2009**; 33:2057–2066.

36) Colbourn T, Masache G, Skordis-Worrall J. Development, reliability and validity of the Chichewa WHOQOL-BREF in adults in lilongwe, Malawi. BMC Res Notes **2012**; 5:346.

37) Balgude A, Sontakke S. Study of impact of antitubercular therapy on quality of life. Indian J Med Sci **2012**; 66:71–77.

38) Dhuria M, Sharma N, Narender Pal Singh, Ram Chander Jiloha, Saha R, Gopal Krishan Ingle. A study of the impact of tuberculosis on the quality of life and the effect after treatment with DOTS. Asia Pac J Public Health **2009**; 21:312–320.

39) Muniyandi M, Rajeswari R, Balasubramanian R, et al. Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients. Int J Tuberc Lung Dis **2007**; 11:887–892.

40) Muniyandi M, Ramachandran R, Balasubramanian R, Narayanan PR. Socio-economic dimensions of tuberculosis control: review of studies over two decades from Tuberculosis Research Center. J Commun Dis **2006**; 38:204–215.

41) 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**; 60:1845–1853.

42) Singh SK, Agrawal A, Tiwari KK. Improvement in quality of life in pulmonary tuberculosis patients: a prospective study. Trop Doct **2017**; 47:97–100.

43) Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Leufkens HG, Mantel-Teeuwisse AK. Adverse events and patients' perceived health-related quality of life at the end of multidrug-resistant tuberculosis treatment in Namibia. Patient Prefer Adherence **2016**; 10:2369–2377.

44) Singla R, Mallick M, Mrigpuri P, Singla N, Gupta A. Sequelae of pulmonary multidrug-resistant tuberculosis at the completion of treatment. Lung India **2018**; 35:4.

45) Al-Qahtani MF, El.Mahalli AA, Al Dossary N, Al Muhaish A, Al Otaibi S, Al Baker F. Health-related quality of life of tuberculosis patients in the Eastern Province, Saudi Arabia. J Taibah Univ Med Sci **2014**; 9:311–317.

46) Kittikraisak W, Kingkaew P, Teerawattananon Y, et al. Health related quality of life among patients with tuberculosis and HIV in Thailand. PLoS One **2012**; 7.

47) Sharma R, Yadav R, Sharma M, Saini V, Koushal V. Quality of life of multi drug resistant tuberculosis patients: a study of North India. Acta Medica Iranica **2014**; 52:448–53.

48) Ahmad N, Javaid A, Sulaiman SAS, et al. Effects of multidrug resistant tuberculosis treatment on patients' health related quality of life: results from a follow up study. PLoS One **2016**; 11:e0159560.

49) Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One **2009**; 4:e6914.

50) Samuels JP, Sood A, Campbell JR, Ahmad Khan F, Johnston JC. Comorbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. Sci Rep **2018**; 8.

51) Duraisamy K, Mrithyunjayan S, Ghosh S, et al. Does alcohol consumption during multidrug-resistant tuberculosis treatment affect outcome? Ann Am Thorac Soc **2014**; 11:712–718.

52) Tiwari SC, Kumar A, Kumar A. Development & standardization of a scale to measure socio-economic status in urban & rural communities in India. Indian J Med Res **2005**; 122:309.

53) Siddiqui AN, Khayyam KU, Siddiqui N, Sarin R, Sharma M. Diabetes prevalence and its impact on health-related quality of life in tuberculosis patients. Trop Med Int Health 22:1394–1404.

54) Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, Smith SM. Managing patients with multimorbidity in primary care. BMJ **2015**; 350:h176.

55) Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Inf Dis **2009**; 9:737–746.

56) Negin J, Abimbola S, Marais BJ. Tuberculosis among older adults – time to take notice. Int J Infect Dis **2015**; 32:135–137.

57) Reis-Santos B, Gomes T, Macedo LR, Horta BL, Riley LW, Maciel EL. Prevalence and patterns of multimorbidity among tuberculosis patients in Brazil: a cross-sectional study. Int J Equity Health **2013**; 12:61.

58) Pai M, Daftary A, Satyanarayana S. TB control: challenges and opportunities for India. Trans R Soc Trop Med Hyg **2016**; 110:158–160.

59) Carr AJ, Gibson B, Robinson PG. Measuring quality of life: Is quality of life determined by expectations or experience? BMJ **2001**; 322:1240–1243.

60) Carr AJ, Higginson IJ. Are quality of life measures patient centered? BMJ **2001**; 322:1357–1360.

**Table 3.1:** Inclusion and exclusion criteria for MDR TB, DS TB and healthy control participants

| MDR TB patients | DS TB patients | Healthy controls |
|---|---|---|
| Inclusion criteria:<br>1) Adults (≥18 years of age) at enrollment<br>2) Diagnosed pulmonary or extrapulmonary TB with detected rifampicin resistance by molecular or culture-based drug sensitivity testing<br>3) Initiating public sector MDR TB treatment (category IV) within Pune or Pimpri-Chinchwad Municipal Corporations<br>4) Able to be interviewed within 2 months of treatment initiation<br>5) Understand spoken Marathi, Hindi or English<br>6) Provide informed consent | Inclusion criteria:<br>1) Adults (≥18 years of age) at enrollment<br>2) Diagnosed pulmonary or extrapulmonary TB<br>3) Initiating public sector DS TB treatment (category I or II) within the same Tuberculosis Unit as the corresponding enrolled MDR TB participant<br>4) Able to be interviewed within 2 months of treatment initiation<br>5) Understand spoken Marathi, Hindi or English<br>6) Provide informed consent | Inclusion criteria:<br>1) Adults (≥18 years of age) at enrollment<br>2) Testing negative for pulmonary TB on two sputum smears per public sector TB program protocol<br>3) Presenting for TB evaluation in same Tuberculosis Unit as the corresponding enrolled MDR TB participant<br>4) No self-reported TB-related symptoms: cough ≥2 weeks, fever, hemoptysis during the previous year, night sweats and unintentional weight loss<br>5) No history of major comorbidities, including: heart disease, high blood pressure, lung disease, diabetes, HIV, tuberculosis, etc.<br>6) Contact number recorded in the microscopy center register<br>7) Able to be interviewed within 2 months of sputum testing<br>8) Understand spoken English, Hindi, or Marathi<br>9) Provide informed consent |
| *Exclusion criteria (all participants):*<br>1) Children (<18 years of age) at the time of treatment initiation<br>2) Presence of any condition that in the opinion of study investigators would make participation in the study unsafe, complicate interpretation of study results, or interfere with achieving the aims of the study | | |

‡MDR-TB suspect criteria leading to molecular or culture-based drug sensitivity testing:[49]
1) Sputum smear (+) or (-) TB patient who has received >1 month of previous TB treatment;
2) Sputum smear (+) patient without prior treatment >1 month, remaining smear (+) after ≥2 months of treatment;
3) HIV-TB co-infection;
4) Close contact of known MDR-TB case
Abbreviations: multidrug resistant (MDR), drug susceptible (DS), human immunodeficiency virus (HIV)

**Table 3.2:** Correlation matrix of WHOQOL-BREF indicator variables and domain scores with domain-level Cronbach's alpha

| WHOQOL-BREF domain | Indicator variable | Physical | Psychological | Social | Environment | Cronbach's alphas |
|---|---|---|---|---|---|---|
| Physical (7 questions) | Physical pain prevents necessary activities | **0.745** | 0.594 | 0.375 | 0.380 | 0.886 |
| | Need medical treatment to function | **0.753** | 0.595 | 0.445 | 0.349 | |
| | Energy for everyday life | **0.848** | 0.777 | 0.552 | 0.567 | |
| | Ability to get around | **0.789** | 0.667 | 0.480 | 0.580 | |
| | Satisfaction with sleep | **0.744** | 0.655 | 0.486 | 0.502 | |
| | Ability to perform daily living activities | **0.892** | 0.814 | 0.551 | 0.605 | |
| | Capacity for work | **0.839** | 0.736 | 0.542 | 0.516 | |
| Psychological (6 questions) | Enjoy life | 0.780 | **0.857** | 0.566 | 0.556 | 0.875 |
| | Feel life is meaningful | 0.571 | **0.759** | 0.524 | 0.491 | |
| | Ability to concentrate | 0.676 | **0.828** | 0.474 | 0.560 | |
| | Accept bodily appearance | 0.745 | **0.809** | 0.459 | 0.564 | |
| | Satisfaction with self | 0.795 | **0.847** | 0.624 | 0.637 | |
| | Negative feelings | 0.595 | **0.779** | 0.572 | 0.583 | |
| Social (3 questions) | Personal relationships | 0.570 | 0.614 | **0.861** | 0.540 | 0.789 |
| | Sex life | 0.538 | 0.607 | **0.912** | 0.574 | |
| | Support from friends | 0.530 | 0.603 | **0.838** | 0.662 | |
| Environment (8 questions) | Feel safe in daily life | 0.666 | **0.766** | 0.550 | 0.698 | 0.788 |
| | Physical environment | 0.261 | 0.345 | 0.256 | **0.638** | |
| | Money to meet needs | 0.422 | 0.488 | 0.454 | **0.752** | |
| | Availability of information needed in daily life | 0.499 | 0.521 | 0.485 | **0.744** | |
| | Opportunities for leisure activities | 0.381 | 0.412 | 0.361 | **0.721** | |
| | Conditions of living place | 0.393 | 0.489 | 0.636 | **0.708** | |
| | Access to health services | 0.320 | 0.436 | 0.426 | **0.666** | |
| | Transport | 0.225 | 0.270 | 0.323 | **0.580** | |

*Missing responses for 3 indicators for one different participant each: need medical treatment, capacity for work, sex life

