Tuberculosis Case Fatality in the Indian Private Healthcare Sector

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i. Abstract

Tuberculosis (TB) remains the leading infectious disease killer worldwide. India is home to the single largest TB epidemic in the world, accounting for more than a quarter of the global TB burden. The World Health Organization (WHO) End TB Strategy highlights the case fatality ratio as a key measure of the quality of TB care. In this manuscript-based thesis, I estimate the case fatality ratio for the Indian TB epidemic from the literature and among privately treated TB patients with primary data from two cohort studies. I have published a systematic review of the recent Indian TB case fatality literature showing that while the overall case fatality ratio is in line with WHO goals, important patient groups are understudied. Chief among these neglected groups are privately treated TB patients. The Indian private healthcare sector is largely unregulated and treats half of Indian TB patients; evidence suggests that the quality of care they receive is suboptimal. Efforts to improve quality of care for TB patients in the Indian private sector include Private Provider Interface Agencies (PPIAs) which provide free treatment and treatment support to patients and training and incentives to providers. To estimate the case fatality ratio and the rate of recurrent TB among PPIA-treated patients, I conducted two 4,000 patient cohort surveys in Patna and Mumbai, India. I estimated the case fatality ratio during the treatment phase and the case fatality ratio and recurrent TB rate during the post-treatment phase. Patient loss to follow-up, a potential source of selection bias, is adjusted for using inverse probability selection weighting (IPSW). I found that the treatment phase case fatality was above the ideal WHO limit and that the crude treatment phase fatality estimates were substantially biased. At 24 months into the post-treatment phase, moderate rates of fatality and recurrence were observed. Selection bias correction is an important step forward for improving estimates of case fatality in India, but it should be noted that IPSW only provides unbiased estimates when all confounders of the observation-outcome relationship are included in the selection model. To investigate the robustness of my results to unmeasured confounding, I conducted a probabilistic bias analysis in which I simulated realistic rates of smoking, HIV and malnutrition and estimated that their influence on the primary results is likely small. This work contributes to the reliable estimation of a critical quality of care metric, the case fatality ratio; an important first step in benchmarking future improvements to quality of care.

ii. Résumé

La tuberculose (TB) demeure la maladie infectieuse la plus meurtrière dans le monde. L'Inde compte plus du quart des cas de TB à travers le monde, et est le site de la plus grande épidémie de TB au niveau mondial. La stratégie de l'Organisation mondiale de la Santé (OMS) pour mettre fin à la tuberculose (« End TB Strategy ») identifie le taux de létalité comme une mesure clé de la qualité des soins de santé en TB. Dans cette thèse de doctorat, j'estime le taux de létalité de l'épidémie de TB en Inde à partir de la littérature, et de données primaires sur des patients de TB du secteur privé provenant de deux études de cohortes. J'ai réalisé une revue systématique de la littérature récente sur la létalité de la TB Inde qui démontre que bien que le taux de létalité global soit en ligne avec les cibles de l'OMS, des groupes importants de patients sont sous-étudiés, en particulier les patients de TB du secteur privé. Le secteur privé du système de santé indien est en grande partie non réglementé et dessert la moitié des patients de TB indiens; les données suggèrent que les soins de santé qu'ils reçoivent sont sous-optimaux. Les efforts pour améliorer la qualité des soins de santé pour les patients de TB indiens dans le secteur privé incluent les agences d'interface avec les fournisseurs privés (AIFP ou « Private Provider Interface Agencies ») qui fournissent un traitement et un soutien au traitement gratuits aux patients, ainsi que des primes d'encouragement aux fournisseurs. Afin d'estimer le taux de létalité et le taux de récurrence de TB chez les patients traités par les AIFP, j'ai réalisé deux enquêtes de cohortes de 4 000 patients chacune, à Patna et à Mumbai, en Inde. J'ai estimé le taux de létalité durant la phase de traitement, ainsi que le taux de létalité et de récurrence de TB durant la phase post-traitement. La perte de suivi du patient, une source potentielle de biais de sélection, est ajustée pour utiliser la pondération de sélection de probabilité inverse. J'ai déterminé que le taux de létalité durant la phase de traitement était supérieur à la limite optimale de l'OMS, et que les estimés bruts de létalité durant cette phase étaient substantiellement biaisés. Après 24 mois dans la phase post-traitement, des taux de létalité et de récurrence modérés ont été observés. La correction du biais de sélection est un pas vers l'avant important pour la littérature indienne sur la TB, mais il faut noter que la pondération de sélection de probabilité inverse ne fournit des estimés non-biaisés que si toutes les variables de confusion de la relation sélection-résultat sont incluses dans le modèle de sélection. Afin d'investiguer la robustesse de mes résultats par rapport aux influences confusionnelles non-mesurées, j'ai réalisé une analyse de biais probabiliste, dans laquelle j'ai simulé des taux réalistes de fumeurs, VIH et malnutrition, et j'ai estimé que leur influence sur les résultats primaires était probablement limitée. Ce travail de recherche contribue à l'estimation fiable d'une mesure critique de qualité des soins de santé, le taux de létalité. Il s'agit d'une première étape importante dans l'étalonnage d'améliorations futures de la qualité des soins de santé.

iii. Acknowledgements

Graduate school has a pretty rough reputation, but from my first day, this was my dream job. Much of that is due to my incomparable supervisor, Dr. Madhu Pai. I offer him my deepest thanks not just for what I have learned about conducting rigorous and impactful science but for showing by example how science can be a force for good. This is the beginning of a career dedicated to moving the needle and I owe that to Madhu.

The other reason this was the world's best PhD was the superstar members of Team Pai. It's a privilege to work with talented and compassionate colleagues who are also dear friends, thank you.

I also thank the many TB champions who have shared their stories and their strength with myself and the TB community, especially Deepti and Nandita. This work seeks to serve these inspiring individuals and all those fighting TB and their families. I am also deeply indebted to my Indian colleagues, especially Dr. Nita Jha, Dr. Shibu Vijayan and Vaishnavi Jondhale, who tirelessly work to improve the lives of people with TB and who made these studies possible.

I am grateful to my committee members, Drs Andrea Benedetti and Alice Zwerling for generously sharing their expertise and invaluable feedback. Thanks also to Dr. Srinath Satyanarayana for his support and feedback during my systematic review, and for you and Roopa always taking me out to dinner in Delhi.

I received and am grateful for financial support during this degree from the McGill Faculty of Medicine, the McGill International TB Centre, McGill Global Health Programs and the Fonds de recherche de santé – Quebec.

I am endlessly grateful for the mentors who led me here, the friends who got me through and my family, for everything.

Finally, thanks to Matthew, who, like a golden retriever, doesn't completely understand what this is about, but is unconditionally loving and supportive regardless.

iv. Preface and contribution of authors

As first author on all manuscripts included in this thesis, with feedback from Dr. Pai, my committee and the other manuscript authors, I personally developed the protocols for all three objectives. I also oversaw the primary data collection in Patna and Mumbai. I conducted all analyses and was responsible for the interpretation of the results and drafting of the manuscripts. The chapters in this thesis were written by me. Detailed author contributions for specific manuscripts are below.

Manuscript 1: Case Fatality among Indian Tuberculosis Patients: A Systematic Review and Meta-Analysis

I developed the study design and objectives with input from Dr. Madhu Pai and Dr. Srinath Satyanarayana. I wrote the study protocol and data collection tools. I developed and executed the search strategy with assistance from Ms. Genevieve Gore. I screened, extracted and adjudicated all included studies with assistance from Ms. Vaidehi Nafade and Ms. Anita Svadzian. I drafted the manuscript and all authors provided critical feedback.

Manuscript 2: Case fatality and recurrent TB among privately treated TB patients in India

I developed the study design and objectives with input from Dr. Madhu Pai. I designed the data collection tools and oversaw data collection performed by Mugdha Singh (Patna), Joseph Edwin (Mumbai) and Priyanka Ingawale (Mumbai) with supervising support from Dr. Shibu Vijayan (Mumbai) and Dr. Nita Jha (Patna). I designed and performed the analysis with input from Dr. Madhu Pai and Dr. Andrea Benedetti. I interpreted the results and drafted the manuscript; all authors provided critical feedback.

Manuscript 3: Unmeasured confounding and inverse probability selection weighting in a tuberculosis patient cohort study: A probabilistic bias analysis

I developed the study design and objectives with input from Dr. Andrea Benedetti and Dr. Madhu Pai. I designed and performed the analysis with input from Dr. Benedetti. I interpreted the results and drafted the manuscript; all authors provided critical feedback.

v. Statement of originality

The three manuscripts that form this thesis are all original scholarship and provide contributions to knowledge. My systematic review (Chapter 2, Manuscript 1), is the first to synthesize tuberculosis case fatality in India and highlight selection bias issues in the available data. The application of the Beta-Binomial Generalized Linear Mixed Model to achieve an unbiased pooled estimate of rare proportions is, to our knowledge, the first implementation of this methodology in the TB field.

My cohort study (Chapter 3, Manuscript 2) is the largest patient outcome study of privately treated TB patients conducted to date. As established in my systematic review, the Indian TB literature has not broadly implemented selection bias correction methods. My use of inverse probability selection weighting to account for patient loss to follow-up when estimating patient outcomes is an improvement over existing estimates. This work provides the first precise and robust estimates of long term outcome rates in TB patients treated by Private Provider Interface Agencies (PPIAs). It also provides a framework for implementing routine monitoring of PPIA TB patient outcomes with adjustments for patient loss to follow-up.

My probabilistic bias analysis (Chapter 4, Manuscript 3) builds on my application of inverse probability selection weighting by establishing that my cohort survey estimates are robust to unmeasured confounders not collected in the PPIA patient database. This simulation work provides a template for the use of probabilistic bias analysis to investigate the impact of sparce data problems in the global health literature.

vi. List of abbreviations

CFR	Case fatality ratio
DOTS	Directly Observed Therapy
DR TB	Drug resistant tuberculosis
DST	Drug sensitivity testing
EPTB	Extrapulmonary TB
GLMM	Generalized Linear Mixed Model
HR	Hazard ratio
IPSW	Inverse probability selection weighting
MDR TB	Multidrug resistant tuberculosis
NSN	New smear negative
NSP	New smear positive
OR	Odds ratio
PBA	Probabilistic bias analysis
PPIA	Private Provider Interface Agency
PTB	Pulmonary TB
RNTCP	Revised National TB Control Programme
TB	Tuberculosis
WHO	World Health Organization
WHP	World Health Partners

vii. List of figures

Chapter 1: Introduction

Tuberculosis (TB) is a bacterial infection that afflicted 10.0 million new people in 2018, resulting in 1.5 million deaths globally. The World Health Organization (WHO) estimates that India accounts for 2·7 million (27%) of the new cases, and 38% of the deaths.[1] TB is one of the top five causes of death among people aged 30–69 years in India.[2]

A key component of the 2015 WHO End TB Strategy[3] is improving the quality of TB care. Case fatality is an important marker of care quality as prompt diagnosis and appropriate treatment should prevent deaths during and after treatment. The End TB Strategy calls for a 95% reduction in TB deaths by 2035 relative to 2015 rates; improving this metric requires accurate measurement of fatality. My manuscript-based thesis seeks to accurately estimate TB case fatality in India, especially fatality in the private sector.