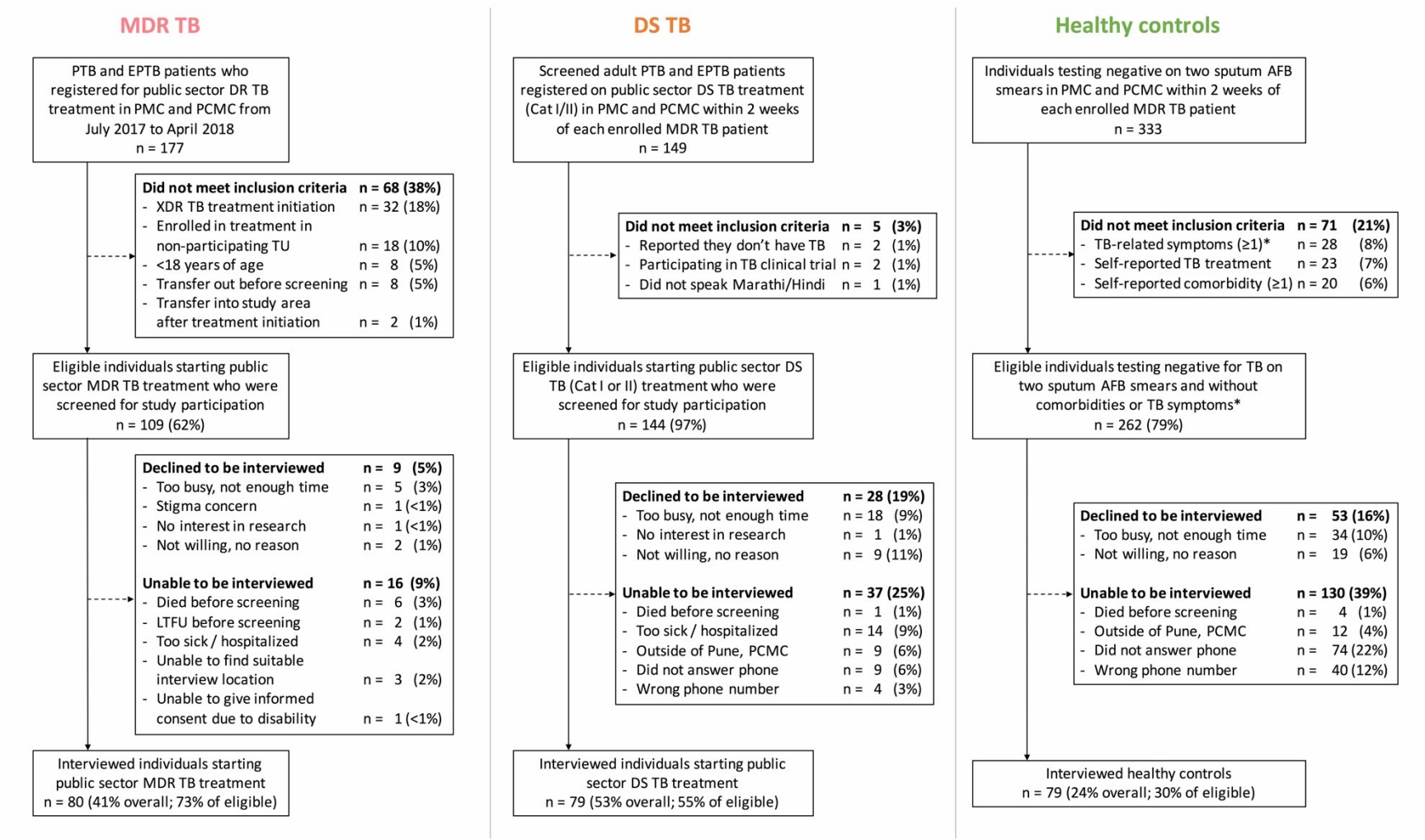


**Figure 3.1:** Eligibility and inclusion of MDR TB, DS TB and healthy control participants in the quality of life study

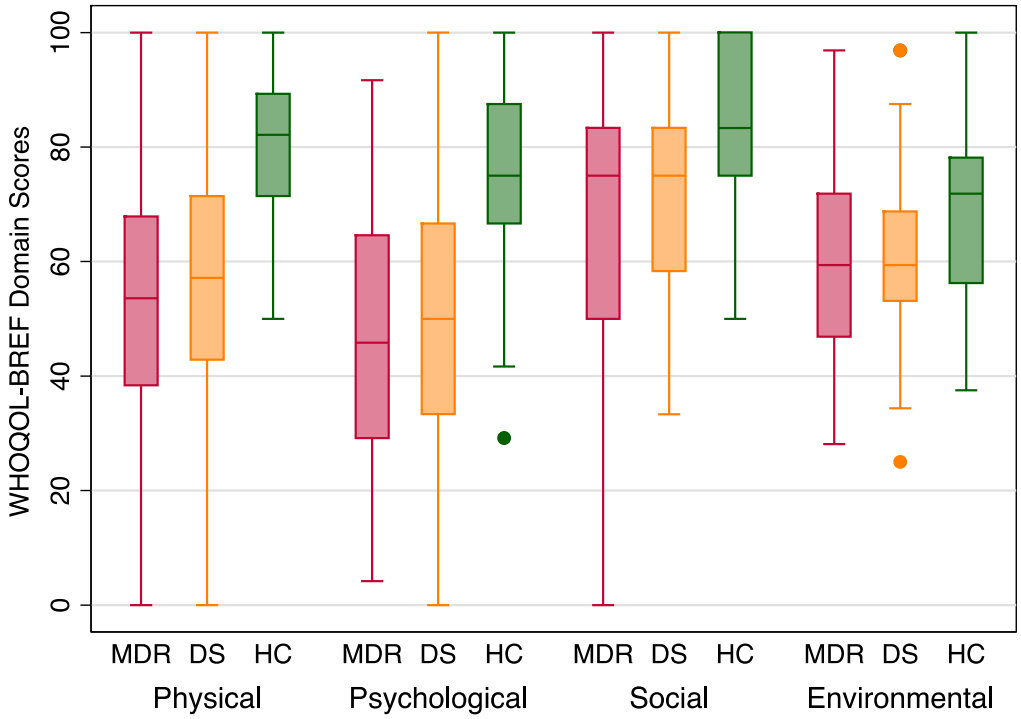


**Figure 3.2:** WHOQOL-BREF domain scores by study group: multidrug-resistant tuberculosis patients (MDR, red); drug susceptible tuberculosis patients (DS, yellow); healthy controls (HC, green)

**Table 3.3:** Baseline characteristics of MDR TB, DS TB and healthy control participants

| Baseline characteristics | Overall | MDR TB | DS TB | Healthy control | p-value* |
|---|---|---|---|---|---|
| | n = 236 (100%) | n = 80 (34%) | n = 79 (33%) | n = 77 (33%) | |
| **Demographics** | | | | | |
| Age (years) | 30 [24-41] | 30 [23-40] | 30 [23-40] | 33 [26-43] | 0.126 |
| Gender | | | | | |
| Male | 133 (56%) | 43 (54%) | 40 (51%) | 50 (65%) | 0.163 |
| Female | 103 (44%) | 37 (46%) | 39 (49%) | 27 (35%) | |
| Marital status | | | | | |
| Never married | 65 (28%) | 25 (31%) | 22 (28%) | 18 (23%) | 0.781 |
| Married | 156 (66%) | 49 (61%) | 53 (67%) | 54 (70%) | |
| Separated, divorced or widowed | 15 (6%) | 6 (8%) | 4 (5%) | 5 (6%) | |
| Education (years) | 9 [5-12] | 10 [6-12] | 8 [3-11] | 9 [7-13] | 0.020 |
| Primary occupation status over last year | | | | | |
| Work (full-time or part-time) | 134 (57%) | 34 (43%) | 45 (57%) | 55 (71%) | <0.001 |
| Studying, not working, retired, housework | 85 (36%) | 33 (41%) | 30 (38%) | 22 (29%) | |
| Unable to work, ill or diasabled | 17 (7%) | 13 (16%) | 4 (5%) | 0 (0%) | |
| **Clinical history** | | | | | |
| Comorbidity (points) | 0 [0-2] | 1 [0-3] | 1 [0-3] | 0 [0-0] | <0.001 |
| Prior TB treatment (months) | 0 [0-6] | 4.5 [0-9] | 0 [0-1] | 0 [0-0] | <0.001 |
| **Social and economic history** | | | | | |
| Smoking tobacco use | | | | | |
| Never | 182 (77%) | 62 (78%) | 61 (77%) | 59 (77%) | 1.000 |
| Current or former | 54 (23%) | 18 (23%) | 18 (23%) | 18 (23%) | |
| Alcohol dependence (AUDIT-C, ≥5) | | | | | |
| No | 192 (81%) | 63 (79%) | 62 (78%) | 67 (87%) | 0.290 |
| Yes | 44 (19%) | 17 (21%) | 17 (22%) | 10 (13%) | |
| Household size (people) | 4 [3.5-6] | 4 [3.5-5] | 4 [4-6] | 5 [3-6] | 0.333 |
| Household assets | | | | | |
| 0-2 assets (1st quartile) | 63 (27%) | 22 (28%) | 28 (35%) | 13 (17%) | 0.172 |
| 3 assets (2nd quartile) | 49 (21%) | 13 (16%) | 17 (22%) | 19 (25%) | |
| 4 assets (3rd quartile) | 62 (26%) | 24 (30%) | 16 (20%) | 22 (29%) | |
| 5-7 (4th quartile) | 62 (26%) | 21 (27%) | 18 (23%) | 23 (30%) | |
| **Study variables** | | | | | |
| Days from baseline to interview | 24 [18-33] | 22.5 [18-28] | 21 [16-31] | 30 [21-38] | <0.001 |

Summary statistics: column percentage listed for all binary and categorical variables; median and interquartile range listed for continuous variables

*p-value: binary and categorical variables using Fisher's exact test; continuous variables using Kruskal Wallis rank test

**Table 3.4:** Factors associated with quality of life domains among MDR TB, DS TB and healthy control study participants

| Baseline characteristics | Physical | | | Psychological | | | Social | | | Environmental | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Beta | 95%CI | p | Beta | 95%CI | p | Beta | 95%CI | p | Beta | 95%CI | p |
| **Participant group and study variables** | | | | | | | | | | | | |
| Participant group (ref = MDR TB) | | | | | | | | | | | | |
| DS TB | 4.7 | [-2.1, 11.6] | 0.176 | 4.3 | [-2.6, 11.2] | 0.223 | 4.8 | [-1.3, 10.8] | 0.120 | -0.4 | [-5.3, 4.4] | 0.856 |
| Healthy control | **23.1** | **[16.9, 29.3]** | **<0.001** | **20.0** | **[13.1, 26.9]** | **<0.001** | **9.7** | **[3.3, 16.1]** | **0.003** | 3.2 | [-2.7, 9.2] | 0.287 |
| Days from baseline to interview | 0.1 | [-0.1, 0.4] | 0.352 | 0.2 | [-0.1, 0.5] | 0.126 | 0.0 | [-0.3, 0.2] | 0.677 | 0.1 | [-0.2, 0.3] | 0.588 |
| **Demographics** | | | | | | | | | | | | |
| Age (per 5 years)* | -0.4 | [-1.5, 0.7] | 0.492 | 0.4 | [-0.7, 1.6] | 0.466 | 0.1 | [-1.0, 1.2] | 0.878 | 0.1 | [-0.8, 1.0] | 0.800 |
| Gender (ref = male) | | | | | | | | | | | | |
| Female | -5.9 | [-12.3, 0.4] | 0.067 | -5.2 | [-12.7, 2.4] | 0.178 | -0.1 | [-5.7, 5.6] | 0.982 | 1.1 | [-4.8, 7.0] | 0.710 |
| Marital status (ref = never married) | | | | | | | | | | | | |
| Married | -5.3 | [-12.4, 1.8] | 0.145 | -1.0 | [-8.7, 6.7] | 0.793 | 1.8 | [-4.7, 8.4] | 0.584 | -0.1 | [-5.9, 5.8] | 0.985 |
| Separated, divorced or widowed | -2.3 | [-13.0, 8.5] | 0.677 | -5.3 | [-16.0, 5.4] | 0.333 | **-16.0** | **[-26.2, -5.7]** | **0.002** | -3.2 | [-12.5, 6.1] | 0.499 |
| Education (years) | 0.1 | [-0.6, 0.9] | 0.687 | 0.2 | [-0.5, 1.0] | 0.537 | **0.6** | **[0.1, 1.2]** | **0.031** | **0.6** | **[0.1, 1.1]** | **0.014** |
| Occupational status (ref = full or part-time work) | | | | | | | | | | | | |
| Studying, not working, retired, housework | 2.1 | [-3.5, 7.8] | 0.453 | -3.2 | [-9.7, 3.3] | 0.327 | 0.0 | [-5.1, 5.0] | 0.994 | -0.9 | [-6.0, 4.2] | 0.723 |
| Unable to work, ill or diasabled | -9.0 | [-20.6, 2.5] | 0.126 | -10.5 | [-22.7, 1.7] | 0.092 | -0.9 | [-12.9, 11.1] | 0.884 | -6.8 | [-14.8, 1.2] | 0.094 |
| **Social and economic history** | | | | | | | | | | | | |
| Smoking tobacco use (ref = never smoker) | | | | | | | | | | | | |
| Current or former | 0.1 | [-6.4, 6.7] | 0.965 | 1.2 | [-5.9, 8.3] | 0.737 | 3.4 | [-3.6, 10.4] | 0.338 | 5.6 | [-0.1, 11.3] | 0.056 |
| Alcohol dependence (ref = AUDIT-C <5) | | | | | | | | | | | | |
| AUDIT-C ≥5 | -4.1 | [-11.6, 3.3] | 0.275 | -6.9 | [-14.6, 0.8] | 0.078 | -7.0 | [-14.4, 0.4] | 0.064 | **-9.5** | **[-15.6, -3.5]** | **0.002** |
| Household size (people), median [IQR] | -0.2 | [-1.3, 1.0] | 0.784 | -0.6 | [-1.9, 0.7] | 0.358 | 0.2 | [-1.0, 1.3] | 0.739 | -0.4 | [-1.3, 0.6] | 0.444 |
| Household assets (ref = 0-2 assets, 1st quartile) | | | | | | | | | | | | |
| 3 assets (2nd quartile) | 2.0 | [-5.0, 9.0] | 0.568 | 2.5 | [-5.0, 10.1] | 0.504 | 2.7 | [-3.9, 9.2] | 0.429 | 2.8 | [-2.5, 8.2] | 0.298 |
| 4 assets (3rd quartile) | -1.0 | [-8.5, 6.5] | 0.794 | 1.9 | [-5.9, 9.7] | 0.638 | 1.1 | [-5.5, 7.8] | 0.739 | 3.2 | [-2.3, 8.8] | 0.253 |
| 5-7 (4th quartile) | 4.9 | [-1.9, 11.8] | 0.158 | **9.9** | **[2.9, 16.8]** | **0.006** | **10.2** | **[4.0, 16.5]** | **0.001** | **9.7** | **[4.2, 15.3]** | **0.001** |
| **Clinical history** | | | | | | | | | | | | |
| Self-administered comorbidity questionnaire (points) | **-2.1** | **[-3.4, -0.8]** | **0.001** | **-1.7** | **[-2.9, -0.6]** | **0.003** | **-2.4** | **[-3.7, -1.2]** | **<0.001** | **-1.0** | **[-1.8, -0.2]** | **0.014** |
| Prior TB treatment (months) | -0.2 | [-0.6, 0.2] | 0.375 | 0.0 | [-0.5, 0.5] | 0.877 | 0.2 | [-0.3, 0.6] | 0.483 | 0.0 | [-0.3, 0.3] | 0.954 |

*Age: scaled by 5 years for regression models

Note: coefficient estimates from all models also adjusted for sub-district of residence (categorical variable)

Abbreviations: CI (confidence interval), p (p-value), Ref (reference), IQR (interquartile range)

# Chapter IV: Willingness to Take Multidrug-Resistant Tuberculosis (MDR TB) Preventive Therapy among Adult and Adolescent Household Contacts of MDR TB Index Cases: A Multi-Site Cross-Sectional Study in Diverse High-TB Burden Countries

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**Abstract:**

**Background:** Household contacts (HHCs) of multidrug-resistant tuberculosis (MDR TB) cases are at high risk of infection and subsequent disease due to prolonged exposure in shared environments. There is limited evidence on the willingness of MDR TB HHCs to take preventive therapy that might decrease their risk of TB.

**Methods:** Enrolled HHCs of MDR and rifampicin resistant (RR)-TB index cases from 16 clinical research sites in 8 countries were interviewed to assess willingness to take a newly developed MDR TB preventive therapy. To identify factors associated with willingness, marginal logistic models were fit using generalized estimating equations (GEE) to account for household-level clustering.

**Results:** Overall, HHC willingness to take preventive therapy was high (79%). Site-level variation in willingness was observed (site-level median 90%, IQR 84-95%;) and was particularly low at one site in India (7%). Increased willingness was significantly associated with current employment or schooling [adjusted Odds Ratio (aOR) 1.82, 95% confidence interval (CI) 1.06-3.12], appropriate TB-related knowledge (aOR 2.23, 95%CI 1.24-4.03), confidence in taking preventive therapy (aOR 7.34, 95%CI 3.39-15.91), and being comfortable telling others about taking preventive therapy (aOR 2.29, 95%CI 1.28-4.09). Decreased willingness was associated with any drug use in the past year (aOR 0.28, 95%CI 0.10-0.78).