1.1 Epidemiology of TB globally

Tuberculosis, caused by the bacterium *Mycobacterium tuberculosis*, is the leading infectious disease killer in the world today. As mentioned above, 10 million new cases occur every year and up to a quarter of the world's population may be latently infected. Between 5% and 15% of these latent infections progress to active disease. Tuberculosis most often infects the lungs but can spread throughout the body. It is spread between people when an individual with active pulmonary TB coughs or sneezes. Common TB symptoms include coughing, fever, weight loss and night sweats; without treatment the disease can be fatal. [4]

Tuberculosis is unevenly distributed around the world with 95% of cases occurring in developing nations (Figure 1-1). Nearly all countries have implemented the WHO-recommended Directly Observed Treatment, Short Course (DOTS) program established in the late 1990's. This program prescribes a standardized multi-drug treatment regimen for drug-sensitive TB where patients take their medication while being observed by a healthcare provider.[5] Drug-sensitive TB is treated in 6-8 months while drug-resistant TB treatment can last up to 24 months.[4]

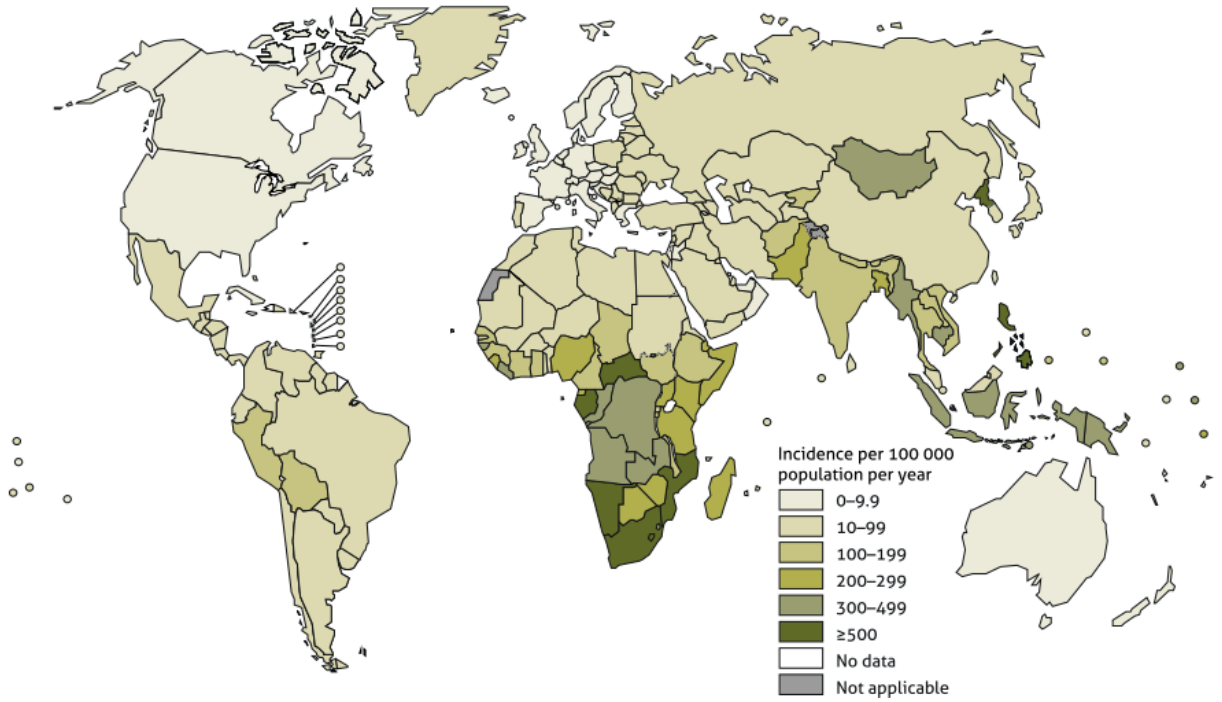

Figure 1-1, Estimated TB incidence by country (2018)[1]

Drug-sensitive TB, which accounts for approximately 95% of annual TB cases, is curable. With the widespread implementation of DOTS, substantial progress has been made at reducing TB mortality worldwide. However, reductions in annual incidence have been much slower, with an average 2% reduction year-on-year. [4]

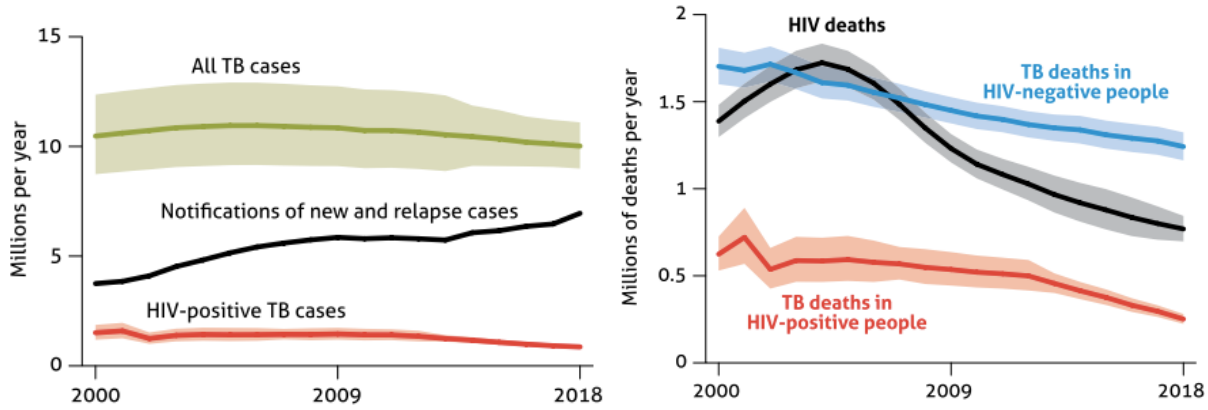

Figure 1-2, Global trends in TB incidence (left) and mortality (right)[1]

Quality of Care and the End TB Strategy

The WHO's End TB Strategy calls for integrated patient-centered care and prevention, bold policies and supportive systems, and intensified research and innovation in order to generate a 95% reduction in TB deaths by 2035. A key measure of progress highlighted in the strategy is the case fatality ratio (CFR), the proportion of TB patients who die in a

defined period. In order to achieve the goals of the End TB Strategy the global treatment phase case fatality ratio must fall from the 2015 level, 15%, to 6.5%.[3] The WHO's ideal global TB CFR is under 5%.[6] The WHO is also concerned with minimizing the number of patients who experience recurrent TB in order to meet goals for reducing the number of incident cases.

Global case fatality and its drivers

The 2018 WHO-estimated global CFR is 15%.[1] As most TB cases are curable, elevated case fatality suggests failures in the healthcare system. Delays in diagnosis and treatment, ineffective treatment and poor treatment adherence due to insufficient patient support are all healthcare system failures that can lead to preventable deaths.[7] Unaddressed comorbidities like HIV, smoking, alcohol addiction, malnutrition and diabetes can also contribute to excess fatality. Finally, social determinants of health such as pollution and poverty can further exacerbate TB disease.[8]

1.2 Epidemiology of TB in India

With 2.7 million new cases in 2018, India has the single largest TB epidemic in the world. India achieved country-wide scale-up of DOTS in 2006 run by the national TB program, the Revised National Tuberculosis Control Program (RNTCP). India's public sector healthcare is historically underfunded with only 1.4% of GDP being allotted to health spending.[9] In 2019, the RNTCP released an ambitious TB elimination plan[10] aiming to end TB in India by 2025, but it has not yet committed commensurate funding to achieve this goal.

Indian TB patients have high rates of comorbidities such as smoking, malnutrition and diabetes that contribute to the TB burden (Table 1-1). Smokers have an increased risk of developing TB[11] and TB is a leading cause of death among people who smoke.[12] Approximately 20% of Indian TB patients are current smokers.[13] Malnutrition is nearly universal among Indian TB patients, with 90% presenting with BMIs below 20. Malnourished patients are more likely to die from TB.[14] Noncommunicable diseases like diabetes are increasingly prevalent in India. Diabetics are more likely to develop TB[15] and more likely to suffer poor treatment outcomes.[16] TB patients are not yet routinely screened for diabetes but its prevalence among TB patients is estimated to be between 15% and 25%.[17–19] HIV is an important driver of TB case fatality globally but is relatively rare in India with less than 5% of Indian TB patients co-infected with HIV.[20]

Table 1-1, Population attributable risk for comorbidities
Interpreted as the proportion of incident TB cases in India due to the given comorbidity.

	Population Attributable Risk
Smoking[21]	10%
Malnutrition[22]	55%
Diabetes[21]	10%

India's public sector TB cascade of care is generally weak with only 39% of patients achieving recurrence free survival (Figure 1-3).[23] There is extremely limited data available on TB patient outcomes and quality of care for the private healthcare sector.

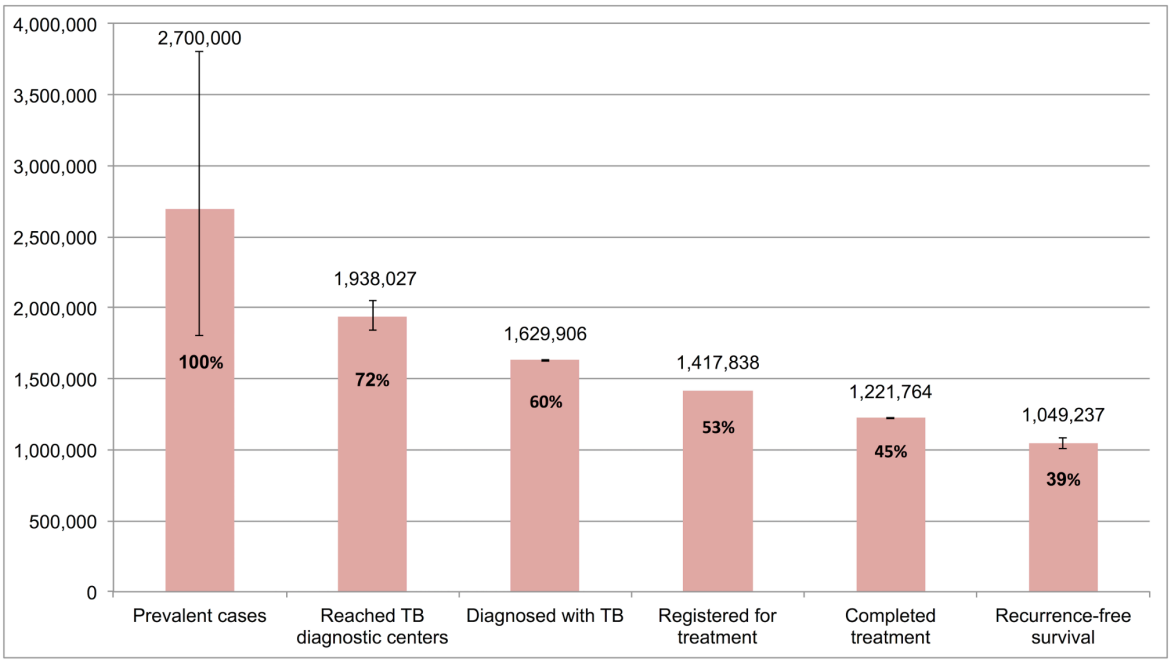

Figure 1-3, India's public sector TB cascade of care[23]

Private Sector TB Care

India has a complex healthcare system with a large private sector, comprised of qualified and unqualified providers, as well as practitioners of alternative health systems. Eighty percent of Indians seek private healthcare first for medical issues and half of Indian TB patients receive treatment in the private sector. Private sector treatment quality is not assured and prescribed treatments often deviate from the WHO-recommended standard. Consistently poor quality of care has been demonstrated by simulated patient (mystery client) studies by the McGill TB Centre and partners.[24,25] Private providers have also demonstrated sub-optimal knowledge of TB which can create diagnosis and treatment delays.[26–29] Diagnosis and treatment delays, as well as poor treatment quality, lead to poor outcomes for patients.

The RNTCP has a treatment monitoring program for publicly treated patients but no such oversight system exists for patients treated in the private sector. While the case fatality in the RNTCP has been estimated to be between 3% and 8% for drug sensitive TB and 22% for drug resistant TB,[30] there are no such programmatic data available for the private sector.

Patients often visit multiple providers in the public and private sector while seeking care (Figure 1-4), but records are not shared between providers, if they exist at all.

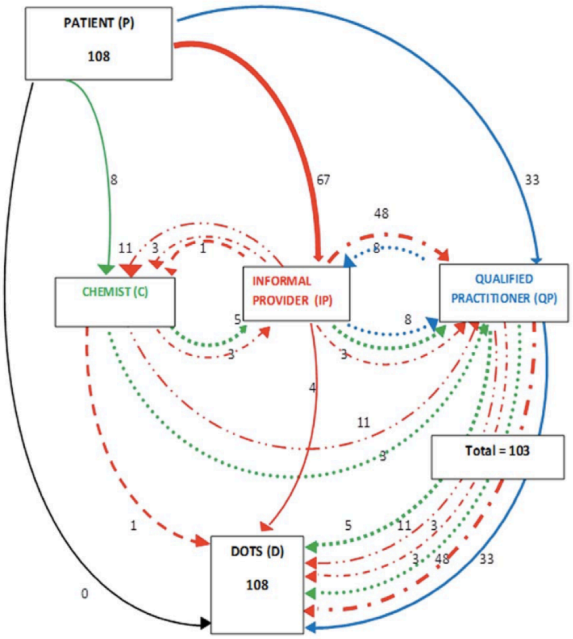

Figure 1-4, Complex TB patient pathways observed in care seeking patients in Delhi[31]

These circuitous pathways cause considerable delays in diagnosis (Figure 1-5) and treatment initiation. Studies from Patna and Mumbai found a median delay in excess of 15 days for diagnosis and another median 7 days delay for treatment initiation.[32,33]

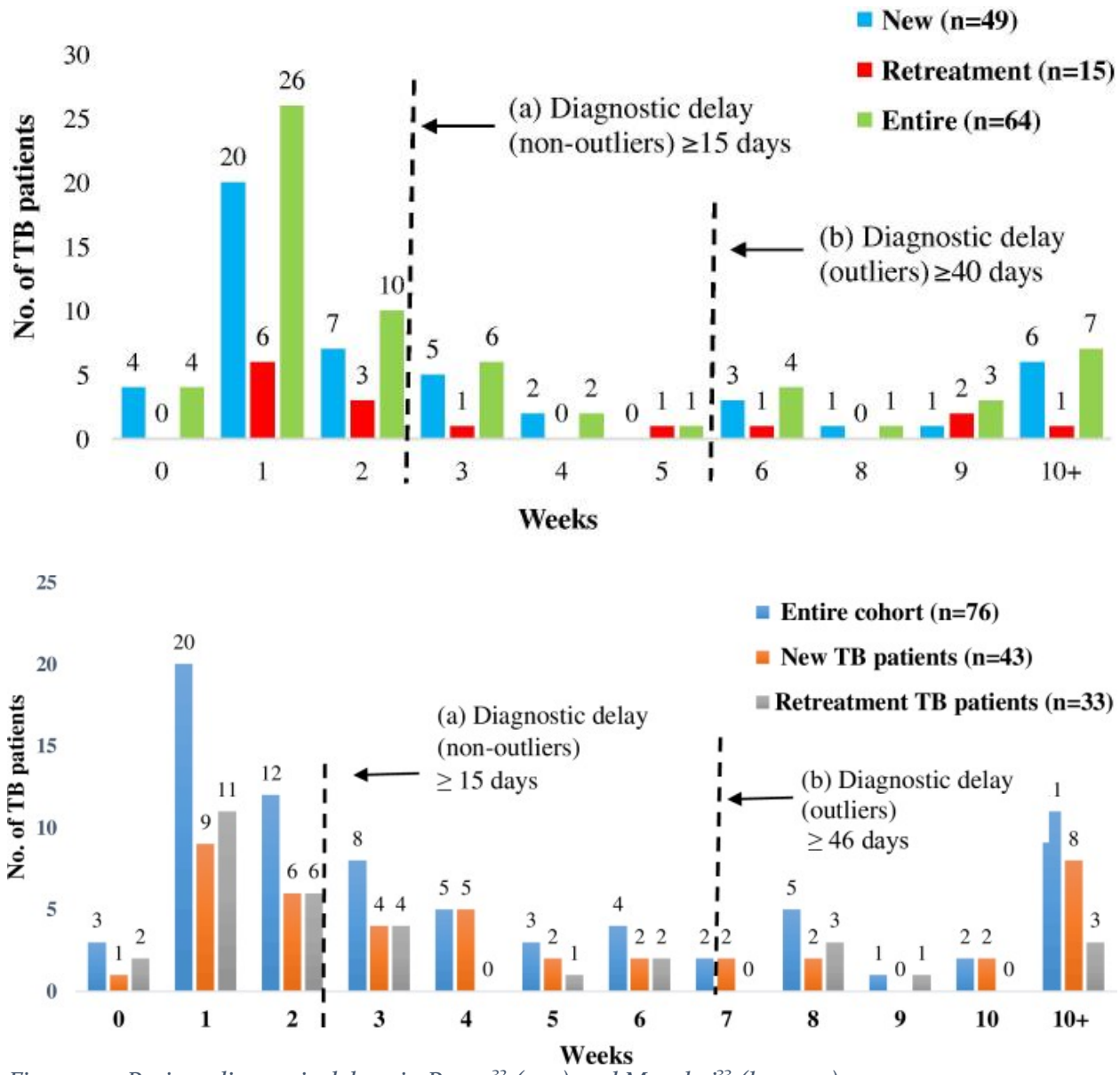

Figure 1-5, Patient diagnosis delays in Patna[32] (top) and Mumbai[33] (bottom)

Private Provider Interface Agencies

The Indian TB community has identified private sector quality of care as a major agenda item as part of its End TB goals. Private providers have little incentive to refer patients into the public sector as this means lost income and many patients prefer to avoid overburdened public facilities. In response, the RNTCP has collaborated with organizations like PATH and World Health Partners, to establish Private Provider Interface Agencies (PPIAs) in three regions in India.[34]

PPIAs offer providers training, free TB diagnostics and medicines, and patient adherence monitoring in exchange for providers notifying patients to the PPIA and the national TB program. Providers retain their patients and revenue but are supported in providing appropriate care.[35] Based on early successes in pilot projects, the government of

India and the Global Fund Against AIDS, TB and Malaria have committed to scaling up the PPIA model as part of the Joint Effort to Eliminate Tuberculosis, which is projected to reach 3.5 million patients across 23 states by 2022.[36]

Challenges to accurate measurement of patient outcomes

In order to monitor progress toward global goals, we must be able to accurately measure patient outcomes. However, there are several practical and methodological challenges when measuring TB patient outcomes in India.

Weak record keeping

The majority of deaths in India occur at home, without a medical attendant, and are not recorded with a death certificate.[37] The RNTCP operates cloud-based recordkeeping[38] of publicly treated patients but private TB patients are not systematically tracked. This weak system makes it nearly impossible to study private sector TB patient outcomes through administrative or vital registration data.

Patient loss to follow-up and selection bias

Both in research projects and programmatically, when following patients over long periods of time, some patients will be lost to follow-up. If these lost patients experience different event rates from retained patients, there is a potential for selection bias. Patients may have lost contact with their healthcare provider because they have moved or felt they no longer needed treatment, but they may also have lost contact because they have died. It is these hidden deaths that pose challenges for accurate measurement of case fatality. As I will establish in Chapter 2, correction methods for selection bias such as inverse probability selection weighting (IPSW) are underutilized in the Indian TB literature.

1.3 Research Gaps addressed by this thesis

In India, there is insufficient data on the experiences of most groups of TB patients. This dearth of information is particularly severe for patients in the private sector, despite representing half of the TB patients in treatment. Currently, privately treated patients are rarely covered in literature assessing fatality rates of Indian TB patients. Even studies of public sector patients rarely investigate post-treatment patient fatality. Studies of post-treatment recurrence risk are short term and focus on publicly treated patients.

Privately treated patients have been historically difficult to study in India because viable sampling frames for the unregulated private sector are difficult to obtain. PPIAs represent not only an access point into the experiences of privately treated patients but, as an increasingly common intervention, it is important to establish their efficacy in promoting positive patient outcomes.

This work will summarize the currently available literature on TB case fatality in any sector of the Indian healthcare system. I will then characterize the risk of fatality and TB recurrence in private sector patients treated by PPIAs, adjusting for selection bias using IPSW. Finally, I will explore the robustness of my fatality and recurrence rate estimates to unmeasured confounding of the IPSW model.

1.4 Objectives

In this manuscript-based thesis, I will address three objectives:

I. Systematically review and meta-analyze the literature on TB patients treated in either the Indian public or private sector for case fatality ratios during and after treatment
II. Estimate the case fatality ratio and recurrence rate among TB patients treated in the private sector through PPIAs in two cities in India
III. Assess the robustness of the selection bias adjustment, inverse probability selection weighting, used in Objective II to unmeasured confounding using probabilistic bias analysis

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Chapter 2: Case Fatality among Indian Tuberculosis Patients: A Systematic Review and Meta-analysis

2.1 Preface

The case fatality ratio (CFR) is a critical measure of quality of TB care, with the WHO calling for a CFR below 6.5%. This systematic review is the first synthesis of the Indian TB case fatality literature. This addresses a major gap in the field as programmatic fatality data for Indian TB patients are only available for patients treated in the public sector while half of Indian TB patients are treated in the private sector.

In the following manuscript, I establish a literature estimate of the Indian TB patient CFR, during and after treatment. I also estimate the CFRs among key subgroups of TB patients. I highlight weaknesses in the literature due to scare data available on privately treated TB patients and a high risk of bias in most studies.

This work was published in January, 2020 in *BMJ Global Health*.

2.2 Title page

Case Fatality among Indian Tuberculosis Patients: A Systematic Review and Meta-Analysis

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2.3 Abstract

Introduction: The WHO End TB Strategy calls for a global reduction in the case fatality ratio (CFR) below 5%. India accounts for a third of global tuberculosis (TB) deaths. This systematic review estimated CFRs among Indian TB patients both during and after treatment.

Methods: We systematically searched Medline, Embase and Global Health for eligible studies published between January 1st, 2006 and January 8th, 2019, including both cohort studies and intervention study control arms that followed Indian TB patients for fatality either during treatment or post-treatment. From relevant studies we extracted CFRs in addition to study demographics. Study quality was assessed using modified SIGN cohort criteria. Sufficiently homogenous studies were pooled using a random effect generalized linear mixed model. A meta-regression was performed to associate study characteristics with resulting CFRs.

Results: 218 relevant studies were identified, of which 211 provided treatment phase CFRs. Most patients (92.4%) were treated in the public sector. Quality concerns were identified in 74% of papers. We estimated a pooled treatment phase CFR of 5.16% (95% CI 4.20%, 6.34%) which fell to 3.78% (2.77%, 5.16%) when restricted to 52 high-quality studies. Treatment phase CFRs were higher for pediatric (n=27, 6.50% [2.65%, 10.36%]), drug resistant (n=43, 14.06% [10.15%, 19.49%]) and HIV-infected (n=35, 10.91% [7.68%, 15.50%]) patients. Nineteen post-treatment CFR studies were too heterogeneous to pool except when restricting to three high-quality studies (2.69% [-0.79%, 6.18%]). Poor study quality (OR=2.27 [2.01, 2.57]) and tertiary centers patients (OR=1.15, [1.03,1.28]) were significantly associated with increased treatment phase case fatality.

Conclusions: Case fatality is a critical measure of the quality of TB care. While India's treatment CFRs are in line with WHO targets, several key patients groups remain understudied and most studies suffer from methodological issues. Increased high quality reporting on patient outcomes will help improve the evidence base on this topic.

2.4 Summary box

What is already known?

- India accounts for more than 25% of global TB incidence but there are concerns about the quality of care that patients receive
- One of the WHO's most important quality of care indicators is the case fatality ratio, with an ideal case fatality ratio below 5%

What are the new findings?

- A systematic review of the literature yielded an overall case fatality ratio among Indian TB patients during treatment of 5.16% (95% CI 4.20%, 6.34%)
- Case fatality was higher among key patient subgroups like those living with HIV or fighting drug resistant TB
- However, the quality of available studies was generally poor meaning that the literature estimates of case fatality may be biased

What do the new findings imply?

- The TB field must better estimate case fatality with improved study design and statistical corrections for common biases
- Special efforts must be made to monitor case fatality in the private sector and among patients who have completed treatment as current evidence for these groups is limited

2.5 Introduction

Tuberculosis (TB) affected 10.0 million new people in 2017 resulting in 1.6 million deaths globally.[1] A key component to the World Health Organization (WHO) End TB Strategy[2] is improving the quality of TB care.

The End TB Strategy calls for a 95% reduction in TB deaths by 2035 relative to 2015. One of the most important measures for quality of TB care is the case fatality ratio (CFR). At the country level, the CFR is estimated as the number of TB deaths divided by the number of incident cases in the same years, expressed as a percentage.[1] In order to achieve the 2025 milestone of a 75% reduction in deaths, the End TB Strategy calls for the global CFR to fall from 15% to 6.5%.[2] The WHO's ideal global TB CFR is under 5%.[1]

India accounts for more than 25% of the global TB incidence.[1] India has a complex healthcare system with a large private sector. Many TB patients seek care from multiple providers before being diagnosed with TB and receiving appropriate treatment.[3] Although India's Revised National TB Control Programme (RNTCP) offers free TB therapy, over half of Indian TB patients pay out-of-pocket to receive treatment in the unregulated private sector, where treatment quality often deviates from international standards.[4,5] Publicly treated TB patients are registered with the RNTCP and their treatment outcomes are recorded, however no such routine treatment follow-up occurs in the private sector. In both the public and private sectors, no systematic post-treatment follow-up is conducted.

Globally, moderate quality data exist on patient fatality during TB treatment, mostly for publicly treated patients. A recent systematic review found a global CFR of 3.5%

among HIV- patients and 18.8% among HIV+ patients of all ages.[6] Of the Indian studies in this review, treatment phase case fatality ranged from 2.2% to 5.7%; these studies reflected only publicly treated patients.[6] Globally, few studies estimate patient mortality after completing treatment. The available evidence suggests that TB patients continue to experience significantly higher mortality after treatment when compared to the general population.[7]

In this systematic review, we summarize the available literature estimating treatment phase and post-treatment phase CFRs of Indian TB patients and provide pooled CFRs among key subpopulations including HIV+, privately treated, drug resistant and pediatric patients.

2.6 Methods

This systematic review sought to estimate the treatment and post-treatment phase CFRs among Indian TB patients after directly observed therapy (DOTS) scale-up in India (2006). A protocol with pre-specified analyses was developed before conducting this review.

Search Strategy

Our search strategy focused on the intersection of concepts related to tuberculosis, death, and India. The full search strategy can be found in S2-1.

On January 8th, 2019, the Medline (1946-Present), Embase (1947-Present) and Global Health (1973-Present) databases were searched. We restricted to papers published in 2006 or afterwards to limit our data to the period where modern DOTS treatment was widely available across India.

Supplemental searches were conducted manually in the Indian Journal of Tuberculosis, Lung India, and Indian Journal of Chest and Allied Diseases. A supplemental search was also conducted in the IndMed database. Additionally, we included programmatic data from RNTCP progress reports from 2007 to 2018.

Outcome measure

A case fatality ratio is defined as the number of patients who die from any cause during the observed period divided by the number of patients forming the cohort at the beginning of the observed period. This differs slightly from the definition used at the country level and seen in the RNTCP reports as the number of incident cases does not need to be estimated, it is fixed by the design of the cohort.