**Conclusions:** The high percentage of HHCs of MDR/RR-TB index cases willing to take a newly developed MDR TB preventive therapy provides important evidence for the potential uptake of effective preventive therapy when implemented. Identified HHC-level variables associated with willingness may inform education and counseling efforts to increase HHC confidence in and uptake of MDR TB preventive therapy.

**Introduction:**

Tuberculosis (TB) is the leading infectious disease cause of mortality worldwide with an estimated 10.4 million new cases and 1.7 million deaths in 2016 alone.[1] Multidrug-resistant (i.e. resistant to at least isoniazid and rifampicin; MDR) and rifampicin resistant-TB (RR-TB) are estimated to have caused 600,000 of these new cases and a disproportionately high number of deaths.[1] Household contacts (HHCs) of individuals with active TB are at high risk of infection due to prolonged exposure in shared environments.[2,3] Furthermore, the development of active MDR TB disease among HHCs[2-4] has severe implications for already TB-affected households due to poor treatment outcomes despite lengthy, costly and toxic regimens.[5,6] Prevention of MDR TB disease, therefore, remains a critical public health priority.

Preventing new TB cases through the treatment of latent TB infection (LTBI) among persons exposed to an infectious TB case is a pillar of TB control programs. Isoniazid and rifamycin-containing regimens have been demonstrated to reduce the risk of TB disease among HHCs exposed to drug susceptible TB (DS TB).[7-9] However, observational studies on MDR TB preventive therapy, primarily describing the use of fluoroquinolone-based regimens, have been inconclusive resulting in a conditional recommendation for treatment of only high risk HHCs.[4,9,10] Ongoing clinical trials are evaluating new potential regimens to treat MDR TB infection,[11] but little evidence exists on the willingness of household contacts to take preventive therapy were it available.

Studies of knowledge, attitudes and practices have the potential to provide insights into the willingness of populations to utilize a proposed prevention or treatment strategy, as well as elucidate barriers and enablers of uptake. These findings can provide context to the acceptability of an intervention,[12] inform health education efforts,[13,14] and characterize provider opinions and preparedness.[15] We conducted a multi-country cross-sectional study of HHCs of MDR TB index cases in diverse high TB burden settings to understand how HHCs' TB-related knowledge, attitudes and practices (KAP) are associated with their willingness to take preventive therapy.

**Methods:**

*Study setting:*

The study was conducted from Oct/2015 to Apr/2016 at 16 clinical research sites in 8 countries: Botswana (1 site), Brazil (1), Haiti (1), India (2), Kenya (1), Peru (2), South Africa (7) and Thailand (1) in preparation for the Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx) trial being conducted by the AIDS Clinical Trials Group (ACTG, https://actgnetwork.org/) and International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT, http://impaactnetwork.org/). Information on local TB program activities related to contact tracing and TB preventive therapy was collected through key informant interviews (**Table 4.1**).

*Study participant eligibility criteria and recruitment:*

Pulmonary MDR TB index cases were eligible for enrollment if they met the following inclusion criteria: (1) documented rifampicin resistance by Xpert MTB/RIF, line probe assay or phenotypic drug-sensitivity testing; (2) MDR TB treatment initiation within 6 months of study enrollment, (3) ≥1 HHC, (4) permission for the study team to enumerate and screen HHCs, and (5) residing at a distance deemed by the site-level study team close enough for study conduct. HHCs were defined as: (1) any person currently living or having lived in the same dwelling unit or plot of land, (2) currently sharing or having shared the same housekeeping arrangements as the index case, and (3) reporting exposure within 6 months prior to the index case starting MDR TB treatment. A convenience sample of index cases was recruited and all their eligible adult and adolescent HHCs (≥13 years of age) without active TB were asked to complete a KAP questionnaire.

*Data collection and variables:*

A semi-structured KAP questionnaire was adapted for MDR TB from a recent World Health Organization (WHO) guide for tuberculosis KAP survey development.[16] The survey was pilot tested among TB community health workers at one study site (India Site #2). The final questionnaire consisted of three sections with 40 total items: TB knowledge (signs, symptoms, mode of transmission, presence of a cure,

treatment – 12 questions), attitudes (fear, stigma, community support – 10 questions) and practices regarding TB (willingness to obtain prerequisite tests for LTBI treatment, take MDR TB preventive therapy and participate in a clinical trial – 18 questions). Additional HHC information obtained included: demographic, social, medical and household characteristics. All questionnaires were completed in-person by trained field staff or clinicians prior to participant education or counseling by anyone affiliated with the study.

The primary outcome in this analysis was willingness to take a hypothetical newly developed MDR TB preventive therapy. Willingness to take this therapy even if it caused mild temporary side effects was analyzed as a secondary outcome. These outcome variables as well as HHC willingness to have a blood test (i.e. interferon gamma release assay), to provide a sputum sample, and to obtain a chest x-ray to determine if the HHC was a good candidate for preventive therapy were collected as categorical (yes, not sure, no) and dichotomized as yes vs. not sure or no for analysis.

TB knowledge was analyzed as a binary variable, where appropriate knowledge was defined as correctly identifying all of the following: cough ≥3 weeks is a symptom of TB; TB is a curable disease; TB is transmitted via air when an infected person coughs or sneezes, and MDR TB cure is possible through directly observed therapy.[17] 'Incomplete' knowledge was defined as not correctly identifying all four items above. Confidence in taking MDR TB preventive therapy was defined as HHCs feeling confident or very confident in being able to perform all five of the following (5-point likert scale): meeting with study staff monthly to take medications, coping with difficulties the medication may cause, taking all doses, continuing to take medications even if feeling healthy, and completing medications. The presence of TB-related symptoms was defined differently for HHCs <15 and ≥15 years of age. For adolescents or children (<15 years), TB-related symptoms included any of the following at the time of interview: neck swelling, fever, night sweats, cough ≥10 days, poor weight gain, less playful, convulsion or decreased consciousness. For

adults (≥15 years), symptoms included any of the following in the past month: cough ≥10 days, fever, night sweats, unintentional weight loss or enlarged lymph nodes.

*Statistical analysis:*

The primary objective of this analysis was to evaluate the association between HHC-level KAP factors and willingness to take a newly developed preventive therapy. Among enrolled HHCs with complete KAP data, aggregate and site-level exploratory data analysis was conducted using summary statistics and scatter plots. Simple (adjusting only for research site) and multivariable marginal logistic models for willingness to take preventive therapy were fit using generalized estimating equations (GEE) with robust variance estimates to account for household-level clustering assuming an exchangeable within-household correlation structure.[18] Fixed effect dummy variables for research sites were included to adjust for variation between sites. Informed by a literature review and the Health Belief Model (**Supplementary Figure 4.1**),[19] covariates of interest were selected prior to analysis from a larger set of variables available through the PHOENIx Feasibility Study.

All HHCs at one site (Thailand) reported willingness to take preventive therapy. To allow model fit, the outcome status of one randomly selected HHC at this site was set to not willing. The sensitivity of model parameter estimates to this random outcome reassignment was examined. The potential confounding of HHC-level associations by corresponding household (HH)-level aggregate variables was also evaluated. Model diagnostics included examining the influence of individual HHCs and research sites on parameter estimates as well as residual plots.[20] All analyses were conducted in Stata v13.1 (StataCorp, College Station, TX, USA) except for the creation of diverging stacked bar charts, which were created in R (v3.3.2) using the *likert* package.[21]

*Human research ethics approvals:*

Ethical approval was obtained from each research site's local institutional review board. Written informed consent was obtained for all participating MDR TB index cases and their household contacts prior to study interviews and procedures.

**Results:**

*Study recruitment:*

Across all sites, 328 adult pulmonary MDR TB index cases were screened during the recruitment period; 20 declined screening or were ineligible. Three declined contact with HHCs, and 27 had no eligible, enrolled HHCs who also completed the KAP questionnaire.

*Characteristics of MDR/RR-TB index cases and their households:*

Among included index cases (n=278), the median time between MDR TB treatment initiation and study enrollment was 68 days [interquartile range (IQR) 29-125] with a majority also reporting a history of prior TB (53%). The median number of eligible, enumerated HHCs of all ages in these index case households was 4 (IQR 2-5) with 32% of households having ≥1 adolescent HHC (13 to <18 years of age), 31% ≥1 HHC <5 years of age and 6% with ≥1 pregnant HHC.

*Characteristics of enrolled HHCs of MDR/RR-TB index cases:*

For the analysis of factors associated with willingness to take preventive therapy, complete KAP data were available for 743 adult and adolescent HHCs (99.7% of the 745 enrolled, and 79% of the 946 without active TB and eligible for the KAP study) from 278 MDR/RR-TB index case households (median 2 enrolled HHCs with complete KAP data per HH, IQR: 1-3) (**Figure 4.1**). The median number of MDR TB index cases and HHCs enrolled per site and included in this analysis was 14 (IQR 10–25) and 39 (IQR 22-70), respectively. Among HHCs participating in the KAP study, the median age was 33 years (IQR 22–49), 62% were women, 58% had a secondary school education or higher, and 46% were currently employed or in

school. In social history, 10% of HHCs reported prior TB treatment and 21% current smoking tobacco use. For alcohol use, 66 HHCs (9%) reported daily or almost daily alcohol use in the last year (n=58) or refused to answer the question (n=8 HHCs). Similarly, 60 reported drug use in the last year (n=57) or refused to answer (n=3) (**Table 4.2**). Participation in the KAP study was not associated with age, but females were more likely to participate than males (83% vs. 72%).

*MDR/RR-TB HHCs and their TB-related knowledge and attitudes:*

Appropriate MDR TB knowledge was demonstrated by 66% of enrolled HHCs with substantial site-level variation (**Supplementary Figure 4.2**), notably at India Site #1 (5%). Although 87% of all adult and adolescent HHCs participating in the KAP study (n=743) reported that TB transmission is airborne, 54% of these HHCs also stated that transmission can occur through sharing utensils, 40% by sharing clothes or towels, 24% by touching items in public places and 15% by handshakes. Among the 595 (74%) HHCs who stated that a cure for MDR TB exists, 94% responded that this cure was possible through directly observed therapy (DOT). These HHCs also reported that a cure was possible through means other than DOT: good nutrition (80%), praying or religious acts (18%), herbal remedies (11%), and rest without medication (7%).A majority of HHCs (64%) were concerned about being infected with MDR TB from their diagnosed household member, and 84% believed that someone could die from MDR TB without proper treatment. Regarding perceived stigma, 28% of HHCs reported that a person with TB is usually rejected by their community, and 34% stated that they would be uncomfortable telling family members or friends they were taking MDR TB preventive therapy (**Table 4.2**).

*Willingness of MDR/RR TB HHCs to take a newly developed MDR TB preventive therapy*

HHC willingness to take a newly developed MDR TB preventive therapy was high overall (79%) with observed site-level variation (site-level median 90%, IQR 84-95%; **Figure 4.2**). Willingness to take a preventive therapy with potential mild temporary side effects was lower (70% overall; site-level median 80%, IQR 66-91%). Reported HHC willingness to complete prerequisite steps to determine preventive

therapy eligibility was also high overall: blood test (96%, IQR 88-98%), provide sputum sample (97%, IQR 95-100%) and obtain chest x-ray (100%, IQR 97-100%). Notably at India Site #1, only 7% of HHCs reported willingness to take a newly developed preventive therapy (29% not willing, 64% not sure) with low percentages willing to have a prerequisite blood test (22%), provide a sputum sample (9%) or obtain a chest x-ray (9%).

In the multivariable model for the primary outcome (**Table 4.2**), increased willingness to take preventive therapy was significantly associated with the following HHC characteristics: currently employed or in school [adjusted Odds Ratio (aOR) 1.82, 95% confidence interval (CI) 1.06, 3.12], appropriate TB-related knowledge (aOR 2.23, 95%CI 1.24, 4.03), confidence in taking preventive therapy (aOR 7.34, 95%CI 3.39, 15.91), and being comfortable telling family or friends about taking preventive therapy (aOR 2.29, 95%CI 1.28, 4.09). Decreased willingness was associated with any drug use in the past year (aOR 0.28, 95%CI 0.10, 0.78) and marginally associated with prior treatment for TB (aOR 0.41, 95%CI 0.15, 1.13). In a multivariable model including the same set of covariates, the secondary outcome of willingness to take preventive therapy with side effects was significantly associated with increased HHC-level concern about being infected from the index case (aOR 2.02, 95%CI 1.30, 3.11) and confidence in taking preventive therapy (aOR 7.89, 95%CI 4.12, 14.08) as well as marginally associated with prior TB treatment (0.53, 95%CI 0.26, 1.09).

Site-level variation was observed in the unadjusted associations between willingness to take preventive therapy and covariates of interest (**Supplementary Table 4.2**); however, the direction of these associations was consistent for the most significant covariates identified through the multivariable model: appropriate TB-related knowledge, comfort telling family or friends about taking preventive therapy, confidence in taking preventive therapy, and substance use in the past year. After adjustment for all covariates included in the multivariable model, the predicted willingness of HHCs at India Site #1 remained significantly lower than all other sites on pairwise comparisons with Bonferroni correction. Potential confounding of observed

HHC-level associations by between-household effects was examined by creating HH-level summary means for all HHC-level covariates.[22] Including all aggregate HH-level variables in the final multivariable model did not qualitatively change any HHC-level association except HHC education, which was not significant in either model. In sensitivity analyses, the direction and magnitude of HHC-level variable associations with willingness to take preventive therapy was robust to exclusion of India Site #1 and primary outcome reassignment of each of the 25 individual HHCs at the Thailand research site (**Supplementary Figures 4.3 and 4.4**).