Our primary outcomes were the CFR during the treatment phase and/or the post-treatment phase. The treatment phase was defined as the time period from treatment initiation to treatment completion or treatment cessation. The post-treatment phase was defined as the time period from treatment completion or cessation to the end of follow-up. If fatality data was not delineated between the treatment and post-treatment phase, an overall CFR was extracted.

Eligibility criteria and study selection

We targeted prospective or retrospective cohort studies or control arms of intervention studies which described case fatality of any Indian TB patients.

The specific inclusion criteria are as follows:

- Published on or after January 1st, 2006
- Covers, prospectively or retrospectively, Indian TB patients after treatment initiation during either the treatment phase, post-treatment phase or both.
- Records case fatality during these phases
- Cohort study or intervention study that allows a case fatality ratio to be estimated

We excluded conference abstracts, study designs that did not allow for estimation of CFRs, study designs where patients were not randomly sampled (e.g. case series), duplicate study populations and study populations where all TB patients had the same co-morbidity unless that co-morbidity was HIV. We also excluded studies where the treatment phase follow-up did not begin at treatment initiation.

A title and abstract screen was performed independently by two reviewers (SH and VN). The full text screen was performed by SH and AS with disagreements resolved by consensus.

Data extraction

Studies were extracted independently by SH and AS and then adjudicated. Extracted data included sample size, number of deaths and length of follow-up for the entire cohort and within any available patient strata in addition to cohort demographics and study quality data. The full list of extracted variables is available in S2-2 and the extracted data is available through journal.

Quality Assessment

Study quality was assessed using a modification of the Scottish Intercollegiate Guidelines Network (SIGN) Cohort criteria.[8] Because the included studies were descriptive cohorts and not intervention assessments, existing cohort evaluation tools were not completely suitable. Additional questions were adopted from ROBINS-I[39] and Newcastle Ottawa Scale[10] as appropriate. Major methodological concerns included cohort generalizability, selection bias due to loss to follow-up and appropriateness of length of follow-up. Studies were deemed to have poor generalizability if all patients were hospitalized or all patients had a rare form of TB (e.g. TB of the ankle). Studies where more than 15% of patients were lost to follow-up were categorized as having a high risk of selection bias. Studies that followed patients for less than a month were categorized as having an inappropriately short follow-up. A study with one or more of the previous issues was

classified as low quality. As a sensitivity analysis, low quality studies were excluded from the meta-analyses.

Meta-analysis methods

Case fatality estimates were pooled using a random-effects generalized linear mixed model (GLMM), which has been shown to outperform Der-Simonian and Laird models for meta-analysis of proportions because it exactly models the variance structure of binomial data.[11] For each pooling, if the crude CFR (the sum of all deaths in all studies divided by the sum of the study sample sizes) was below 5% a Beta-Binomial GLMM was fit. If the crude CFR was above 5% a Normal-Binomial GLMM was fit. Beta-Binomial GLMMs have been shown via simulation to minimize error compared to Normal-Binomial GLMMs for rare events under 5%.[12]

While a forest plot was generated for each strata of interest, results were not pooled if there was substantial methodological or clinical heterogeneity in either the design or populations of the studies or if there is substantial statistical heterogeneity. As the more common I^2 statistic is not available for GLMMs[13], statistical heterogeneity was assessed using τ^2, a measure of inter-study heterogeneity.[14] The decision to pool was made based on an assessment of clinic heterogeneity and a $\tau^2<4$. Values of τ^2 are unique to each dataset and as such a universally applicable cut-off does not exist. For this work, a cut-off of four for τ^2 was based on a holistic assessment of the range of τ^2 across the strata and the precision of pooled confidence intervals.

Treatment phase CFRs were pooled separately from post-treatment phase CFRs. In addition to the overall results, results within the following strata were examined: adult and pediatric patients, primary/secondary health center and tertiary health center patients, public and private sector patients, HIV+ and HIV- patients, and drug sensitive (DS) and drug resistant (DR) patients. Studies with <2 patients in a given strata were excluded from the relevant strata pooling.

Routinely collected data on patient outcomes, including CFRs, are provided in annual RNTCP reports. The CFRs stratified by patient type are presented here from 2006 onwards, however they are presented separately from the peer-reviewed literature and are not included in the pooled analyses. RNTCP reports were not included in pooling as they contain the data of many of the patients described in the included studies and thus would not be independent datapoints, a methodological requirement of meta-analysis. Additionally, they use the country level definition of CFR rather than the exact cohort definition used in the peer-reviewed studies.

Meta-regression

A logistic meta-regression was fit for both the treatment phase and post-treatment phase studies with the relevant CFRs as the dependent variable. In order to not overfit the model, a limited number of study-level covariates were included in each model.

Covariates were selected based on degree of missingness in order to maximize the number of studies which could be included in each meta-regression. For the treatment CFR meta-regression, those covariates were the proportion of patients with extrapulmonary TB (EPTB), treated in the private sector, living with HIV, and with drug resistant (DR) TB, as well as study quality (high or low) and study setting (primary/secondary center or tertiary center). The post-treatment CFR meta-regression included the proportion of patients with EPTB and study quality (High or Low). Model coefficients are presented as odds ratios (ORs). An example interpretation of an OR of 2 for study setting would be that the odds of case fatality are double for patient populations in tertiary centers compared to patient populations in primary and secondary centers, after adjustment for all other included variables.

Data analyses were performed in R (version 3.6.1) using the *metafor* (version 2.1) package and SAS (version 9.4M6).

Patient and public involvement

This research was done without patient or public involvement.

2.7 Results

Our search identified 4,399 unique papers of which 733 full texts were screened. After screening, 218 relevant papers were identified (Figure 2-1). Two hundred and eleven papers with treatment CFR information were included as well as 19 papers with post-treatment CFR information (one of which did not cover the treatment phase and thus is not included in the count of 211 treatment phase studies), for a total of 212 unique studies included in the quantitative analysis (full citations in S2-4). Six papers had the necessary information to calculate a CFR but did not delineate between treatment and post-treatment phases. These studies were not included in the quantitative analyses but can be viewed in S2-3.

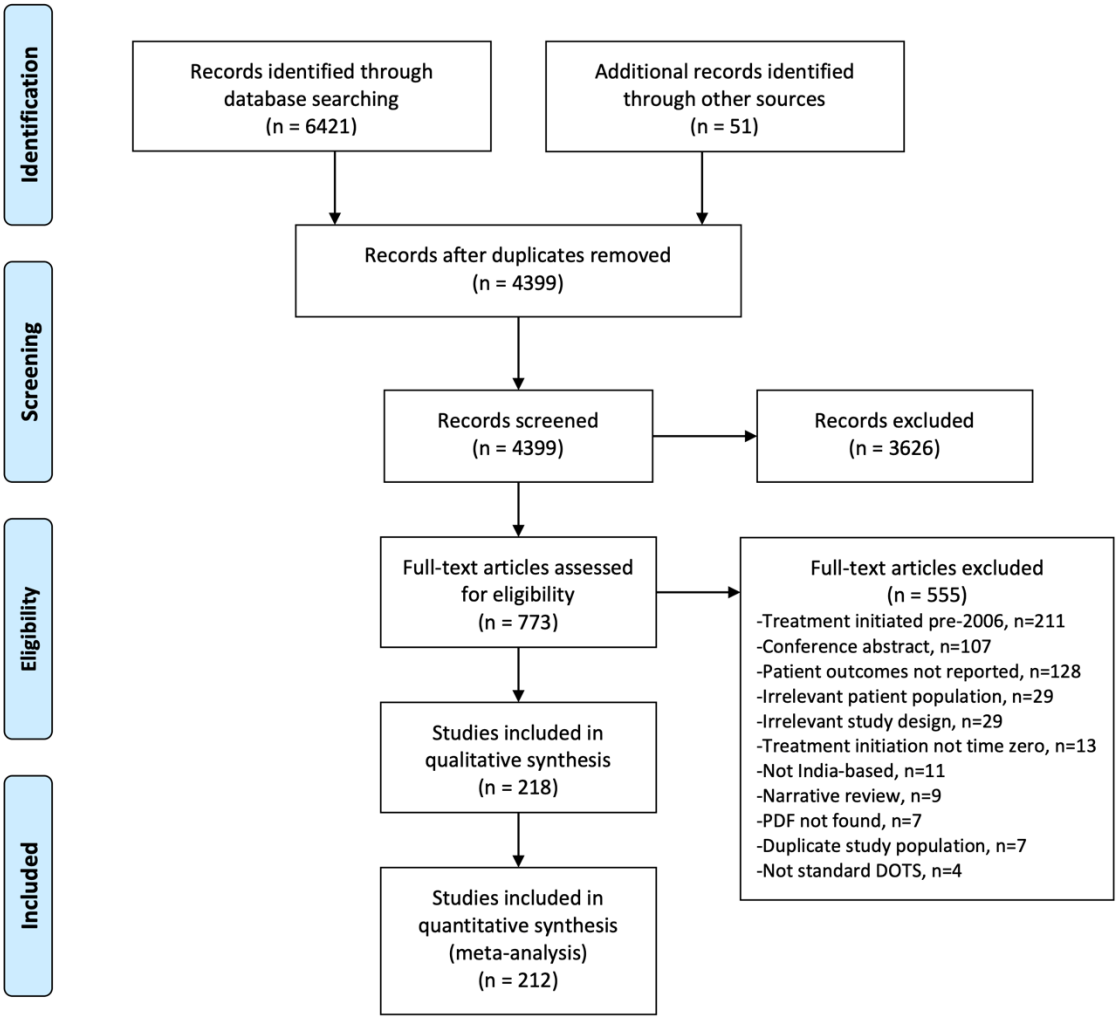

Figure 2-1, PRISMA flow chart of study selection

The included studies provide good representation of the highly diverse[40] Indian states (Figure 2-2). About half the studies included patients from tertiary centers. With the exception of patient sex, level of the health center, and study location (which allowed for a public/private sector determination), critical patient demographics were often missing from studies (Table 2-1). More than three quarters of studies failed to report the proportion of patients who received drug sensitivity testing and almost two thirds did not report the proportion of patients who were smear positive or the proportion of patients microbiologically versus clinically diagnosed.

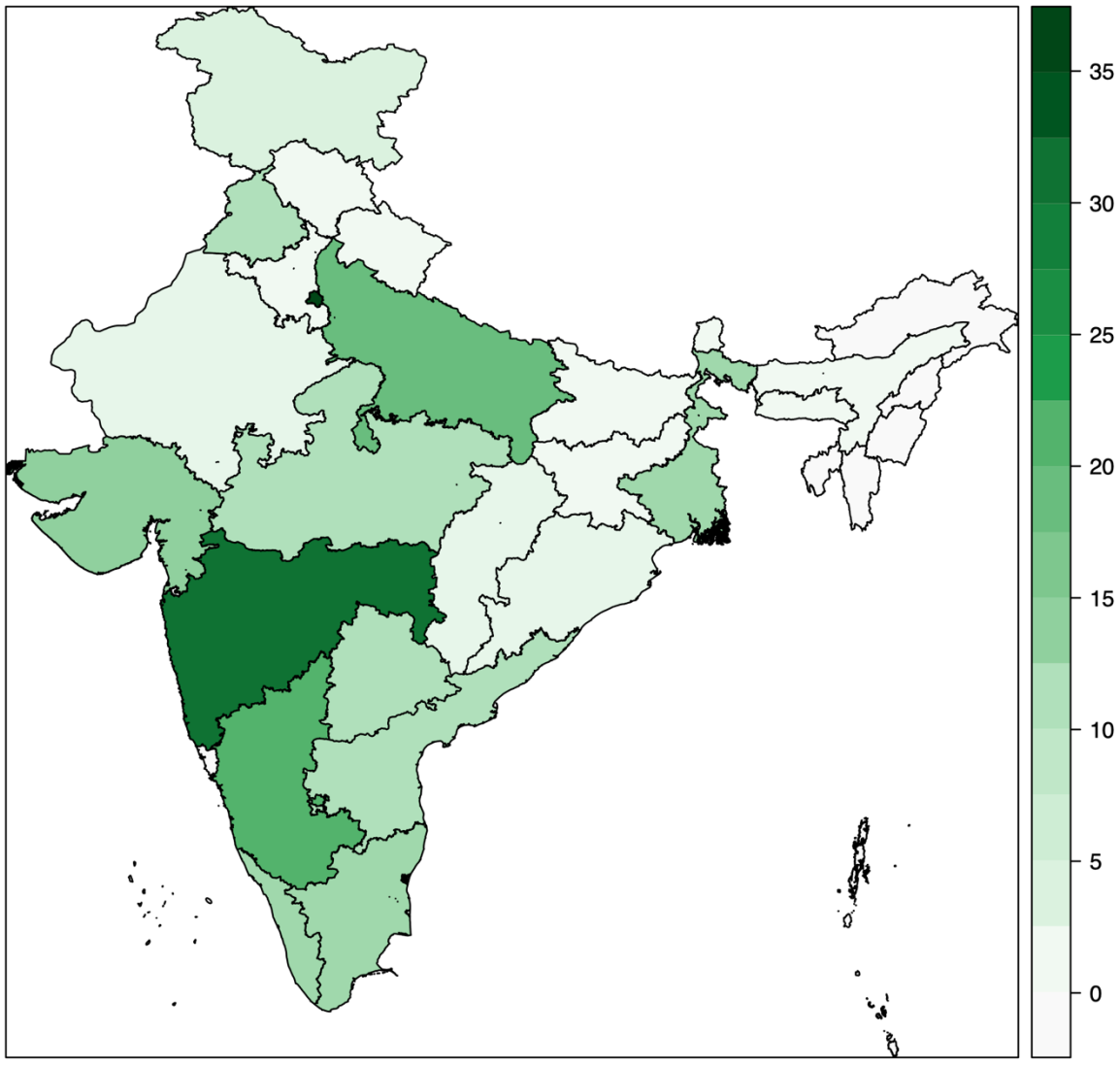

Figure 2-2, Heat map of included studies across Indian states.
X-axis indicates the number of studies from each state.

Table 2-1, Summary of available study characteristics, n=218

	Average value	**Percent of studies not reporting demographic**
Mean age (years) of patients included*	31.1	45.9
Percent of studies in tertiary centers	55.5	0.0
Percent <14 years old	18.5	42.7
Percent female	52.9	8.3
Percent people living with HIV	21.8	36.2
Percent DR-TB	27.9	30.3
Percent treated in the private sector	7.6	0.5
Percent re-treated	33.7	48.6
Percent EPTB	49.5	18.3
Percent smear positive	54.7	60.1
Percent microbiologically diagnosed	87.6	64.2
Percent receiving DST	85.8	75.7

**Some studies reported median ages which are included in this average.*
Abbreviations: DR-TB – drug resistant TB, EPTB – extra-pulmonary TB, DST – drug sensitivity testing

Study quality

A high risk of poor generalizability was found in 61.0% of papers and a high risk of selection bias was identified in 27.5% of papers. Finally, 5.0% of papers had follow-up periods too short to adequately capture fatality. Overall, 73.9% of papers were of poor quality for the reliable estimation of CFRs (Figure 2-3).

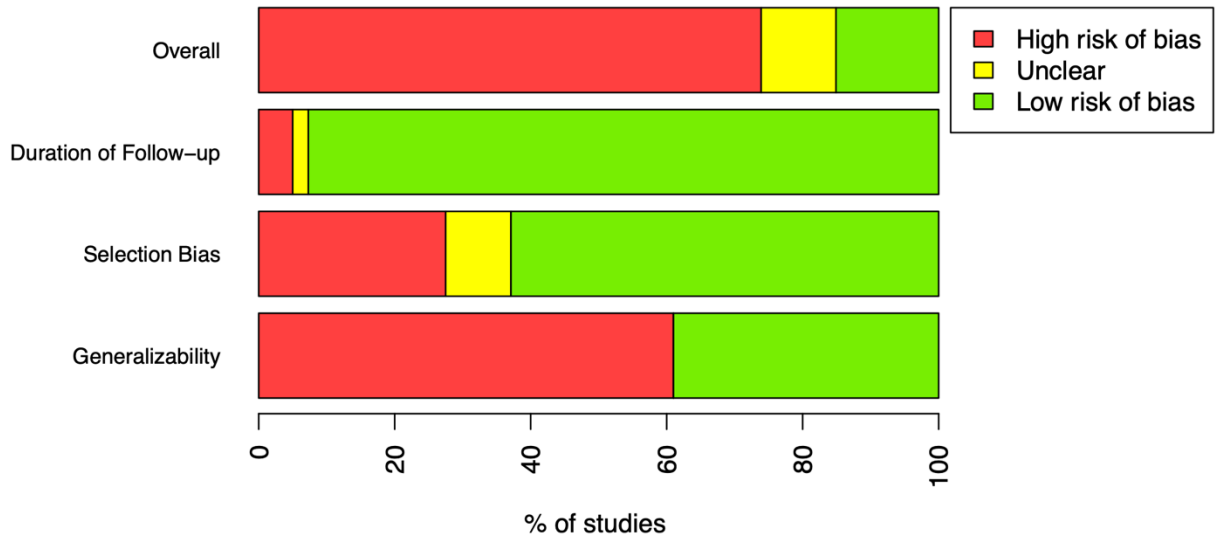

Figure 2-3, Summary of study quality assessment.
If duration of follow-up was less than one month, studies were classified as having a high risk of bias. If more than 15% of patients were lost to follow-up, studies were classified as having a high risk of bias. If all patients were hospitalized or had a rare form of TB, studies were classified as having a high risk of bias. Unclear classifications indicate that insufficient information was available to assess these areas. If studies had a high risk of bias in any of the aforementioned areas, the study was classified as low quality.

RNTCP reports

The RNTCP prepares annual reports of the previous year's TB program activity including treatment outcomes stratified by patient categories. The reports from 2007 (covering 2006 patient data) to 2018 (covering 2017 patient data) were included in this systematic review. Beginning in 2017, treatment outcome data was stratified by clinical and microbiological diagnosis status versus sputum smear status. Additionally, in 2011 the reports began to include multi-drug resistant (MDR) TB treatment outcomes and in 2013 HIV-TB specific treatment outcomes. The 2007 to 2016 report CFRs are available in Table 2 and the 2017 to 2018 report CFRs are available in Table 3. MDR TB and HIV-TB data from the 2011 to 2018 reports are available in Table 4. The average CFRs for new smear positive (NSP), new smear negative (NSN), and new extrapulmonary TB cases were 4.1%, 3.7% and 2.6% respectively (Table 2-2). The average CFRs for new microbiologically diagnosed and new clinically diagnosed cases were 4.0% and 3.0% respectively (Table 2-3). Average CFRs for new HIV-TB, re-treatment HIV-TB and MDR TB cases were 13.0%, 14.4% and 21.0% respectively (Table 2-4).

Table 2-2, RNTCP report treatment CFRs during old classification system

	NSP	NSN	New EPTB	Smear positive re-treatment	New HIV-TB	HIV-TB re-treatment	MDR TB
2007	4.5	3.4	2.4	7.8			
2008	4.4	3.4	2.6	7.7			
2009	4.3	3.4	2.5	7.8			
2010	4.2	3.3	2.5	7.8			
2011	4	3	2	8			20
2012	4	4	2	8			18
2013	4	4	3	8	13	14	22
2014	4	4	3	8	13	14	22
2015	4	4	3	8	13	14	22
2016	4	4	3	8	13	14	22
Average	**4.1**	**3.7**	**2.6**	**7.9**	**13.0**	**14.0**	**21.0**

NB: The significant digits appear here as they were reported by the RNTCP
Abbreviations: NSP – new smear positive, NSN – new smear negative, EPTB – extrapulmonary TB, MDR TB – multidrug resistant TB

Table 2-3, RNTCP report treatment CFRs with new classification system

	New - microbiological diagnosis	New - clinical diagnosed	Re-treatment – microbiological diagnosis	Re-treatment – clinical diagnosis	New HIV-TB	Re-treatment HIV-TB	MDR TB
2017	4	3	8	5			22
2018	4	3	8	4.8	13	16	20
Average	**4.0**	**3.0**	**8.0**	**4.9**	**13.0**	**16.0**	**21.0**

Abbreviations: MDR TB – multidrug resistant TB

Table 2-4, RNTCP report treatment CFRs for HIV-TB and MDR TB across classification systems.

	New HIV-TB	Re-treatment HIV-TB	MDR TB
2011			20
2012			18
2013	13	14	22
2014	13	14	22
2015	13	14	22
2016	13	14	22
2017			22
2018	13	16	20
Average	**13.0**	**14.4**	**21.0**

Abbreviations: MDR TB – multidrug resistant TB

Peer-reviewed literature

Treatment phase case fatality ratios:

The 211 studies which described treatment phase CFRs had an overall pooled CFR of 5.16% (4.20%, 6.34%) (Table 2-5). The pediatric pooled CFR (n=27) was 6.50% (2.65%, 10.36%) while higher CFRs were observed for HIV-infected (n=35, 10.91% [7.68%, 15.50%]) and DR-TB patients (n=43, 14.06% [10.15%, 19.49%]). The pooled treatment phase CFRs for primary/secondary centers (n=91, 5.18% [4.07%, 6.60%]) and tertiary centers (n=116, 4.87% [3.42%, 6.94%]) were similar. Fourteen papers with private sector CFRs were identified but their results were too heterogenous to reliably pool (Figure 2-4).

Table 2-5, Treatment CFRs for all studies

	# studies	**Pooled Treatment CFR, % (95% CI)**	τ^2
Overall	211	5.16 (4.20, 6.34)	1.961
Adult	73	4.62 (3.17, 6.75)	2.155
Pediatric	27	6.50 (2.65, 10.36)	3.463
HIV-	52	3.33 (2.00, 5.52)	2.640
HIV+	35	10.91 (7.68, 15.50)	0.900
Drug sensitive	104	3.58 (2.59, 4.97)	2.389
Drug resistant	43	14.06 (10.15, 19.49)	0.921
Public sector	193	5.40 (4.39, 6.64)	1.811
Private sector	14	Not pooled	4.058
Primary/secondary center	91	5.18 (4.07, 6.60)	1.247
Tertiary center	116	4.87 (3.42, 6.94)	2.936

Private sector was not pooled due to high heterogeneity

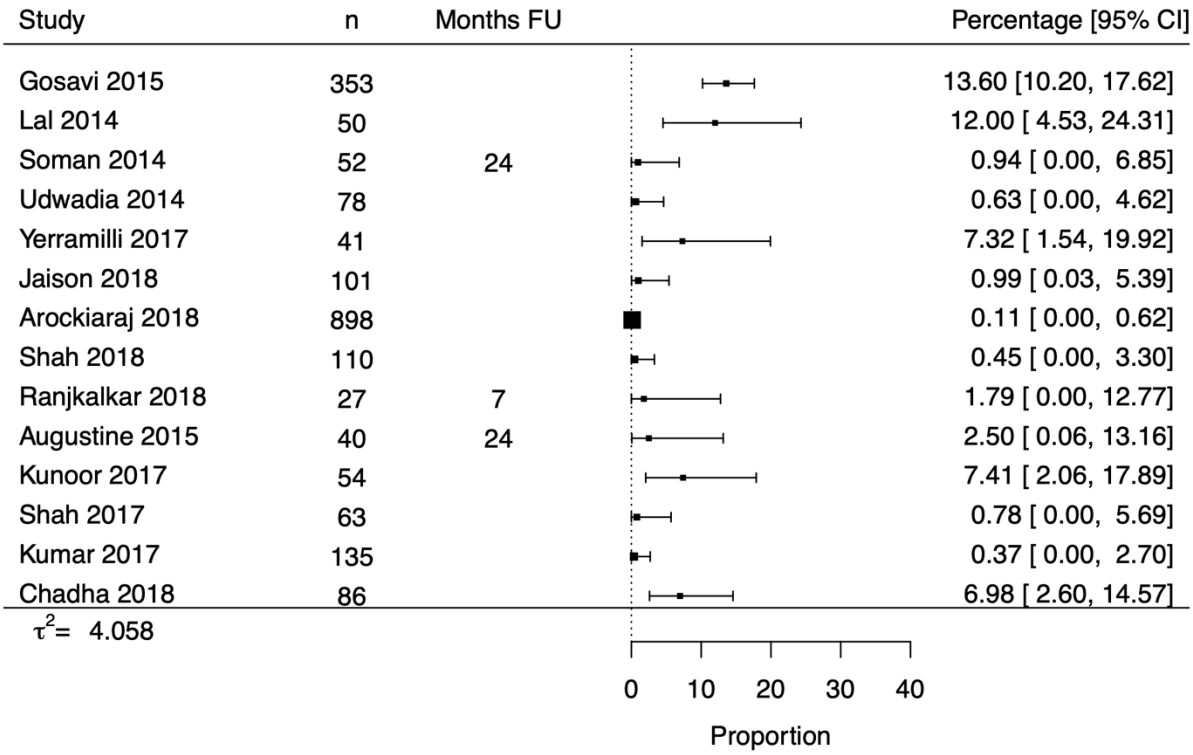

Figure 2-4, Forest plot of private sector treatment phase CFRs

Post-treatment phase case fatality ratios:

The 19 studies which described post-treatment phase CFRs were more heterogenous than the treatment CFRs (Table 2-6). Only the HIV-infected patient stratum was sufficiently homogenous giving a pooled post-treatment phase CFR of 4.15% (1.06%, 16.24%). There were substantially fewer studies that examined post-treatment fatality with only one study each providing post-treatment follow-up in the key populations of pediatric, DR and privately treated TB patients.