**Discussion:**

In this large multi-country study of HHCs of MDR TB index cases residing in diverse high TB burden regions, willingness to take a newly developed preventive therapy was high (79%) along with willingness to complete prerequisite steps to determine eligibility for treatment. These findings are similar to prior observational studies and case series from limited settings that have documented high levels of MDR TB preventive therapy initiation among contacts. In studies identified through recent systematic reviews on MDR TB preventive therapy,[4,9,23] data on treatment initiation has been reported for eight generally small cohorts (median 30 contacts, IQR 22-36) (**Supplementary Table 4.1**). For these studies, treatment initiation, defined as taking any MDR TB preventive therapy for ≥2 weeks, was reported to be high overall (median 85.6%, IQR 71.2-93.4%); however, no data were available on factors associated with uptake.[24-30] Considerably more evidence exists for DS TB preventive therapy. In a recent meta-analysis of 25 cohorts, 88% of individuals were estimated to have started preventive therapy if it was recommended, and factors associated with initiation, included: younger age, high perceived risk of TB and no prior LTBI treatment.[31]

In the context of multiple ongoing clinical trials to identify effective MDR TB preventive therapy regimens,[11] the present study provides evidence from diverse geographic settings for the potential high uptake of these therapies when implemented in the high risk population of household contacts. The identification of factors associated with increased willingness to take preventive therapy can inform

counseling efforts, generate hypotheses for more contextualized local studies of KAP factors, and identify populations where implementation of preventive therapy may be particularly effective or challenging. Appropriate TB-related knowledge, being comfortable speaking with family and friends about taking preventive therapy and most notably confidence in properly taking the regimen were all associated with increased willingness to start treatment. The marginal association between current HHC tobacco smoking and increased willingness to take MDR TB preventive therapy suggests a possible opportunity for increased preventive therapy uptake among a population at higher risk of both LTBI and active disease.[32] Many of these identified factors have been previously identified to be associated with DS TB preventive therapy initiation or completion.[31,33-34] Factors included in the present study's KAP questionnaire were primarily patient-level, social and lifestyle;[34] however, health system factors (e.g. clinic wait times, provider opinions on preventive therapy, and provider-patient communication) and therapy characteristics (e.g. duration, side effects) have also been demonstrated to be important predictors of treatment initiation and completion.[31,33-36] Observed associations may furthermore be confounded by unmeasured HHC- or HH-level variables.

The decreased willingness of HHCs to take preventive therapy with mild side effects is also consistent with prior research, which has identified side effects as a primary reason for treatment discontinuation.[26,30] Although some studies have documented high completion rates of preventive therapy regimens among initiators,[25,27-28] completion has been demonstrated to be one of the primary gaps in the LTBI cascade of care.[31] Self-reported willingness to initiate treatment may not be a strong proxy for HHC completion of treatment or even future initiation due to social desirability bias or changes in beliefs, attitudes or circumstances over time.[37,38] Additional limitations of this work include variable site-level sample sizes due to a constrained period of enrollment after the overall target of 300 index cases was met. As a result, the study sample is weighted toward sites starting enrollment earlier and with faster rates of recruitment (**Figure 4.2**) as well as households with greater numbers of HHCs. Although this study may have lacked power to detect differences in associations among sites, identified associations were highly consistent across sites; however, the possibility that these associations might vary across locations cannot be ruled out.

In conclusion, the high percentage of HHCs of MDR/RR-TB index cases willing to take a newly developed MDR TB preventive therapy provides important evidence for the potential uptake of effective preventive therapy when implemented. Identified HHC-level variables associated with decreased willingness to take preventive therapy may inform education and counseling efforts to increase HHC confidence in and uptake of MDR TB preventive therapy. While the present research focused on willingness to take preventive therapy at the HHC-level, further research examining the site-specific context of TB-related KAP through qualitative or mixed methods studies offers promise in guiding the rollout of preventive therapy to reduce the burden of TB in these high-risk populations.

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**References:**


1) Global tuberculosis report, 2017. WHO/HTM/TB/2017.23. Geneva, Switzerland: World Health Organization, **2017**. License: CC BY-NC-SA 3.0 IGO.

2) Becerra MC, Appleton SC, Franke MF, et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. Lancet **2011**; 377:147–152.

3) Shah NS, Yuen CM, Heo M, Tolman AW, Becerra MC. Yield of Contact Investigations in Households of Patients with Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis. Clin Infect Dis **2014**; 58:381–391.

4) Fox GJ, Schaaf HS, Mandalakas A, Chiappini E, Zumla A, Marais BJ. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. Clin Microbiol Infect **2017**; 23:147–153.

5) Ahuja SD, Ashkin D, Avendano M, et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients. PLoS Med **2012**; 9:e1001300.

6) Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis **2004**; 8:1382–1384.

7) Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev **2010**; CD000171.

8) Sharma SK, Sharma A, Kadhiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst Rev **2013**; CD007545

9) Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. WHO/CDS/TB/2018.4. Geneva, Switzerland: World Health Organization, **2018**. License: CC BY-NC-SA 3.0 IGO.

10) van der Werf MJ, Langendam MW, Sandgren A, Manissero D. Lack of evidence to support policy development for management of contacts of multidrug-resistant tuberculosis patients: two systematic reviews. Int J Tuberc Lung Dis **2012**; 16:288–296.

11) Moore DAJ. What can we offer to 3 million MDRTB household contacts in 2016? BMC Med **2016**; 14:64.

12) Madhivanan P, Li T, Srinivas V, Marlow L, Mukherjee S, Krupp K. Human papillomavirus vaccine acceptability among parents of adolescent girls: Obstacles and challenges in Mysore, India. Prev Med **2014**; 64:69–74.

13) Shu E, Sobieszczyk ME, Sal y Rosas VG, et al. Knowledge of tuberculosis and vaccine trial preparedness in Lima, Peru. Int J Tuberc Lung Dis **2017**; 21:1288–1293.

14) Chang S-H, Cataldo JK. A systematic review of global cultural variations in knowledge, attitudes and health responses to tuberculosis stigma. Int J Tuberc Lung Dis **2014**; 18:168–173.

15) Karris MY, Beekmann SE, Mehta SR, Anderson CM, Polgreen PM. Are We Prepped for Preexposure Prophylaxis (PrEP)? Provider Opinions on the Real-World Use of PrEP in the United States and Canada. Clin Infect Dis **2013**; 1-9.

16) Advocacy, communication and social mobilization for TB control a guide to developing knowledge, attitude and practice surveys. WHO/HTM/STB/2008.46. Geneva, Switzerland: World Health Organization & Stop TB Partnership, **2008**.

17) Sagili KD, Satyanarayana S, Chadha SS. Is knowledge regarding tuberculosis associated with stigmatising and discriminating attitudes of general population towards tuberculosis patients? Findings from a community based survey in 30 districts of India. PLoS One **2016**; 11:e0147274.

18) Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika **1986**; 73:13–22.

19) Becker MH. The health belief model and personal health behavior. Health Educ Monogr **1974**; 2:324–473.

20) Hosmer Jr, D. W., Lemeshow, S. & Sturdivant, R. X. *Applied Logistic Regression*. Hoboken, New Jersey, United States: John Wiley & Sons, **2013**, 354-375.

21) Bryer J, Speerschneider, K. likert: Analysis and Visualization Likert Items. R package version 1.3.5. https://CRAN.R-project.org/package=likert. **2016**

22) Rabe-Hesketh S, Skrondal A. Multilevel and longitudinal modeling using Stata, 2nd edition. College Station, Texas, USA: STATA press, **2012** :109-122.

23) Fraser A, Paul M, Attamna A, Leibovici L. Treatment of latent tuberculosis in persons at risk for multidrug-resistant tuberculosis: systematic review. Int J Tuberc Lung Dis **2006**; 10:19–23.

24) Adler-Shohet FC, Low J, Carson M, Girma H, Singh J. Management of Latent Tuberculosis Infection in Child Contacts of Multidrug-Resistant Tuberculosis: Pediatr Infect Dis J **2014**; 33:664–666.

25) Bamrah S, Brostrom R, Dorina F, et al. Treatment for LTBI in contacts of MDR TB patients, Federated States of Micronesia, 2009–2012. Int J Tuberc Lung Dis **2014**; 18:912–918.

26) Bedini A, Garlassi E, Stentarelli C, et al. Multidrug-resistant tuberculosis outbreak in an Italian prison: tolerance of pyrazinamide plus levofloxacin prophylaxis and serial interferon gamma release assays. New Microbes New Infect **2016**; 12:45–51.

27) Denholm JT, Leslie DE, Jenkin GA, et al. Long-term follow-up of contacts exposed to multidrug-resistant tuberculosis in Victoria, Australia, 1995–2010. Int J Tuberc Lung Dis **2012**; 16:1320–1325.

28) Garcia-Prats AJ, Zimri K, Mramba Z, Schaaf HS, Hesseling AC. Children exposed to multidrug-resistant tuberculosis at a home-based day care centre: a contact investigation. Int J Tuberc Lung Dis **2014**; 18:1292–1298.

29) Trieu L, Proops DC, Ahuja SD. Moxifloxacin Prophylaxis against MDR TB, New York, New York, USA. Emerg Infect Dis **2015**; 21:500–503.

30) Younossian AB, Rochat T, Ketterer J-P, Wacker J, Janssens J-P. High hepatotoxicity of pyrazinamide and ethambutol for treatment of latent tuberculosis. Eur Respir J **2005**; 26:462–464.

31) Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Inf Dis **2016**; 16:1269–1278.

32) Lin H-H, Ezzati M, Murray M. Tobacco Smoke, Indoor Air Pollution and Tuberculosis: A Systematic Review and Meta-Analysis. PLoS Med **2007**; 4:e20.

33) Talbot EA, Kenyon TA, Halabi S, Moeti TL, More K, Binkin NJ. Knowledge, attitudes and beliefs regarding tuberculosis preventive therapy for HIV-infected persons, Botswana, 1999. Int J Tuberc Lung Dis **2000**; 4:1156–1163.

34) San Sebastian M, Bothamley GH. Tuberculosis preventive therapy: perspective from a multi-ethnic community. Resp Med **2000**; 94:648–653.

35) Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection—the promise and the challenges. Int J Infect Dis **2017**; 56:68–76.

36) Pease C, Hutton B, Yazdi F, et al. Efficacy and completion rates of rifapentine and isoniazid (3HP) compared to other treatment regimens for latent tuberculosis infection: a systematic review with network meta-analyses. BMC Infect Dis **2017**; 17:265.

37) Stanton BF, Clemens JD, Aziz KMA, Rahman M. Twenty-four-hour recall, knowledge-attitude-practice questionnaires, and direct observations of sanitary practices: a comparative study. Bull World Health Organ **1987**; 65:217–222.

38) Launiala A. How much can a KAP survey tell us about people's knowledge, attitudes and practices? Some observations from medical anthropology research on malaria in pregnancy in Malawi. Anthropol Matters **2009**; 11.

**Table 4.1:** Routine practices of TB Control Programs affiliated with participating clinical research sites

| Routine practices of TB Control Program | Botswana | Brazil | Haiti | India | | Kenya | Peru | | South Africa | | | | | | | Thailand |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Site 1 | Site 2 | | Site 1 | Site 2 | Site 1 | Site 2 | Site 3 | Site 4 | Site 5 | Site 6 | Site 7 | |
| **Evaluation of HHCs of MDR TB patients** | | | | | | | | | | | | | | | | |
| Evaluation of HHCs of MDR TB patients | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes |
| HH visits conducted to evaluate HHCs | Yes | Yes | No | No | Yes | Yes | Yes | Yes | | Yes | Yes | | Yes | Yes | Yes | Yes |
| Evaluation of adult contacts of MDR TB patients | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | | Yes | Yes | | Yes | Yes | Yes | Yes |
| Symptom screen | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | | Yes | Yes | | Yes | No | Yes | Yes |
| Tuberculin skin test | No | Yes | No | Yes | No | Yes | Yes | Yes | | No | No | | No | No | No | Yes |
| Interferon gamma release assay | No | No | No | No | No | No | No | No | | No | No | | No | No | No | No |
| Chest radiograph | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | | Yes | No | | No | No | No | Yes |
| Follow-up with contacts of MDR TB patients (months) | Yes* | No | 3 | No | 9 | 24 | 24 | 24 | No | No | 24 | No | No | 6 | 24 | 4 |
| **Preventive therapy for MDR TB HHCs** | | | | | | | | | | | | | | | | |
| Preventive therapy given to HHCs of MDR TB patients | No | Yes | No | No | No | No | No | No | No | Yes | Yes | No | Yes | Yes | Yes | No |
| Fluoroquinolone alone | | No | | | | | | | | No | No | | No | No | No | |
| Fluoroquinolone + ethambutol[∞] | | No | | | | | | | | No | No | | Yes + INH | Yes | Yes + PZA | |
| Fluoroquinolone + ethionamide | | No | | | | | | | | No | No | | No | No | No | |
| Isoniazid + rifampicin | | No | | | | | | | | No | No | | No | No | No | |
| Isoniazid | | Yes | | | | | | | | Yes | Yes | | Yes | Yes | No | |

*Follow-up with contacts of MDR TB patients: unknown duration
∞Two sites in South Africa routinely provide three-drug therapy: fluoroquinolone + ethambutol + an additional medication
Abbreviations: HHCs (household contacts); MDR TB (multidrug-resistant tuberculosis); INH (isoniazid); PZA (pyrazinamide)