Table 2-6, Post-treatment CFRs for all studies

	# studies	Pooled Post-treatment CFR, % (95% CI)	τ^2
Overall	19	Not pooled	5.214
Adult	11	Not pooled	4.041
Pediatric	1		
HIV-	4	Not pooled	0.000
HIV+	5	4.15 (1.06, 16.24)	1.902
Drug sensitive	11	Not pooled	5.159
Drug resistant	1		
Public sector	19	Not pooled	6.042
Private sector	1		
Primary/secondary center	9	Not pooled	4.265
Tertiary center	9	Not pooled	4.868

Overall, adult, drug sensitive, public sector, primary/secondary center and tertiary center strata were not pooled due to high heterogeneity. The HIV- strata was not pooled as the model failed to converge.

Restricting to high quality studies

Treatment case fatality ratios:

Restricting to high quality studies left 52 (52/211, 24.6%) studies concerning treatment phase CFRs (Table 2-7). The overall pooled CFR reduced slightly to 3.78% (2.77%, 5.16%). The pediatric (n=11) CFR was substantially reduced to 1.08% (1.06%, 1.10%) while the HIV+ (n=7, 12.17% [5.68, 26.11%]) and DR-TB (n=5, 11.78% (2.96%, 46.78%)) remained high. No high-quality private sector studies were identified. The high-quality study treatment phase CFRs were similar or slightly lower than the overall results with the exception of the HIV-infected strata, which increased slightly. All tertiary center studies were excluded as low quality due to poor generalizability, thus this stratum is not presented for the high-quality studies

Table 2-7, Treatment CFRs for high quality studies

	# studies	Pooled Post-treatment CFR, % (95% CI)	τ^2
Overall	52	3.78 (2.77, 5.16)	1.132
Adult	14	4.34 (2.65, 7.12)	0.782
Pediatric	11	1.08 (1.06, 1.10)	3.463
HIV-	6	1.93 (0.86, 4.38)	0.706
HIV+	7	12.17 (5.68, 26.11)	0.782
Drug sensitive	34	3.94 (2.87, 5.01)	0.739
Drug resistant	5	11.78 (2.96, 46.78)	1.946
Public sector	52	3.78 (2.77, 5.16)	1.132
Private sector	0		

Post-treatment case fatality ratios:

Only three (3/19, 15.8%) high quality post-treatment CFR studies remained after quality restriction though they were now sufficiently homogenous to pool for an overall post-treatment phase CFR of 2.69% (-0.79%, 6.18%). The three studies were all from the public sector. No high-quality post-treatment phase studies were available for pediatric, DR-TB or HIV-TB patients.

Meta-regression

CFRs were regressed on study covariates for both treatment and post-treatment phase CFRs. There were 71 studies which had non-missing values for the required coefficients and a treatment phase CFR (Table 2-8) and 19 studies which had non-missing values for the required coefficients and a post-treatment phase CFR (Table 2-9).

For treatment phase CFRs, increasing proportions of EPTB (OR= 0.95, [0.94, 0.97]) and privately treated (OR=0.86, [0.84, 0.89]) patients were significantly associated with lower odds of case fatality. Increasing proportions of HIV-infected (OR= 1.15, [1.13, 1.17]) and DR-TB (OR= 1.09, [1.08, 1.10]) patients were significantly associated with higher odds of case fatality. Studies set in tertiary settings were significantly associated with higher case fatality (OR=1.15, [1.03, 1.28]) as was poor study quality (OR=2.27, [2.01, 2.57]).

Post-treatment CFRs were not significantly associated with either proportion of patients with EPTB or study quality.

Table 2-8, Odds Ratios (OR) from meta-regression of treatment CFRs, n=71

	Adjusted Odds Ratios (OR)	**95% CI**
EPTB (per 10% increase)	0.95	(0.94, 0.97)
Private (per 10% increase)	0.86	(0.84, 0.89)
HIV+ (per 10% increase)	1.15	(1.13, 1.17)
DR TB (per 10% increase)	1.09	(1.08, 1.10)
Tertiary setting (vs. Primary/Secondary)	1.15	(1.03, 1.28)
Poor quality (vs. high quality)	2.27	(2.01, 2.57)

Abbreviations: EPTB – extrapulmonary TB, DR TB – drug resistant TB

Table 2-9, Odds Ratios (OR) from meta-regression for post-treatment CFRs, n=19

	Adjusted Odds Ratios (OR)	**95% CI**
EPTB (per 10% increase)	1.03	(0.98, 1.07)
Poor quality (vs. high quality)	0.75	(0.55, 1.04)

Abbreviations: EPTB – extrapulmonary TB

2.8 Discussion

Treatment phase

Our systematic review of the literature found an overall treatment phase CFR for Indian TB patients of 5.16% (4.20%, 6.34%) among 211 papers. The pooled treatment phase CFR dropped slightly when restricted to high quality studies to 3.78% (2.77%, 5.16%). Elevated treatment phase CFRs were identified for key patient sub-populations like those with HIV (10.91% [7.68%, 15.50%]) and those with DR-TB (14.06% [10.15%, 19.49%]). The pediatric TB CFR was found to be 6.50% (2.65%, 10.36%) in the full data but when restricting to high quality studies it dropped to 1.08% (1.06%, 1.10%). In general, when restricting to high quality studies, which were defined in part by having good generalizability to the entire TB population, pooled treatment phase CFRs were lower than the mixed quality pooled treatment phase CFRs. Generalizability concerns were the leading cause of declaring a study low quality suggesting that much of the available TB literature focuses on the sickest TB patients like those who are treated in hospitals. This skewing toward sicker TB patients may be artificially elevating reporting of TB CFRs in the literature. Interestingly, the pooled treatment phase CFRs for primary/secondary health centers (5.18% [4.07%, 6.60%]) and tertiary health centers (4.87% [3.42%, 6.94%]) were similar but when adjusted for other study characteristics, tertiary center studies were significantly associated (OR=1.15, [1.03, 1.28]) with increased case fatality.

The overall pooled treatment phase CFR (5.16% [4.20%, 6.34%]) from the peer-reviewed studies since 2006 was higher than the average annual RNTCP reported CFR for NSP (4.1%), NSN (3.6%) and new EPTB (2.6%) cases over the same period. The pooled treatment CFRs for HIV (10.91% [7.68%, 15.50%]) and DR-TB (14.06% [10.15%, 19.49%]) patients were lower than the RNTCP reported CFRs for these groups (new HIV-TB: 13.0%, re-treatment HIV-TB: 14.4%, MDR TB: 21.0%).

Our meta-regression associated pulmonary TB, public sector treatment, HIV positivity, drug resistance, and tertiary health center settings with increasing CFRs during treatment. Additionally, poor quality studies were associated with finding higher CFRs.

Post-treatment phase

The 19 papers that described post-treatment CFRs were highly heterogeneous and could only be reliably pooled when restricted to the three high quality studies. The high quality

study post-treatment CFR was estimated to be 2.69% (-0.79%, 6.18%). Patient deaths after treatment may indicate either ineffective anti-TB treatment or a failure to address the socioeconomic determinants and physical environment that led to developing a disease like TB in the first place. TB treatment may also leave patients more susceptible to other diseases, both infectious and non-communicable. The goal of anti-TB treatment must extend beyond simply curing the current bout of TB to promoting long-lasting health for the patient.

Extensive quality concerns

As discussed above, 61.0% of studies had poor generalizability due to hospitalized or other specialized patient populations. It is likely that these patients were sicker than the average Indian TB patient and thus those studies had higher than representative CFRs. Many studies (27.5%) also had selection bias concerns. No study, including the RNTCP reports, corrected for patients lost to follow up or those who transferred to other TB centres meaning that these patient outcomes are not reflected in the reported CFR. Patients lost to follow-up may have been lost because they had died which could bias reported CFRs downward. Overall, after adjusting for other study variables, poor study quality was associated with higher CFRs (OR= 2.27 [2.01, 2.57]) in our meta-regression.

Strengths and Limitations

The pooled overall treatment phase CFR estimated in this work is in line with the WHO End TB Strategy goal which is an important and positive step for India. However, key patient sub-populations are understudied or described in studies with potential biases. In more than a decade, only 14 studies have addressed case fatality during private TB treatment in India, a country where half of TB patients are treated in the private sector.[4,5] None of these 14 studies was of high quality. For all patient subgroups, post-treatment CFRs are understudied with only 19 studies identified. Support for TB patients cannot stop when treatment is completed as patients are often in the same or worse social and environmental condition than when they first contracted TB.[16] Study quality is also a major concern as almost three quarters of studies had potential biases. Our meta-regression suggested that studies with methodological issues were likely to find higher CFRs, potentially overestimating patient fatality.

Critically, this study focused on a WHO-identified key indicator of treatment quality: the CFR. This is a value monitored by TB programs around the world and is relevant for programmatic planning. We were also able to include more than 200 studies thanks to flexible inclusion criteria that allowed for CFRs to be calculated from multiple study designs. Finally, our pooling methodology improved upon the more common Der-Simonian and Laird models by exactly modelling the binomial variance of the CFRs and adapting as needed to rare events by using a Beta-Binomial GLMM.

However, it is important to keep in mind that the patients in the published literature are unlikely to perfectly represent the complete patient distribution of India. The literature

likely over-represents rare forms of TB and hospitalized patients. We attempted to correct for this by restricting to high quality studies that were evaluated for generalizability of the studied patient population. While we have reported on CFRs from the RNTCP government reports, we have excluded other grey literature that may exist. Additional data from the grey literature may have added power to this work but it is often difficult to assess the quality of non-peer-reviewed literature. Additionally, this work only reflects fatality during and after treatment. Studies that estimate case fatality before treatment initiation were not included thus we cannot speak to pre-treatment CFRs. Similarly, the CFR is a measure of all-cause mortality and does not distinguish between TB or non-TB causes of death. In our meta-regression, which associated patient demographics and study characteristics with case fatality, we had to exclude many studies due to incomplete reporting of patient and study variables. Future studies on CFR and patient outcomes must fully report patient characteristics and patient selection. Moving forward, researchers and programs must apply correction methods for patient loss to follow-up in order to minimize selection bias.[17] Researchers should also recognize that hospitalized patients may systematically differ from most TB patients and that only limited conclusions can be drawn from these populations.

Case fatality is a critical measure of the quality of TB care. While India's overall treatment CFR is in line with WHO targets, several key patients groups remain understudied. Increased monitoring of patients treated in the private sector as well as follow-up of patients post-treatment will help ensure that all patients are able to achieve and maintain health after TB.

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S2-1Search Strategy

Medline search string follows. Search string was translated for each database.
(exp Tuberculosis/ OR tuberculosis.mp. OR TB.mp.) AND
(exp India/ OR india.mp. OR indian.mp.) AND
(mortality.mp. OR exp Mortality/ OR exp Death/ OR death*.mp. OR fatality.mp. OR CFR.mp. OR Follow-Up Studies/ OR follow*.mp. OR Prospective Studies/ OR Retrospective Studies/ OR exp Treatment Outcome/ OR treatment outcome*.mp. OR Survival Analysis/ OR Survival/ OR survival.mp.)

S2-2 Extracted Variables

First author last name
Study year
Source population
Setting of the study (in hospitals, tertiary care vs primary/secondary)
Study location (state)
Avg. patient age
Percentage <15 years old
Percentage female
Percentage HIV+
Percentage MDR or any drug-resistance
Percentage treated in public vs private sector
Percentage re-treatment
Percentage EPTB
Percentage Smear positive
Percentage Microbiologically Confirmed (from any source
Percentage urban
Patients received standard WHO DOTS? (Y/N)
Sample size (before loss to follow-up)
Average length of total follow-up
Maximum length of total follow-up
Person-years of follow-up
Number of patient deaths during entirety of follow-up
Overall case fatality proportion

{Average length of treatment follow-up
Maximum length of treatment follow-up
Person-years of treatment follow-up
Sample size of patient at beginning of treatment phase
Number of patients died during treatment phase
Number of patients with known outcome
Treatment case fatality rate
Average length of post-treatment follow-up
Maximum length of post-treatment follow-up

Person-years of post-treatment follow-up
Sample size of patient at beginning of post-treatment phase
Number of patients died during post-treatment phase
Number of patients with known outcome
Post-treatment case fatality rate}
{} Repeat again for HIV positive/negative, adult/child, public/private, drug sensitive/drug resistant as available

S2-3 Studies which did not delineate between treatment and post-treatment phase

	N	Max follow-up (months)	CFR (95% CI)
Sadana 2015	326	8	11.04 (7.95, 15.08)
Alvarez-Uria 2015	79	9	60.76 (49.1, 71.36)
Tutu 2017	115	12	0.87 (0.05, 5.45)
Sinha 2017	140	24	12.14 (7.44, 19)
Sinha 2017	31	12	6.45 (1.13, 22.84)
Gupta 2017	478	12	13.39 (10.53, 16.85)

S2-4 Table of included studies

	First Author's Last Name	Year	Title	State	Source Population	Total Patients Enrolled
1	Ahmad	2013	*STUDY OF TREATMENT OUTCOME OF NEW SPUTUM SMEAR POSITIVE TB CASES UNDER DOTS – STRATEGY*	Maharashtra	Newly diagnosed smear positive TB patients in urban Mumbai slum treated at DMC	281
2	Akshata	2016	*Management of multidrug resistant tuberculosis (MDR-TB) – Monitoring is the key to successful outcome*	Karnataka	RNTCP-confirmed MDR TB patients treated at a Rajiv Gandhi Institute of Chest Diseases in Bangalore between Aug 2011 and June 2012	69
3	Alvarez-Uria	2012	*Natural History and Factors Associated with Early and Delayed Mortality in HIV-Infected Patients Treated of Tuberculosis under Directly Observed Treatment Short-Course Strategy: A Prospective Cohort Study in India*	Andhra Pradesh	all antituberculosis treatment (ATT) episodes of patients from the VFHCS database from September 1st 2009, to September 1st 2011	1000
4	Ambadekar	2015	*Treatment outcome and its attributes in TB-HIV co-infected patients registered under Revised National TB Control Program: a retrospective cohort analysis*	Maharashtra	TB-HIV co-infected patients registered with RNTCP in Yavatmal district, from 2008 through 2011	886
5	Andries	2013	*High Rate of Hypothyroidism in Multidrug-Resistant Tuberculosis Patients Co-Infected with HIV in Mumbai, India*	Maharashtra	Patients initiated on a multidrug-resistant TB regimen between October 2006 and March 2013 at an MSF HIV project in Mumbai	116
6	Andries	2013	*Viral Load for HIV Treatment Failure Management: A Report*	Maharashtra	DR TB/HIV patients treated at MSF center in	8

			of Eight Drug-Resistant Tuberculosis Cases Co-Infected with HIV Requiring Second-Line Antiretroviral Treatment in Mumbai, India		Mumbai between Oct 2006 and July 2013	
7	Angadi	2016	*A FOLLOW UP STUDY ON NEWLY DETECTED SPUTUM POSITIVE PULMONARY TUBERCULOSIS CASES ON ANTI-TUBERCULAR TREATMENT IN BIJAPUR TALUK*	Karnataka	All newly detected pulmonary TB cases during November 1st 2011- October 31st 2012 registered from Bijapur Taluk at DTC, Bijapur	248
8	Anuradha	2010	*Predictors of stroke in patients of tuberculous meningitis and its effect on the outcome*	Uttar Pradesh	Adult patients with TB meningitis at outpatient and inpatient Medical University in Lucknow	100
9	Arathi	2013	*Osteoarticular Tuberculosis-A Three Years' Retrospective Study*	Uttar Pradesh	Osteoarticular TB patients diagnosed be tween Jan 2010 and Dec 1012 at a medical college in Uttar Pradesh	16
10	Armstrong	2014	*Treating drug-resistant tuberculosis in a low-intensity chronic conflict setting in India*	Andhra Pradesh-Chhattisgarh	DR TB patients treated as outpatients at MSF mobile clinic between Jan 2011 and Oct 2013	10
11	Ashwini	2009	*A Study on Treatment Outcome of Registered Tuberculosis Cases under RNTCP in Udupi Taluk, Karnataka*	Karnataka	TB patients registered under Udupi RNTCP between Jan and Dec 2007	563
12	Awasthi	2015	*Abdominal Tuberculosis: A Diagnostic Dilemm*a	NA	HIV- abdominal TB patients treated at a tertiary teaching hospital in N. India between Jan 2010 and Dec 2014	48
13	Babu	2012	*A COMPARATIVE STUDY OF DOT AND SAT IN RURAL TERTIARY CARE HOSPITAL: A TWO YEARS RETROSPECTIVE STUDY*	Karnataka	Pulmonary TB patients treated at a Karnataka hospital in 2010 and 2011	131
14	Bag	2015	*RESURGENCE OF EXTRA PULMONARY TUBERCULOSIS*	Odisha	EPTB cases treated at a medical college between 2009-2013	2596
15	Banu Rekha	2012	*Efficacy of the 6-month thrice-weekly regimen in the treatment of new sputum smear-positive pulmonary tuberculosis under clinical trial conditions*	Tamil Nadu	Newly diagnosed SS+ HIV- pulmonary adult TB patients, above 30kg	249
16	Brahmapurkar	2016	*Death and defaulted trends among registered TB cases at Jagdalpur TU in Bastar district of Chattisgarh, India*	Chhattisgarh	TB patients registered at TU in Jagdalpur between 2010 and 2014	2533
17	Brahmapurkar	2016	*TREATMENT OUTCOME OF REGISTERED TUBERCULOSIS CASES FOR YEAR 2013 IN TUBERCULOSIS UNIT IN TRIBAL DISTRICT BASTAR OF CHHATTISGARH, INDIA*	Chhattisgarh	TB patients registered in 2013 at TU in Jagdalpur	468
18	Chandra	2017	*Factors Determining the Clinical Spectrum, Course and Response to Treatment, and Complications in Seronegative Patients with Central Nervous System Tuberculosis*	Karnataka	CNS TB patients seeking trt at medical institute between Oct 2011 and Dec 2012	43

19	Chennaveerappa	2014	TBDOTS Outcome in Relation to HIV Status: Experience in a Medical College	Karnataka	Patients being treated at tertiary teaching hospital in South India	280
20	Daley	2015	Adjunctive vitamin D for treatment of active tuberculosis in India: a randomised, double-blind, placebo-controlled trial	Tamil Nadu	Participants (aged 18–75 years) who were HIV negative and had pulmonary tuberculosis, with at least one documented positive sputum smear, treated at RNTCP clinics, who had taken one dose of ATT or fewer	126
21	Dandekar	2014	THE FATE OF TUBERCULOSIS CASES AFTER TWO YEARS OF DOTS CHEMOTHERAPY IN AURANGABAD CITY, MAHARASHTRA	Maharashtra	TB patients registered with RNTCP in Aurangabad in 2006	304
22	Das	2014	HIV, multidrug-resistant TB and depressive symptoms: when three conditions collide	Maharashtra	Adult MDR TB/HIV patients treated at MSF clinic in Mumbai between Aug 2012 and March 2014 with mental health assessment performed before trt initiation	45
23	Dave	2015	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	Gujarat	Children aged <15 years with newly diagnosed TB and registered for treatment under the RNTCP in Gujarat between June 2012 and Sept 2012	265
24	De	2011	Incidence and risk factors of immune reconstitution inflammatory syndrome in HIV-TB coinfected patients	West Bengal	Recently diagnosed HAART naive HIV-TB patients on ATT who started ART after 15 days of ATT, excluded non-adherent patients	96
25	Deepa	2013	The Impact of Isoniazid Resistance on the Treatment Outcomes of Smear Positive Re-Treatment Tuberculosis Patients in the State of Andhra Pradesh, India	Andhra Pradesh	Smear positive re-treatment TB patients w/o rif resistance registered for treatment in three selected districts of Andhra Pradesh from April 2011 to March 2012 1077	
26	Baburao	2009	Study of Tuberculosis cases under RNTCP attending Designated Microscopy Centre at Pravara Rural Hospital, Loni	Uttar Pradesh	DMC patients registered from Jan 2006 to June 2008	611
27	Bhardwaj	2010	Evaluation of adequacy of short-course chemotherapy for extraspinal osteoarticular tuberculosis using 99mTc ciprofloxacin scan	Delhi	Spinal TB patients treated at tertiary hospital between Oct 2006 and Jan 2008	25
28	Chaudhri	2013	Impact of psychiatric profile and personality trait on directly observed tuberculosis treatment outcome	Uttar Pradesh	Adult new TB patients with psychiatric disorder diagnosed at DMC or initiated at DOTS center between Jan 2008 and Jan 2009, control arm of RCT on psychiatric intervention	88
29	Das	2016	Initial Sputum Smear Grading Is A Predictor Of Smear Conversion And Treatment	West Bengal	SS+ patients registered at TU between Sep 2014 to Aug 2015	355

			Outcome In Pulmonary Tuberculosis: A Retrospective Cohort Study			
30	Dave	2013	Assessment Of Long-Term Outcome Among New Smear Positive Pulmonary Tb Patients Treated With Intermittent Regimen Under Rntcp – A Retrospective Cohort Study	Gujarat	Cured/Treatment completed NSP patients who finished between Jan and June 2009	706
31	Dave	2015	Has introduction of rapid drug susceptibility testing at diagnosis impacted treatment outcomes among previously treated tuberculosis patients in Gujarat, India?	Gujarat	All SS+ previously treated patients registered with RNTCP Jan-Jun 2013 in Gujarat	5829
32	Dewan	2014	Early Outcome of Intermittent Directly Observed Treatment–Short Course, for Tuberculous Meningitis in Children: A Descriptive Analysis	Delhi	Children with TBM admitted to medical college hospital between May 2008 and March 2009	30
33	Dhawan	2016	Predictors of Neurological Outcome of Tuberculous Meningitis in Childhood: A Prospective Cohort Study From a Developing Country	NA	Children with TBM at a research/treaching hospital in N. India	130
34	Dhingra	2009	TUBERCULOSIS MORTALITY TRENDS IN DELHI AFTER IMPLEMENTATION OF RNTCP	Delhi	All Delhi patients registered with RNTCP in 2006	47608
35	Dholakia	2013	Clinical profile and treatment outcomes of drug-resistant tuberculosis before directly observed treatment strategy plus: Lessons for the program	Maharashtra	DR TB patients attending a TU in Mumbai between Aug 2006 and Nov 2010	29
36	Duraisamy	2014	Does Alcohol Consumption during Multidrug-resistant Tuberculosis Treatment Affect Outcome?: A Population-based Study in Kerala, India	Kerala	Culture-confirmed MDR TB patients treated under Kerala RNTCP between Jan 2009 and June 2010	179
37	Garg	2013	Evaluation of prognostic factors in medically treated patients of spinal tuberculosis	Uttar Pradesh	Spinal TB patients at Med. uni hospital July 2010 to Dec 2011	78
38	George	2011	Predictors of mortality in patients with meningeal tuberculosis	Kerala	TBM patients treated at govt hospital between Jan 2006 and Dec 2008	98
39	Gohel	2016	A study of 150 cases of intraperitoneal tuberculosis	Gujarat	Intraperitoneal TB treated at hospital between 2006 and 2009	150
40	Gosavi	2015	A STEP TOWARDS CONTROL OF MULTIDRUG RESISTANT TUBERCULOSIS: HOSPITAL BASED STUDY FROM NASHIK INDIA	Maharashtra	MDR TB cases treated at private hospital between Jan 2012 and March 2014	353
41	Goyal	2012	Clinical and radiological prognostic indicators in childhood tuberculous meningitis	Uttar Pradesh	Pediatric TBM patients treated at tertiary govt hospital between Sep 2010 and Aug 2011	53
42	Gupta	2015	Spinal Cord and Spinal Nerve Root Involvement (Myeloradiculopathy) in Tuberculous Meningitis	Uttar Pradesh	TBM patients diagnosed at government hospital between Nov 2011 and Nov 2013	71
43	Isaakidis	2012	Adverse Events among HIV/MDR-TB Co-Infected Patients Receiving Antiretroviral and Second Line Anti-TB Treatment in Mumbai, India	Maharashtra	MDR-TB patients who were initiated on ATT and ART between May 2007 and Sep 2011 at MSF clinic in Mumbai	67

44	Isaakidis	2011	*Ambulatory Multi-Drug Resistant Tuberculosis Treatment Outcomes in a Cohort of HIV-Infected Patients in a Slum Setting in Mumbai, India*	Maharashtra	HIV MDR TB patients treated at an outpatient MSF clinic in Mumbai between May 2007 and May 2011	58
45	Isaakidis	2015	*Outcomes in Adolescents Undergoing Treatment for Drug-Resistant Tuberculosis in Mumbai*	Maharashtra	Adolescent DR-TB patients treated at MSF clinic in Mumbai between July 2007 and April 2015	44
46	Isaakidis	2013	*Poor Outcomes in a Cohort of HIV-Infected Adolescents Undergoing Treatment for Multidrug-Resistant Tuberculosis in Mumbai, India*	Maharashtra	MSF treated teen MDR TB patients, Jul 2007 to Jan 2013	8
47	Iype	2011	*In-hospital mortality of intermittent vs daily antitubercular regimen in patients with meningeal tuberculosis - a retrospective study*	Kerala	TBM patients treated at medical college in Kerala between jan 2006 and Dec 2009	98
48	Iype	2014	*Major outcomes of patients with tuberculous meningitis on directly observed thrice a week regime*	Kerala	Adult TBM patients registered under RNTCP between Jan 2010 and Dec 2011 with Thwaites index 4 or below	47
49	Iype	2009	*Preliminary report of directly observed treatment, short course in tuberculous meningitis*	NA	TBM patients at medical college treated between Nov 2006 and Apr 2008	12
50	Jain	2010	*Outcomes of category III and I in immunocompetent patients of tuberculous lymphadenopathy treated in revised national tuberculosis control programme*	Madhya Pradesh	All CAT I and III TB lymphadenopathy treated at hospital in Indore	295
51	Jain	2013	*Pediatric Tuberculosis in Young Children in India: A Prospective Study*	Maharashtra	Children under 5 with suspected TB treated at government hospital and associated clinic between Aug 2010 and Mar 2012	26
52	Jain	2011	*Profile of patients with gastrointestinal TB at a tertiary care centre in western India*	Maharashtra	Patients with abdominal TB treated at a Mumbai hospital between Jan and Dec 2009	32
53	Jain	2014	*Treatment outcome of standardized regimen in patients with multidrug resistant tuberculosis*	NA	All Cat IV patients treated under RNTCP in an area in W. India between Jan 2009 and Dec 2009	130
54	Jha	2015	*Definite (microbiologically confirmed) tuberculous meningitis: predictors and prognostic impact*	Uttar Pradesh	Adult TBM patients at a teritiary hospital between Oct 2012 and Jan 2014	118
55	Joseph	2011	*Outcome of standardized treatment for patients with MDRTB from Tamil Nadu, India*	Tamil Nadu	DST confirmed adult MDR TB patients treated in Chennai RNTCP program between June 2006 and Sep 2007	38
56	Joseph	2011	*Treatment outcomes among new smear positive and retreatment cases of tuberculosis in Mangalore, South India – a descriptive study*	Karnataka	CAT I (NSP) and II patients registered at Mangalore TU between June 2008 and May 2009	286
57	Kadarkar	2016	*Correlates of non-compliance to follow up sputum examination and treatment outcomes among tuberculosis patients under*	Maharashtra	TB patients registered in Ganeshpuri DTC Jan to Dec 2013	126