**Table 4.2:** Characteristics of 743 enrolled MDR TB household contacts from 278 index case households and factors associated with their willingness to take a newly developed MDR TB preventive therapy

| Variables | Summary statistics | | Marginal logistic models | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total n (col %)* | Willing to take MDR-TB PT n (row %)* | Simple | | | Multivariable | | |
| | | | aOR | 95%CI | p | aOR | 95%CI | p |
| **Sociodemographic Characteristics** | | | | | | | | |
| Age (rescaled to 10 years for logistic models) | | | | | | | | |
| Median [IQR], years | 33 [22-49] | 33 [22-48] | 1.06 | [0.90, 1.23] | 0.495 | 1.06 | [0.88, 1.28] | 0.524 |
| Sex | | | | | | | | |
| Female | 461 (62.1%) | 366 (79.4%) | 1.32 | [0.86, 2.01] | 0.201 | 1.23 | [0.74, 2.06] | 0.424 |
| Male | 282 (38.0%) | 219 (77.7%) | 1.00 | ref | | 1.00 | ref | |
| Education (highest completed) | | | | | | | | |
| Secondary, university or higher | 430 (57.9%) | 343 (79.8%) | 1.11 | [0.64, 1.93] | 0.717 | 0.89 | [0.44, 1.81] | 0.745 |
| None or primary | 313 (42.1%) | 242 (77.3%) | 1.00 | ref | | 1.00 | ref | |
| Currently employed or in school | | | | | | | | |
| Yes | 343 (46.2%) | 277 (80.8%) | 1.34 | [0.86, 2.09] | 0.192 | **1.82** | **[1.06, 3.12]** | **0.029** |
| No / Refused to answer | 400 (53.8%) | 308 (77.0%) | 1.00 | ref | | 1.00 | ref | |
| **Medical and Social History** | | | | | | | | |
| Tobacco use: current smoking | | | | | | | | |
| Yes | 152 (20.5%) | 139 (91.5%) | 1.40 | [0.63, 3.08] | 0.408 | 2.36 | [0.96, 5.84] | 0.062 |
| No | 591 (79.5%) | 446 (75.5%) | 1.00 | ref | | 1.00 | ref | |
| Alcohol use: ever drank alcohol daily in past 12m | | | | | | | | |
| Yes / Refused to answer | 66 (8.9%) | 60 (90.9%) | 1.53 | [0.57, 4.09] | 0.398 | 2.32 | [0.61, 8.87] | 0.219 |
| No | 677 (91.1%) | 525 (77.6%) | 1.00 | ref | | 1.00 | ref | |
| Drug use: ever used in past 12m | | | | | | | | |
| Yes / Refused to answer | 60 (8.1%) | 49 (81.7%) | **0.38** | **[0.17, 0.86]** | **0.021** | **0.28** | **[0.10, 0.78]** | **0.014** |
| No | 683 (91.9%) | 536 (78.5%) | 1.00 | ref | | 1.00 | ref | |
| Previously treated for TB | | | | | | | | |
| Yes | 77 (10.4%) | 67 (87.0%) | 0.75 | [0.36, 1.58] | 0.447 | 0.41 | [0.15, 1.13] | 0.086 |
| No / Unknown | 666 (89.6%) | 518 (77.8%) | 1.00 | ref | | 1.00 | ref | |
| **Perceived Susceptibility to and Severity of MDR-TB** | | | | | | | | |
| Knowledge-related to TB | | | | | | | | |
| Appropriate | 493 (66.4%) | 445 (90.3%) | **2.92** | **[1.74, 4.90]** | **<0.001** | **2.23** | **[1.24, 4.03]** | **0.008** |
| Incomplete | 250 (33.7%) | 140 (56.0%) | 1.00 | ref | | 1.00 | ref | |
| Can die of MDR-TB without treatment | | | | | | | | |
| Yes | 627 (84.4%) | 544 (86.8%) | **3.89** | **[1.77, 8.55]** | **0.001** | 2.47 | [0.99, 6.14] | 0.052 |
| No / Don't know | 116 (15.6%) | 41 (35.3%) | 1.00 | ref | | 1.00 | ref | |
| Typical treatment of person with TB in community | | | | | | | | |
| Most people reject them | 206 (27.7%) | 138 (67.0%) | 1.19 | [0.62, 2.29] | 0.591 | 1.12 | [0.61, 2.06] | 0.708 |
| Other responses | 537 (72.3%) | 447 (83.2%) | 1.00 | ref | | 1.00 | ref | |
| Concerned about getting MDR-TB from recently diagnosed HH member | | | | | | | | |
| Yes | 478 (64.3%) | 406 (84.9%) | **2.33** | **[1.52, 3.57]** | **<0.001** | 1.61 | [0.93, 2.80] | 0.089 |
| No / Neutral | 265 (35.7%) | 179 (67.6%) | 1.00 | ref | | 1.00 | ref | |
| Sleeping arrangement in HH with index case | | | | | | | | |
| Same room, same bed | 87 (11.7%) | 72 (82.8%) | 0.77 | [0.40, 1.48] | 0.430 | 0.67 | [0.30, 1.48] | 0.324 |
| Same room, different bed | 164 (22.1%) | 126 (76.8%) | 1.06 | [0.61, 1.82] | 0.840 | 1.36 | [0.72, 2.57] | 0.351 |
| Different room or building | 492 (66.2%) | 387 (78.7%) | 1.00 | ref | | 1.00 | ref | |
| **Cues to Action** | | | | | | | | |
| Presence of any TB-related symptom | | | | | | | | |
| Yes | 128 (17.2%) | 112 (87.5%) | 0.92 | [0.51, 1.66] | 0.789 | 1.01 | [0.52, 1.96] | 0.980 |
| No / Unknown | 615 (82.8%) | 473 (76.9%) | 1.00 | ref | | 1.00 | ref | |
| Perception that TB is serious problem in community | | | | | | | | |
| Yes | 454 (61.1%) | 390 (85.9%) | 1.29 | [0.75, 2.20] | 0.358 | 0.84 | [0.45, 1.58] | 0.592 |
| No / Neutral | 289 (38.9%) | 195 (67.5%) | 1.00 | ref | | 1.00 | ref | |
| **Barriers and Enablers to Preventive Therapy** | | | | | | | | |
| Comfortable telling family about taking MDR TB PT | | | | | | | | |
| Yes | 494 (66.5%) | 440 (89.1%) | **3.07** | **[1.88, 4.99]** | **<0.001** | **2.29** | **[1.28, 4.09]** | **0.005** |
| No / Neutral | 249 (33.5%) | 145 (58.2%) | 1.00 | ref | | 1.00 | ref | |
| Confident in properly taking preventive therapy | | | | | | | | |
| Yes | 405 (54.5%) | 388 (95.8%) | **7.66** | **[3.72, 15.79]** | **<0.001** | **7.34** | **[3.39, 15.91]** | **<0.001** |
| No / Neutral | 338 (45.5%) | 197 (58.3%) | 1.00 | ref | | 1.00 | ref | |

*Column and row percentages unless otherwise specified; confidence intervals not overlapping odds ratio null value are bolded
Abbreviations: MDR TB (multidrug resistant tuberculosis); PT (preventive therapy); col (column); aOR (adjusted odds ratio); CI (confidence interval); p (p-value); IQR (interquartile range); ref (reference group); 12m (12 months); HH (household)

**Figure 4.1:** Eligibility, enrollment, and participation of 743 adult and adolescent household contacts from 278 MDR/RR-TB index case households participating in the PHOENIx feasibility knowledge, attitudes and practices study

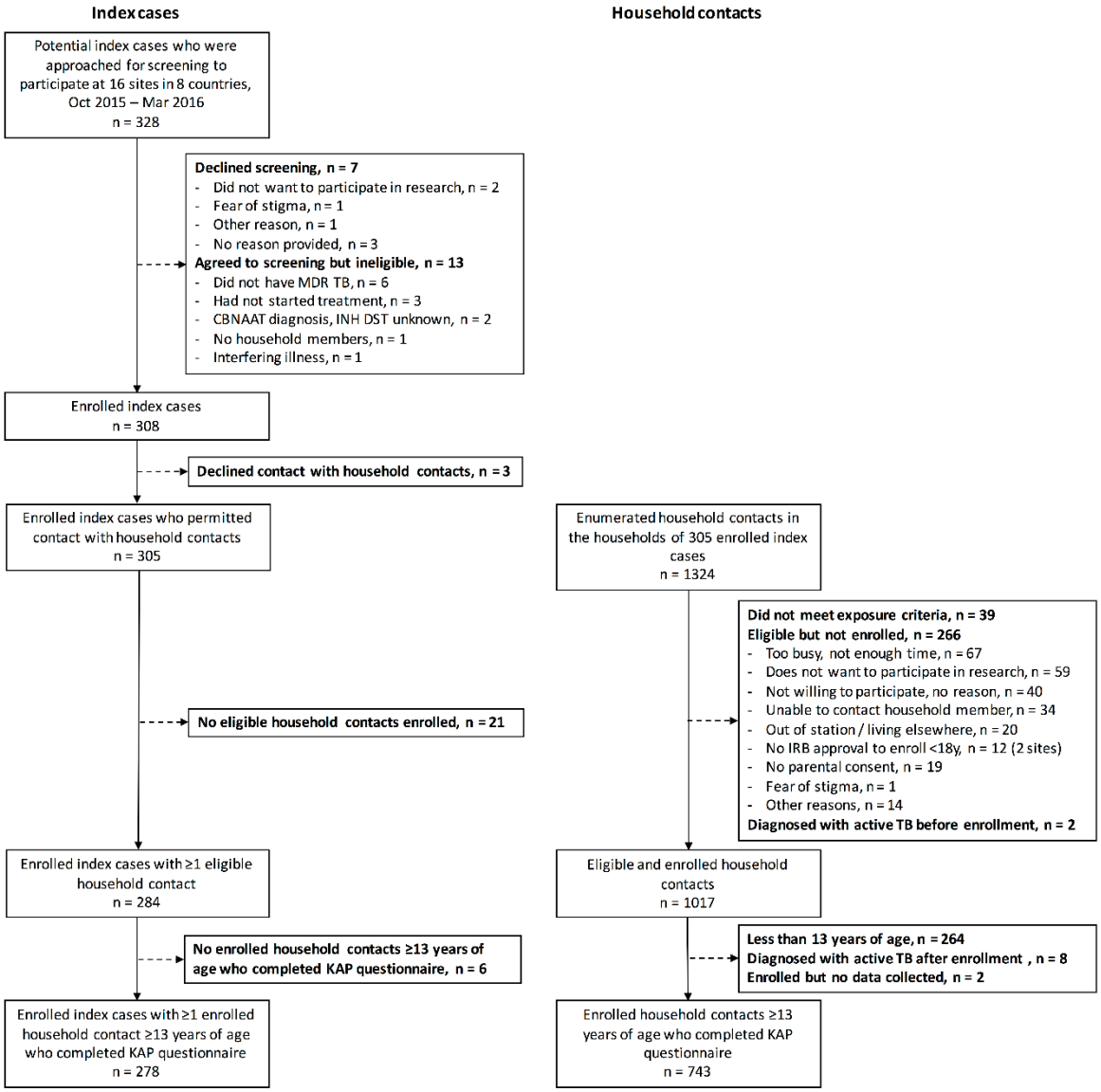
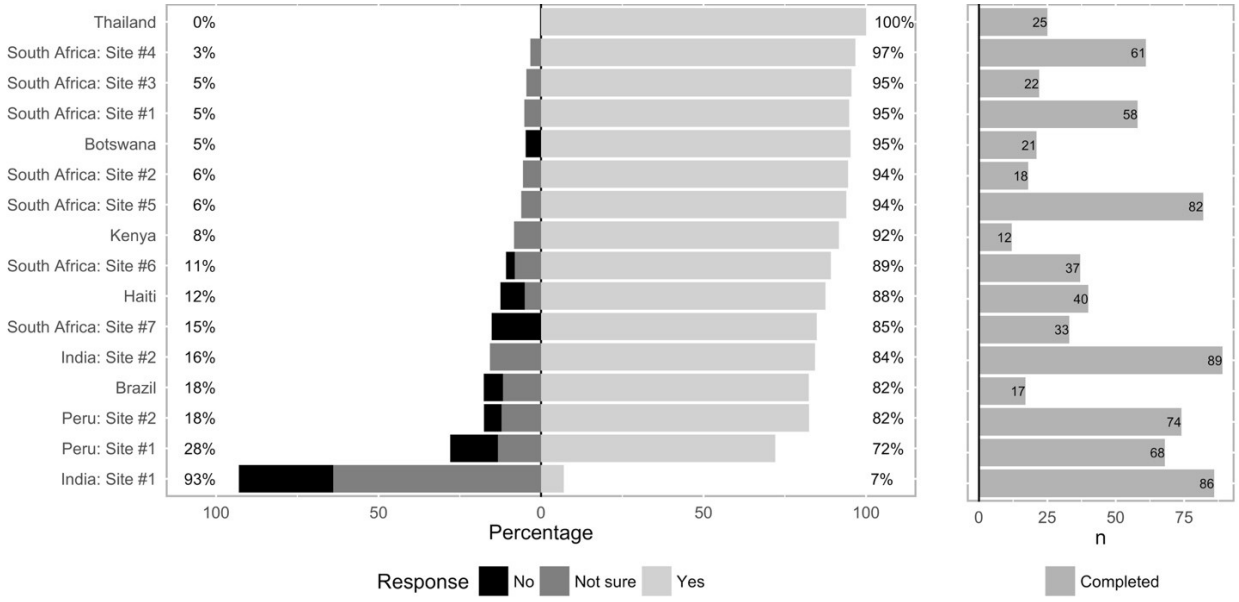


**Figure 4.2:** Willingness of MDR/RR-TB household contacts to take newly developed MDR TB preventive therapy stratified by clinical research site (left panel). Number of enrolled MDR/RR-TB household contacts at each clinical research site (right panel)



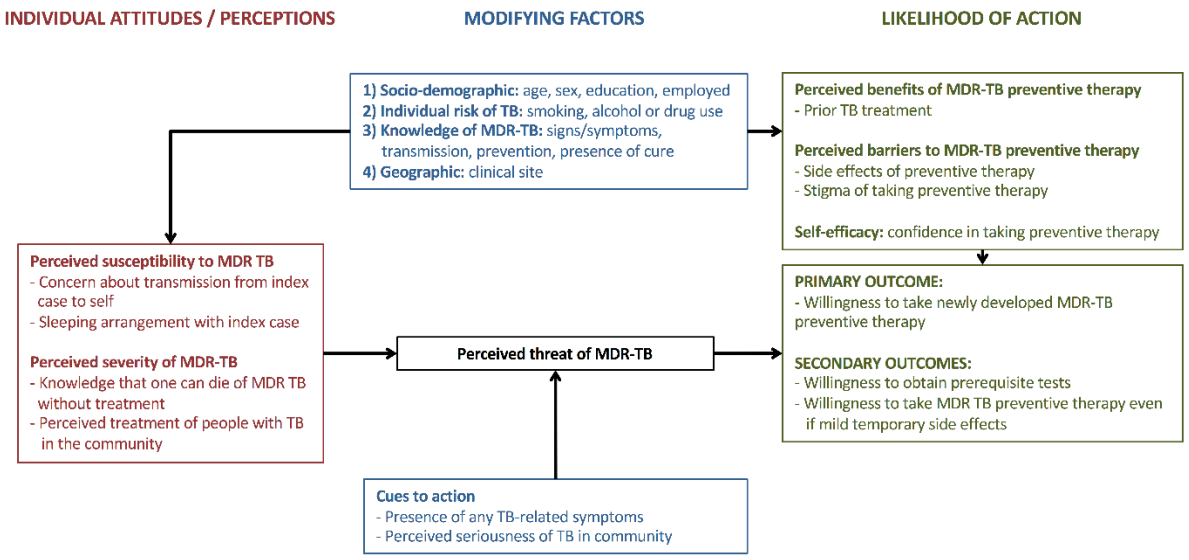
**Supplementary Table 4.1:** Prior studies on MDR TB preventive therapy reporting treatment initiation

| Reference | Country | Year | Exposed group age | Exposed group category | Total contacts | Eligibility criteria for offering preventive therapy | Preventive therapy | Initiation of preventive therapy |
|---|---|---|---|---|---|---|---|---|
| Adler-Shohet et al. (2014) | United States of America | Not reported | <5 years | School | **118** | 1) TST ≥5mm on initial testing or TST ≥5mm on repeat testing (8-10 weeks after initial) **AND** 2) No evidence of active disease on CXR | 9m LFX + PZA | **26/31 (83.9%)** - n = 5: parents refused treatment |
| Bamrah et al. (2014) | Micronesia | 2009-2012 | All ages | Household or healthcare facility staff | **232** | TST ≥5mm on initial testing **AND** No evidence of active TB disease on clinical exam, symptom review and CXR | 12m MFX + EMB / ETH (adults) 12m LFX + EMB / ETH (children) | **104/119 (87.4%)** - n = 15: contacts refused treatment or discontinued treatment within 2 weeks of starting |
| Bedini et al. (2016) | Italy | 2010 | ≥21 years | Prison | **39** | TST ≥10mm **AND** QGIT (+) ≥0.35 IU/mL above nil control value (and >25% of nil control value) **AND** No evidence of active disease on CXR and high-resolution chest CT | 6m LFX + PZA | **12/17 (70.5%)** - n = 5: did not agree to receive therapy, but reasons not reported |
| Denholm et al. (2012) | Australia | 1995-2010 | All ages | Contacts | **570** | >8hr cumulative exposure to index case **AND** TST ≥10mm (adults) **OR** TST ≥5mm (<5y or immunocompromised) If above criteria met, contact was referred to specialist for evaluation and potential preventive therapy. Decision on preventive therapy based on medical specialist evaluation in medical charts, clinical review, additional investigations (e.g. TST, QGIT) | 6-9m FQ and/or PZA + other drugs prescribed | **14/28 (50%)** Not included in numerator above: prescribed DS-TB LTBI preventive therapy (n = 4) Included in denominator above: contacts declined follow-up (n = 3), contacts opted for serial CXR and clinical review (n = 11) Not included in denominator above: lost to follow-up (n = 5), prescribed drug sensitive LTBI treatment (n = 4), preventive therapy considered high-risk due to comorbidities (n = 4), past history of TB (n = 3), active TB (n = 1), no reason identified (n = 4) |
| Garcia-Prats et al. (2014) | South Africa | 2011-2013 | <5 years | Daycare centre | **38** | No evidence of active disease on CXR, clinical examination. All children were prescribed preventive therapy regardless of initial TST result | 6m high-dose INH + EMB + OFX | **24/24 (100%)** |
| Trieu et al. (2015) | United States of America | 2005 | Not reported | Care facilities for homeless, previously homeless or PLHIV | **241** (detailed information only available for HIV-negative contact (n = 1) PLHIV contacts (n = 167) | Exposure to an index case: resident of a building on the floor on which an index case resided or visited during the infectious period **OR** health care staff members who provided direct care to index cases **AND** Person living with HIV **OR** HIV-negative individual with history of TST-negativity before exposure AND TST-positivity after exposure (i.e. conversion) | MFX (outbreak A) MFX + PZA (outbreak B) Alternative regimens (details not reported) (duration not reported for any regimen) | Outbreak A: n = 85 eligible contacts **30/42 (71.4%)** Included in numerator and denominator: eligible HIV-negative contact, who also started preventive therapy (n = 1) Not included in denominator: loss to follow-up (n = 39), died before evaluation (n = 1), physician decision (n = 3) Outbreak B: n = 83 total PLHIV contacts **31/34 = 91.2%** Not included in denominator: loss to follow-up (n = 26), died before evaluation (n = 14), physician decision (n = 9) |
| Younossian et al. (2005) | Switzerland | 2003-2004 | 31-48 years | Contacts | **18** | TST >10mm (all contacts unaware of previous TST) **AND** 'Definite' contact with index case | 9m PZA + EMB | **12/12 = 100%** |

**Abbreviations:**

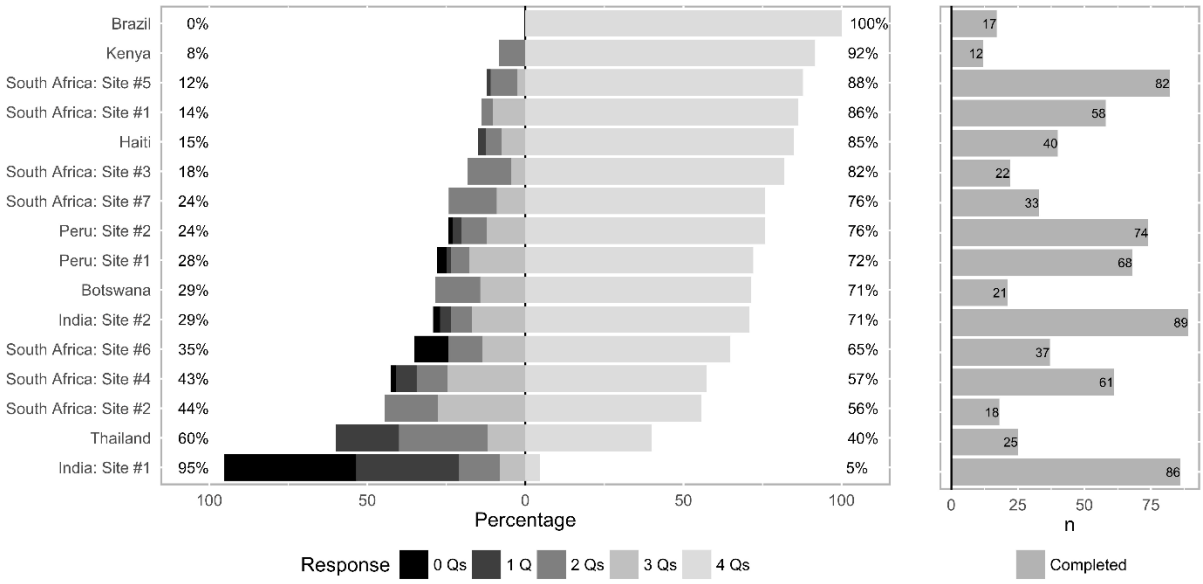
- **General:** TB (tuberculosis); DR (drug-resistant); DS (drug-susceptible); PLHIV (person living with human immunodeficiency virus); LTBI (latent TB infection)
- **Eligibility criteria:** TST (tuberculin skin test); mm (millimeter); CXR (chest x-ray); QGIT (QuantiFERON-TB Gold In-Tube); IU (international units); CT (computed tomography); hr (hour); y (year)
- **Preventive therapy:** m (months); LFX (levofloxacin); PZA (pyrazinamide); MFX (moxifloxacin); EMB (ethambutol); ETH (ethionamide); FQ (fluoroquinolone); INH (isoniazid); OFX (ofloxacin)

**Supplementary Figure 4.1:** Conceptual framework for the relationship between KAP factors and willingness to take a newly developed MDR TB preventive therapy was informed by the Health Belief Model, which is grounded in social psychological theory

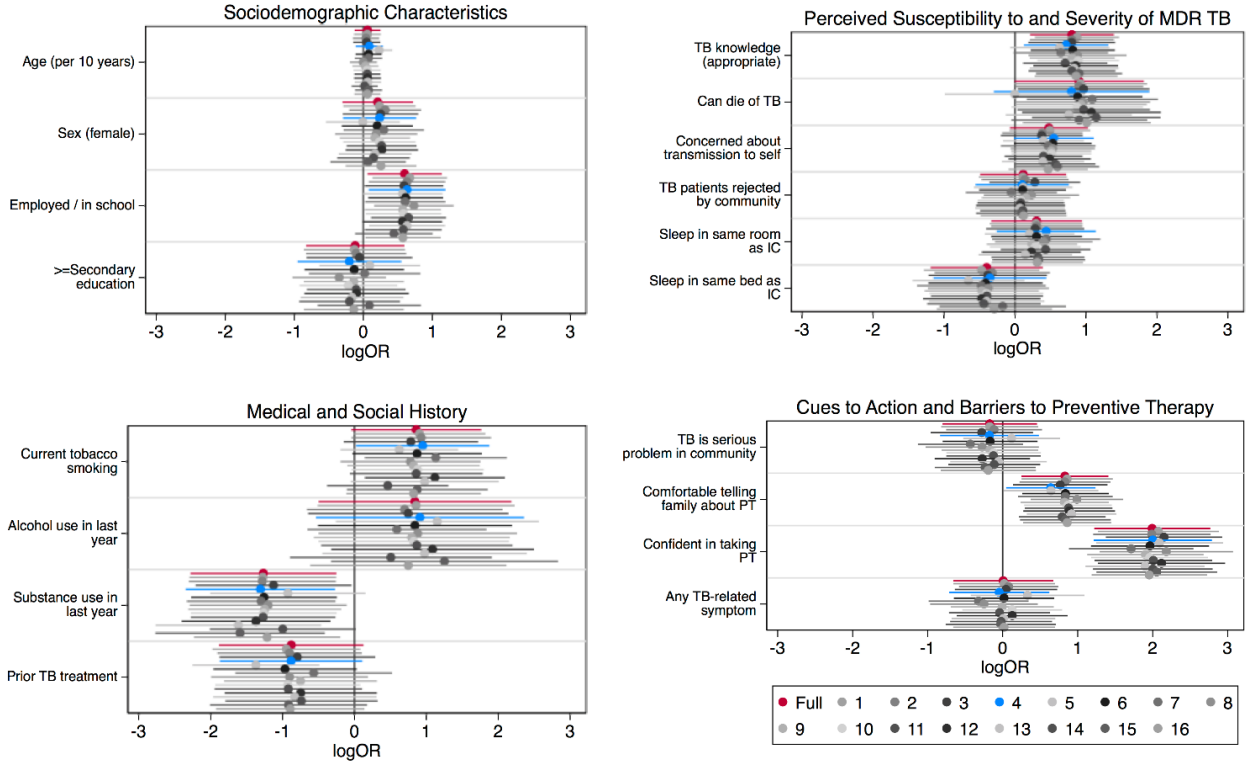



In this conceptual framework, the likelihood of action (i.e., taking preventive therapy) is dependent upon four categories of factors: 1) an individual's perception of the severity of TB and their susceptibility; 2) presence of cues to action, such as a prior history of TB; 3) an individual's assessment of the benefits of and barriers to preventive therapy; and 4) modifying factors, including knowledge of TB, geographic location, social and demographic characteristics, as well as risk of TB. The causal relationships between these factors and the outcome of interest are likely complex and were not investigated in the present risk factor analysis.

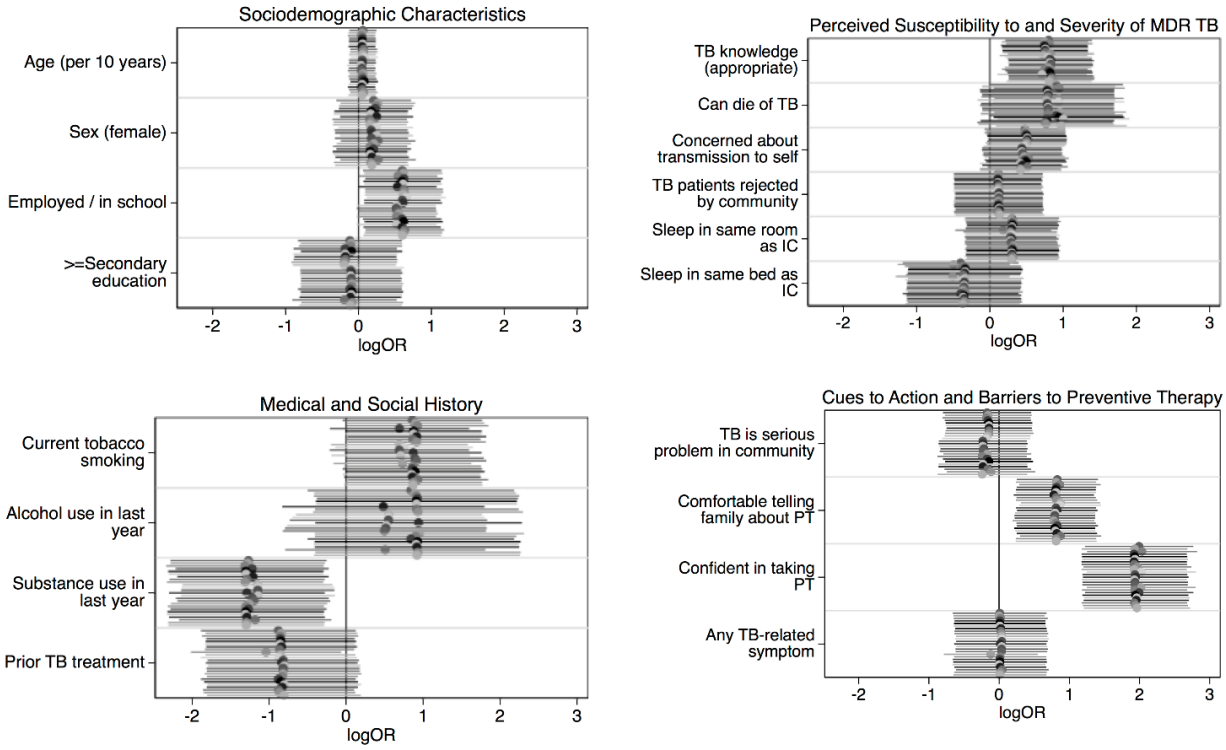
**Supplementary Figure 4.2:** Correct number of responses to four TB knowledge questions among adult and adolescent HHCs of MDR/RR-TB index cases by clinical research site. Knowledge was defined as correctly identifying each of the following: 1) symptoms of TB: cough ≥3 weeks is a symptom of TB, 2) TB is a curable disease: yes (vs. no or not sure), 3) TB transmission: via air when an infected person coughs or sneezes, and 4) MDR TB cure: is possible through directly observed therapy. In the above graph, blue is the percent of HHCs at a clinical research site who identified the correct response to the above four questions; dark red is the percent who did not identify the correct response to any question.



**Supplementary Figure 4.3:** Sensitivity of final multivariable model (outcome: willingness to take a newly developed preventive therapy) parameter estimates to the exclusion of each research site. Labeling of each point estimate and 95%CI: full multivariable including all sites (red) 1: Botswana, 2: Brazil, 3: Haiti, 4: India Site #1 (blue), 5: India Site #2, 6: Kenya, 7: Peru Site #1, 8: Peru Site #2, 9: South Africa Site #1, 10: South Africa Site #2, 11: South Africa Site #3, 12: South Africa Site #4, 13: South Africa Site #5, 14: South Africa Site #6, 15: South Africa Site #7, 16: Thailand.



**Supplementary Figure 4.4:** Sensitivity of final multivariable model (outcome: willingness to take preventive therapy) parameter estimates to outcome reassignment of single HHC from willing to take preventive therapy to not willing to take preventive therapy. Outcome reassignment was necessary to allow model fit for HHC data from the Thailand clinical research site where all enrolled HHCs reported willingness to take preventive therapy.



**Supplementary Table 4.2:** Unadjusted site-level associations between willingness to take preventive therapy and HHC-level covariates

| Clinical Research Site | HHCs | Willing to take PT | Not willing to take PT | Age (rescaled 10 years) | Female | Employed or in school | Secondary education or higher | Appropriate TB Knowledge | Can die of MDR TB | TB serious in community | Concern about transmission | Community rejects TB patients | Comfortable telling family about PT | Confident in taking PT | TB-related Sx | Current smoking | Alcohol use in last year | Substance use in last year | Prior TB treatment | IC: sleep in same room different bed | IC: sleep in same room, same bed |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Botswana | 21 | 20 (95.2%) | 1 (4.8%) | 1.26 | P0 (3/21) 100%, 94.4% | P0 (10/21) 100%, 90.9% | P0 (4/21) 100%, 94.1% | P0 (6/21) 100%, 93.3% | P0 (2/21) 100%, 94.5% | P0 (2/21) 100%, 94.7% | P0 (3/21) 100%, 94.4% | P1 (1/21) 95.0%, 100% | P0 (2/21) 100%, 94.7% | P0 (6/21) 100%, 93.3% | P1 (2/21) 94.7%, 100% | P1 (1/21) 95.0%, 100% | P1 (1/21) 95.0%, 100% | NV0 | P1 (2/21) 94.7%, 100% | P1 (3/21) 93.3%, 100% | P2 (3/21) 93.3%, 100% |
| Brazil | 17 | 14 (82.4%) | 3 (17.7%) | 2.45 | P0 (5/17) 100%, 75.0% | 0.27 | 0.09 | NV1 | NV1 | 0.72 | 7.60 | 0.58 | 2.04 | P1 (3/17) 78.6%, 100% | 0.56 | 1.30 | P1 (2/17) 80.0%, 100% | P1 (1/17) 81.3%, 100% | P1 (2/17) 80.0%, 100% | P1 (1/17) 83.3%, 100% | 0.63 |
| Haiti | 40 | 35 (87.5%) | 5 (12.5%) | 0.84 | 1.36 | 4.56 | 0.77 | 1.91 | NV1 | 3.53 | 5.66 | 0.10 | 3.04 | 1.32 | 0.13 | P1 (4/40) 86.1%, 100% | P1 (3/40) 86.5%, 100% | P1 (1/40) 89.7%, 0% | 0.11 | 0.93 | 0.52 |
| India: Site 1 | 86 | 6 (7.0%) | 80 (93.0%) | 0.90 | 1.08* | 1.67* | 2.10 | 19.50* | 7.41* | 3.00* | 2.44* | 0.78* | 17.19 | NV0 | P1 (1/86) 7.1%, 0% | P1 (2/86) 7.1%, 0% | P1 (2/86) 7.1%, 0% | P1 (1/86) 7.1%, 0% | NV0 | 0.44* | P2 (3/86) 8.6%, 0% |
| India: Site 2 | 89 | 75 (84.3%) | 14 (15.7%) | 0.60 | 1.61 | 3.47 | 1.80 | 15.66 | 18.52 | 0.81 | P1 (24/89) 78.5%, 100% | 0.49 | P1 (49/89) 65.0%, 100% | 8.20 | 0.37 | P1 (5/89) 83.3%, 100% | P1 (1/89) 85.2%, 0% | P1 (2/89) 86.2%, 0% | P1 (5/89) 83.3%, 100% | 2.82 | 1.47 |
| Kenya | 12 | 11 (91.7%) | 1 (8.3%) | 0.57 | NV1 | NV0 | P1 (4/12) 87.5, 100% | P0 (1/12) 100%, 90.9% | NV1 | P0 (1/12) 100%, 90.9% | P0 (5/12) 100%, 85.7% | P1 (2/12) 90.0%, 100% | NV1 | P1 (8/12) 75.0%, 100% | NV0 | NV0 | P1 (1/12) 90.9%, 100% | NV0 | P1 (1/12) 90.9%, 100% | NV1 | P2 (4/12) 87.5%, 100% |
| Peru: Site 1 | 68 | 49 (72.1%) | 19 (27.9%) | 1.17 | 1.50 | 0.80 | 0.73 | 3.79 | 1.39 | 2.43 | 2.30 | 3.98 | 2.46 | 18.03 | 2.02 | 0.44 | P1 (1/68) 71.6%, 100% | 0.71 | 0.59 | 0.54 | 0.52 |
| Peru: Site 2 | 74 | 61 (82.4%) | 13 (17.6%) | 1.20 | 1.19 | 0.90 | 1.73 | 1.71 | P0 (1/74) 100%, 82.2% | 1.17 | 2.06 | 1.63 | 1.57 | 3.98 | P1 (9/74) 80.0%, 100% | P1 (5/74) 81.2%, 100% | P1 (2/74) 81.9%, 100% | 0.67 | 0.85 | 1.03 | 0.61 |
| South Africa: Site 1 | 58 | 55 (94.8%) | 3 (5.2%) | 1.93 | 7.87 | 1.44 | P0 (10/58) 100%, 93.8% | 3.47 | P0 (2/58) 100%, 94.6% | P0 (11/58) 100%, 93.6% | 1.58 | 1.02 | 2.00 | P1 (44/58) 78.6%, 100% | 0.31 | 0.20 | P1 (4/58) 94.4%, 100% | 0.14 | 0.08 | P1 (8/58) 93.5%, 100% | P2 (4/58) 93.5%, 100% |
| South Africa: Site 2 | 18 | 17 (94.4%) | 1 (5.6%) | 0.77 | P0 (5/18) 100%, 92.3% | P1 (8/18) 90%, 100% | P1 (16/18) 50%, 100% | P0 (8/18) 100%, 90.0% | P0 (2/18) 100%, 93.8% | P0 (7/18) 100%, 90.9% | P0 (6/18) 100%, 91.7% | P1 (2/18) 93.8%, 100% | P0 (4/18) 100%, 92.9% | P1 (10/18) 87.5%, 100% | P0 (15/18) 100%, 66.7% | P1 (1/18) 94.1%, 100% | NV0 | NV0 | P1 (2/18) 93.8%, 100% | NV1 | P2 (1/18) 94.1%, 100% |
| South Africa: Site 3 | 22 | 21 (95.5%) | 1 (4.6%) | EPPO | P0 (7/22) 100%, 93.3% | P0 (15/22) 100%, 85.7% | P0 (5/22) 100%, 94.1% | P1 (18/22) 75.0%, 100% | P0 (2/22) 100%, 95.0% | P0 (5/22) 100%, 94.1% | P1 (15/22) 85.7%, 100% | P1 (4/22) 94.4%, 100% | P0 (4/22) 100%, 94.4% | P1 (12/22) 90.0%, 100% | P1 (4/22) 94.4%, 100% | P1 (4/22) 94.4%, 100% | NV0 | P1 (1/22) 95.2%, 100% | P1 (2/22) 95.0%, 100% | P0 (13/22) 100%, 80.0% | P2 (4/22) 100%, 100% |
| South Africa: Site 4 | 61 | 59 (96.7%) | 2 (3.3%) | 0.86 | P0 (22/61) 100%, 94.9% | P1 (28/61) 93.9%, 100% | P0 (15/61) 100%, 95.7% | 1.39 | P0 (7/61) 100%, 96.3% | 4.50 | P0 (9/61) 100%, 96.2% | P1 (5/61) 96.4%, 100% | P0 (8/61) 100%, 96.2% | P0 (7/61) 100%, 96.3% | P0 (33/61) 100%, 92.9% | P0 (32/61) 100%, 93.1% | 0.55 | 0.31 | 0.18 | P1 (17/61) 95.0%, 100% | P2 (4/61) 95.0%, 100% |
| South Africa: Site 5 | 82 | 77 (93.9%) | 5 (6.1%) | 1.05 | 2.83 | 0.89 | P1 (10/82) 93.1%, 100% | 1.54 | P0 (1/82) 0%, 95.1% | P0 (12/82) 100%, 92.9% | 4.33 | P1 (10/82) 93.1%, 100% | P0 (9/82) 100%, 93.2% | P1 (42/82) 87.5%, 100% | 1.97 | 0.97 | NV0 | 1.26 | 0.59 | P1 (26/82) 91.5%, 100% | 0.79 |
| South Africa: Site 6 | 37 | 33 (89.2%) | 4 (10.8%) | 5.13 | 3.65 | 0.22 | 1.17 | 2.20 | P0 (4/37) 100%, 87.9% | P0 (3/37) 100%, 88.2% | 0.51 | NV0 | 16.20 | 7.75 | P1 (5/37) 87.5%, 100% | P0 (16/37) 81.0%, 100% | 1.74 | 0.28 | 0.46 | 0.21 | P2 (5/37) 94.7%, 100% |
| South Africa: Site 7 | 33 | 28 (84.9%) | 5 (15.2%) | 1.19 | 2.77 | 5.30 | P0 (11/33) 100%, 77.3% | 0.87 | P0 (1/33) 100%, 84.4% | 1.31 | 0.74 | P1 (4/33) 82.8%, 100% | 1.51 | 3.33 | 2.23 | 1.06 | 0.88 | 0.41 | P1 (3/33) 83.3%, 100% | P1 (3/33) 85.7%, 100% | 0.61 |
| Thailand | 25 | 25 (100%) | 0 (0%) | 1.03 | P0 (10/25) 100%, 93.3% | P1 (8/25) 94.1%, 100% | P1 (7/25) 94.4%, 100% | P0 (15/25) 100%, 90.0% | P0 (7/25) 100%, 94.4% | P1 (10/25) 93.3%, 100% | P1 (10/25) 93.3%, 100% | NV0 | P0 (4/25) 100%, 95.2% | P0 (21/25) 75.0%, 100% | P0 (1/25) 95.8%, 100% | P1 (6/25) 94.7%, 100% | P1 (8/25) 94.1%, 100% | NV0 | P1 (1/25) 95.8%, 100% | P1 (1/25) 100%, 100% | P0 (21/25) 100%, 66.7% |
| Multivariable Model | 743 | aOR | | 1.06 | 1.23 | 1.82 | 0.89 | 2.23 | 2.47 | 0.84 | 1.61 | 1.12 | 2.29 | 7.34 | 1.01 | 2.36 | 2.32 | 0.28 | 0.41 | 1.36 | 0.67 |
| | | p value | | 0.524 | 0.424 | 0.029 | 0.745 | 0.008 | 0.052 | 0.592 | 0.089 | 0.708 | 0.005 | 0.000 | 0.980 | 0.062 | 0.219 | 0.014 | 0.086 | 0.351 | 0.324 |

*Simple logistic model fit using GEE and robust SE did not converge; point estimate of OR is from simple logistic model fit using robust SE (Huber and White sandwich estimator)
Abbreviations: HHCs (household contacts); PT (preventive therapy); TB (tuberculosis); MDR (multidrug-resistant); Sx (symptom); IC (index case)
EPPO = exposure perfectly predicts outcome
NV0 = no variation in exposure variable (all HHCs opposite exposure status as listed at top of table, i.e. exposure status = 0)
NV1 or NV2 = no variation in exposure variable (all HHCs with exposure status as listed at top of table, i.e. exposure status = 1 (NV1) or 2 (NV2))
P0 (## / ##) = no variation in outcome status conditional on exposure; all HHCs with exposure variable = 0 had same outcome. (## / ##) = number of HHCs with exposure status = 0 out of total number of HHCs at site
P1 (## / ##) = no variation in outcome status conditional on exposure; all HHCs with exposure variable = 1 had same outcome. (## / ##) = number of HHCs with exposure status = 1 out of total number of HHCs at site
%, % = percentage of HHCs with exposure status = 0 who were willing to take preventive therapy // percentage of HHCs with exposure status = 1 who were willing to take preventive therapy
Font color-code:
Red font = percentage of HHCs with exposure = 0 that were willing to take preventive therapy was greater than percentage HHCs with exposure = 1 that were willing
Blue font = percentage of HHCs with exposure = 1 that were willing to take preventive therapy was greater than percentage HHCs with exposure = 0 that were willing
Background color-coding: odds ratio
Exposure status = 1 associated with lower unadjusted odds of willingness to take preventive therapy: light red: OR <1.00 and >=0.667; medium red: OR <0.667 and >=0.4; dark red: OR <0.4
Exposure status = 1 associated with higher unadjusted odds of willingness to take preventive therapy: Light blue: OR = >1.00 and <=1.50; medium blue: OR >1.50 and <=2.50; dark blue: OR >2.50
Background color-coding: p values for multivariable model: green: p <0.05; yellow: p <1.00 and >0.05

# Chapter V: Conclusion

The previous chapters highlight the importance of understanding both traditional and patient-reported MDR TB treatment outcomes as well as associated factors. This understanding at both centralized and local levels can provide crucial context about TB program functioning and inform the development or evaluation of patient support programs. The strong associations of anemia and malnutrition, manifestations of severe TB disease, with mortality suggest potential needs for earlier MDR TB diagnosis and more aggressive treatment in efforts to improve outcomes. Indeed, the finding that mortality rates were significantly lower for MDR TB patients registered in 2015 compared to 2016 is a positive indicator of progress. The higher hazard of loss follow-up as well as impaired environmental quality of life for patients with a history of alcohol use was highly consistent with prior research and points to the need of moving from descriptive studies to piloting novel methods of alcohol treatment interventions or scaling up known effective ones. Ongoing efforts within RNTCP to conduct effective operational research in order to guide the implementation of novel diagnostic, treatment, and patient support strategies will continue to improve MDR TB care in India.

In general, leveraging existing and largely standardized programmatic data offers promise to both inform local practices as well as share developed research tools and lessons learned with other interested sites. The cultivation of strong local collaborations can provide important context to data, help focus research questions on topics meaningful to the program and facilitate the rapid translation of substantive research findings into practice. The utilization of multiple imputation to address missing data challenges as well as competing events approaches can enhance the strength of analyses from programmatic data with near ubiquitous challenges of data quality.

Lastly, the incorporation of patient-reported outcomes, such as quality of life, depressive symptoms, rigorously collected adverse drug events or TB-related stigma, into routine practice will be important for the future evaluation of activities and also provide key data for TB programs to be increasingly responsive to patient needs. Achieving the 2015 WHO *End TB Strategy* and the recent Government of India target of TB elimination by 2025 will require substantial efforts and funding to continue to improve MDR TB

care. Critical to meeting these targets is action based on a more systematic and granular understanding of the extent and severity of TB patient needs and the barriers to treatment retention.

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# Matthew Tyge Murrill

## Education

**MD-PhD Candidate (MD 3rd year, PhD 4th year)** Aug 2011 – May 2019 (expected)
Johns Hopkins University School of Medicine – Baltimore, MD
Johns Hopkins Bloomberg School of Public Health – Baltimore, MD
PhD student: Department of Epidemiology
Mentors: Dr. David Dowdy, Dr. Amita Gupta

**Bachelor of Arts *(summa cum laude)*** Aug 2004 – May 2008
Maryville College – Maryville, TN
Major: Chemistry; Minor: Mathematics

## Research and Work Experience

**Dissertation Research (Epidemiology)** Jun 2016 – Present
Johns Hopkins Bloomberg School of Public Health – Baltimore, MD Jun 2015 – Aug 2015
Collaborating with State Tuberculosis Office – Maharashtra

Understanding Quality of Life during and Loss to Follow-up from Drug-Resistant Tuberculosis Treatment in Pune, India

**History of Medicine – Scholarly Concentration** Feb 2012 – Mar 2013
Johns Hopkins University School of Medicine – Baltimore, MD
Dr. Randall Packard, Mentor

Conducted oral history and archival research on the development of groundwater water supply in 19th and 20th century West Bengal

**Calcutta Kids – Diarrhea Treatment Center Project Coordinator** Sep 2010 – Jul 2011
Calcutta Kids Trust – Howrah, West Bengal, India
Mr. Noah Levinson, Director; Mr. Kalyan Kumar Roy, Managing Director

Established clinical and monitoring systems to identify, treat, and prevent childhood diarrhea in a peri-urban slum community

**Fulbright-Nehru Student Research Fellow** Aug 2009 – Jul 2010
Jadavpur University – Kolkata, West Bengal, India
Dr. Dipankar Chakraborti, Principal Investigator

Epidemiologic investigations on groundwater arsenic contamination in eastern and central India in collaboration with Jadavpur University

**Strong Children's Research Center Summer Training Program** May 2007 – Dec 2007
University of Rochester Medical Center – Rochester, NY May 2009 – Aug 2009
Dr. Arshad Rahman, Principal Investigator

Investigated signaling pathways regulating NF-kappaB-dependent adhesion molecule expression in endothelial cell inflammation

## Publications and Presentations

**Peer-reviewed Journal Publications:**
Murrill M., Jain Y., Patil S. Selected Summary; People with Tuberculosis Falling Through the Cracks, *The National Medical Journal of India*, 2017 30(6), 274-276.

Murrill M., & Dowdy D. W. Describing the global burden of MDR-TB: Missing cases or different metrics? *International Journal of Tuberculosis and Lung Disease*, 2017 Jan; *21*(1), 1

Michel S.J., Wang H., Selvarajah S. **Murrill M.**, Chi A., Efron D.T., Schneider E.B. Investigating the relationship between weather and violence in Baltimore, Maryland, USA, *Injury,* 2016 Jan; 47(1), 272-276

Goswami R., Rahman M.M., **Murrill M.**, Sarma K.P., Thakur R., Chakraborti D. Arsenic in the groundwater of Majuli - the largest river island of the Brahmaputra: magnitude of occurrence and human exposure, *Journal of Hydrology*, 2014 Oct; 518, 354-362

Chakraborti D., Rahman M.M., **Murrill M.**, Das R., Siddayya, Patil S.G., Sarkar A., Dadapeer H.J., Yendigeri S., Ahmed R., Das K.K. Groundwater arsenic contamination and its health effects in a gold mining area of Northeastern Karnataka, India, *Journal of Hazardous Materials*, 2013 Nov 15; 262, 1048-1055

Hossain M.A. Rahman, M.M., **Murrill, M.**, Das B., Roy B., Dey S., Maity D., Chakraborti D. Water consumption patterns and factors contributing to water consumption in arsenic-affected populations of rural West Bengal, India, *Science of the Total Environment*, 2013 Oct; 463, 1217-1224

Fazal F., Bijli K.M., **Murrill M.**, Leonard A., Minhajuddin M., Anwar K.N., Finkelstein J.N., Watterson D.M., Rahman A. Critical role of non-muscle myosin light chain kinase in thrombin-induced endothelial cell inflammation and lung PMN infiltration, *PLoS One*, 2013 Mar 21; 8(3), e59965

Chakraborti D., Das B., **Murrill M.T.** Examining India's groundwater quality management, *Environmental Science & Technology*, 2011 Jan 1; 45(1), 27-33

Chakraborti D., Rahman M.M., Das B., **Murrill M.**, Dey S., Chandra Mukherjee S., Dhar R.K., Biswas B.K., Chowdhury U.K., Roy S., Sorif S., Selim M., Rahman M., Quamruzzaman Q. Status of groundwater arsenic contamination in Bangladesh: A 14-year study report, *Water Research*, 2010 Nov; 44(19), 5789-5802

**Conference Presentations**
Murrill M., More S.W., Kamble, S.W. Kulkarni V.S., Dowdy D.W., Gupta, A. Factors Associated with Loss to Follow-up and Mortality in Public Sector MDR TB Treatment in Western Maharashtra, India from 2015-2016. The 49th Union World Conference on Lung Health 2018 (accepted for short oral presentation)

Suryavanshi N., Murrill M., Gupta A., et al. Knowledge, attitudes and practices about multidrug-resistant tuberculosis (MDR-TB) and preventive therapy among adult and adolescent household contacts of MDR-TB index cases. *American Thoracic Society Conference* 2017. (poster presentation)

***Invited Lectures and Presentations:***
*Clinical Biomarkers for Type II Diabetes: Historical Perspectives and Current Guidelines for Diagnosis Partnering Toward Discovery: Conversations on Research and Medicine, Johns Hopkins University School of Medicine and School of Public Health; joint presentation with Christina Parrinello (SPH) and Dr. Marc Halushka (SOM) - December 2, 2013)*

*The Human Right to Water: Implications and Consequences for Health*
*Maryville College Community Conversations Lecture Series, Maryville College - (September 1, 2010)*

*From Panacea to Poison: Tubewells and Arsenic in West Bengal – Johns Hopkins Medical Student Research Day (podium presentation - January 24, 2013)*

## Scholarships and Awards

| | |
|---|---|
| UJMT Fogarty Global Health Fellowship | Aug 2017 – Jun 2018 |
| Infectious Disease Society of America Medical Student Fellowship | Mar 2015 – Mar 2016 |
| Center for Global Health Established Field Placement Award | Jun 2015 – Aug 2015 |
| Society of Thoracic Surgeons (STS) – Looking to the Future Medical Student Scholarship to attend STS Annual Conference 2014 | Jan 2014 |
| National Institutes of Health – Medical Scientist Training Program, Training Grant (T32), Johns Hopkins University | Aug 2011 – Present |
| Fulbright-Nehru Student Research Fellowship | Aug 2009 – Aug 2010 |
| East Tennessee American Chemical Society Outstanding Senior | May 2008 |

## Additional Activities

| | |
|---|---|
| State Tuberculosis Demonstration and Training Center, Revised National Tuberculosis Control Programme, Government of India - Operational Research Workshop Organizer and Lecturer (Pune, India) | Nov 2016 |
| Teaching Assistant: Epidemiologic Methods III, Outbreak Investigation<br>Johns Hopkins Bloomberg School of Public Health (Baltimore, MD) | Jan 2016 – May 2016 |
| Infectious Disease Epidemiology: Research in Progress and Dissertation Proposal Seminar Coordinator<br>Johns Hopkins Bloomberg School of Public Health (Baltimore, MD) | Aug 2015 – May 2016 |
| Bengali: Junior and Senior Level Certificate Courses<br>Ramakrishna Mission Institute of Culture (Kolkata, India) | Aug 2009 – May 2010 |
| Volunteer Water Quality Surveying – Belize and Southern Appalachia<br>Living Waters for the World (Spring Hill, TN) | Apr 2008 – May 2009 |
| Hurricane Katrina Relief Work<br>Presbyterian Disaster Assistance (Pearlington, MS) | May 2006, Dec 2006, May 2007 |

## Professional Development

**Computer Skills:** Stata (biostatistics computing software), Adobe Photoshop, Zotero reference manager
**Language Skills:** Hindi (intermediate), Bengali (beginner)