			RNTCP in tribal area of Thane district			
58	Kalita	2014	Predictors of paradoxical tuberculoma in tuberculous meningitis	NA	Microbiologically confirmed TBM patients treated at a teritiary hospital between Aug 2009 and Feb 2012	34
59	Kalita	2014	Safety and efficacy of levofloxacin versus rifampicin in tuberculous meningitis: an open-label randomized controlled trial	NA	Adult new TBM patients treated at tertiary medical center between Jul 20079 and June 2012	60
60	Kapadia	2016	ADVERSE DRUG REACTIONS AND OUTCOME ANALYSIS OF MDR TB PATIENTS ON DOTS PLUS REGIMEN	Gujarat	MDR TB patients who completed treatment between Aug 2007 and June 2014 in Ahmedabad	102
61	Karmakar	2011	Clinical Characteristics of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome in North Indian Population of HIV/AIDS Patients Receiving HAART	Delhi	HIV-TB ART-naive patients treated a Delhi hospital ART clinic	134
62	Kaur	2015	Prospective Analysis of 55 Cases of Tuberculosis Meningitis (TBM) in North India	Chandigarh	TBM patients treated in a tertiary referral centre between Aug 2010 and Feb 2011	55
63	Kumar	2016	Prevalence and outcome of headache in tuberculous meningitis	Uttar Pradesh	New HIV- TBM patients with headache attending tertiary hospital between Oct 2012 and March 2014	95
64	Lal	2014	Study of gastro intestinal tuberculosis and role of surgery in its management in Navi Mumbai: analysis of 50 cases	Maharashtra	GI TB patients treated at private hospital between Aug 2010 and Oct 2012	50
65	Lodha	2014	Effect of micronutrient supplementation on treatment outcomes in children with intrathoracic tuberculosis: a randomized controlled trial	Delhi	Pediatric intrathorasic TB patients in control arm of micronutrient RTC, Jan 2008 to Jun 2012	100
66	Lone	2014	Impact of clinicoradiological parameters on the outcome of treatment in brain tuberculosis	Jammu and Kashmir	Brain TB patients presenting at tertiary hospital between Nov 2009 and Nov 2011	61
67	Makharia	2015	Intermittent Directly Observed Therapy for Abdominal Tuberculosis: A Multicenter Randomized Controlled Trial Comparing 6 Months Versus 9 Months of Therapy	NA	Adult HIV- new abdominal TB patients at three tertiary centers	191
68	Malhotra	2013	Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis	Uttar Pradesh	Control arm of RTC in adult TBM patients treated at govt hospital between Jan 2006 and Jul 2007	32
69	Mandal	2013	Comparing the Daily Versus the Intermittent Regimens of the Anti-Tubercular Chemotherapy in the Initial Intensive Phase in Non-HIV, Sputum Positive, Pulmonary Tuberculosis Patients	West Bengal	HIV- sputum positive PTB patients at tertiary care center between Jan 2010 and Dec 2011	83
70	Mishra	2007	A study of effectiveness of DOTS on tuberculosis patients treated under RNTCP programme	Madhya Pradesh	Patients registered at DOTS centres between Jul and Sep 2006 in Gwalior	312

71	Mukhopadhyay	2011	*Comparative Analysis of RNTCP Indicators in a Rural and an Urban Tuberculosis Unit of Burdwan District in West Bengal*	West Bengal	Patients at TU in 2007	898
72	Nagaraja	2011	*How Do Patients Who Fail First-Line TB Treatment but Who Are Not Placed on an MDR-TB Regimen Fare in South India?*	Andhra Pradesh	Re-treatment resistant RNTCP patients who were not given CAT IV	202
73	Naik	2015	*Treatment Outcome of Patients with Extrapulmonary Tuberculosis on DOTS in a Teaching Hospital*	Karnataka	RNTCP treated EPTB patients diagnosed at private teaching hospital between 2010 and 2012	669
74	Nair	2016	*Impact of rapid molecular diagnostic tests on time to treatment initiation and outcomes in patients with multidrug-resistant TB, Tamil Nadu, India*	Tamil Nadu	MDR-TB patients in Tamil Nadu diagnosed with culture and sputum smear tresting between Sep 2010 and Sep 2011	524
75	Nair	2017	*Predictors of unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India*	Kerala, Delhi and West Bengal	all patients en- rolled for MDR-TB treatment in three states from Jan 2009 to Dec 2011	788
76	Nelliyanil	2012	*A Study Of The Socio-Demographic Profile And Treatment Outcome Of Paediatric Tuberculosis Patients In Bangalore Mahanagar Palike Area*	Karnataka	Ped patients registered in 2009	209
77	Padda	2015	*Treatment outcome of TB patients in a district of north India: a three year study*	Punjab	RNTCP patients registered between Jan 2011 and Dec 2013	2571
78	Panigatti	2014	*Profile and Outcome of Childhood Tuberculosis Treated with DOTS—An Observational Study*	Karnataka	Pediatric cases at govt hospital receiving std DOTS from Nov 2009 to Apr 2011	93
79	Parida	2014	*Comparison of Directly Observed Treatment Short Course (DOTS) with Self-Administered Therapy in Pulmonary Tuberculosis in Udupi District of Southern India*	Bangalore	PTB patients diagnosed between Mar 2010 and Feb 2011, DOT arm of study	75
80	Patel	2016	*A STUDY OF THE TIMING OF DEATH IN PATIENTS WITH TUBERCULOSIS WHO DIE DURING ANTI-TUBERCULOSIS TREATMENT*	Gujarat	All TB patients treated between Jan 2007 and Apr 2012 at charitable hospital	376
81	Patel	2016	*Treatment outcome among cases of multidrug-resistant tuberculosis (MDR TB) in Western India: A prospective study*	Gujarat	MDR patients registered at DOTS centre in govt hospital, Feb to Dec 2010	145
82	Pathan	2014	*HIV Serostatus And Treatment Outcome Among Patients Registered Under RNTCP*	Gujarat	TB patients registered with the RNTCP in 2009	395
83	Phageshwar	2013	*Incidence of Multidrug-Resistant (MDR) and Extensively drug Resistant (XDR) Tuberculosis among Different age Groups in Tertiary Care Hospitals of Chandigarh, India*	Punjab	PTB patients registered to RNTCP at govt hospital between Mar 2008 and Feb 2012	52
84	Piparva	2017	*Treatment Outcome Of Tuberculosis Patients On Dots*	Gujarat	Cat I and II patients registered at DTC in 2013 and 2014	1340

			Therapy For Category 1 And 2 At District Tuberculosis Centre			
85	Raizada	2009	Linking HIV-Infected TB Patients to Cotrimoxazole Prophylaxis and Antiretroviral Treatment in India	Andhra Pradesh	TB-HIV patients reported to RNTCP Mar to Aug 2007	734
86	Ramachandran	2017	Factors Influencing Tuberculosis Treatment Outcome in Adult Patients Treated with Thrice-Weekly Regimens in India	Tamil Nadu	Adult patients at RNTCP treatment centers from Oct 2013 to Sep 2015	1912
87	Ramachandran	2016	Low Serum Concentrations of Rifampicin and Pyrazinamide Associated with Poor Treatment Outcomes in Children with Tuberculosis Related to HIV Status	Tamil Nandu, Uttar Pradesh, Karnataka	Pediatric TB patients treated at hospital TB centres, 2010-2013	161
88	Ramzam	2013	Childhood Tubercular Meningitis: An Institutional Experience and Analysis of Predictors of Outcome	Kashmir	TBM ped patients treated at govt hospital from June 2007 to May 2011	65
89	Rathee	2016	Comparative study of clinico-bacterio-radiological pro le and treatment outcome of smokers and nonsmokers suffering from pulmonary tuberculosis	NA	Adult pulmonary DS TB patients registered with RNTCP	101
90	Raut	2013	Hydrocephalus in tuberculous meningitis: Incidence, its predictive factors and impact on the prognosis	Uttar Pradesh	TBM patients at tertiary state university hospital treated from Oct 2010 to Aug 2012	80
91	Sadana	2015	Socio-Demographic Factors Affecting The Treatment Outcome In Patients Of Tuberculosis	Punjab	Cat I, II and III patients registered at DTC between Apr 2010 and Mar 2011	326
92	Saha	2016	Predictors of Treatment Outcome for Retreatment Pulmonary Tuberculosis Cases among Tribal People of an Eastern India District: A Prospective Cohort Study	West Bengal	Retreatment tribal TB cases registered in TUs in 2013	177
93	Samual	2016	Relationship between Nutritional Support and Tuberculosis Treatment Outcomes in West Bengal, India	West Bengal	SSP PTB patients living below poverty line registered at TU between 2012 and 2013, some received nutritional support but not RCT	573
94	Sarpal	2014	Treatment Outcome Among the Retreatment Tuberculosis (TB) Patients under RNTCP in Chandigarh, India	Punjab	Retreatment cases registered under RNTCP between Jun 2010 and Dec 2011	545
95	Satyanarayana	2010	Characteristics and Programme-Defined Treatment Outcomes among Childhood Tuberculosis (TB) Patients under the National TB Programme in Delhi	Delhi	Pediatric TB patients registered with the RNTCP between Jan and June 2008	1074
96	Satyanarayana	2011	Tuberculosis 'retreatment others': profile and treatment outcomes in the state of Andhra Pradesh, India	Andhra Pradesh	Retreatment patients registered at TUs between Jul and Sep 2008	1009
97	Sharma	2015	Clinicopathologic Spectrum of Cutaneous Tuberculosis: A Retrospective Analysis of 165 Indians	Delhi	BCG vaccinated CTB patients treated at tertiary public hospital	165
98	Sharma	2015	Comparative Study of Laparoscopic Abdominopelvic and Fallopian Tube Findings	Delhi	FGTB patients at tertiary public hospital	50

			Before and After Antitubercular Therapy in Female Genital Tuberculosis With Infertility			
99	Sharma	2013	Directly observed treatment, short course in tuberculous meningitis: Indian perspective	Meghalaya	TBM patients at govt tertiary hospital, diagnosed between Sep 2008 and Mar 2011	42
100	Sharma	2017	Multi drug resistant female genital tuberculosis: A preliminary report	Delhi	Female genital TB patients at tertiary hospital between Jan 2012 and June 2016	6
101	Sharma	2012	Outcomes of Category III DOTS treatment in immunocompetent patients with tuberculosis pleural effusion	Delhi, Andhra Pradesh, Gujarat, Rajasthan	Unilateral pleural effusion patients aged between 15 and 65 years treated as outpatients four tertiary hospitals across India between 2006 and 2011	351
102	Shastri	2013	TB treatment outcomes among TB-HIV co-infections in Karnataka, India: how do these compare with non-HIV tuberculosis outcomes in the province?	Karnataka	Programmatic data of TB and TB HIV patients registered between Apr 2010 and Mar 2011	58446
103	Shibin	2014	A Case Control Study on Clinical Characteristics And Treatment Outcomes In Tuberculosis Patients With Diabetes in Palakkad District	Kerala	DTC adult TB patients enrolled Jan to Jul 2014	130
104	Shivam	2014	Gender Differentials in Tuberculosis: An Experience from a Rural Tuberculosis Unit of Burdwan District, West Bengal, India	West Bengal	Patients registered at TU between Nov 2010 and Dec 2011	758
105	Siddiqui	2016	Effect of Diabetes Mellitus on Tuberculosis Treatment Outcome and Adverse Reactions in Patients Receiving Directly Observed Treatment Strategy in India: A Prospective Study	Delhi	TB patients diagnosed at PHC Jan to Sep 2014	316
106	Singh	2015	Clinicoradiological Profile of Lower Lung Field Tuberculosis Cases among Young Adult and Elderly People in a Teaching Hospital of Madhya Pradesh, India	Madhya Pradesh	Adult (>12yo) PTB patients treated at public tertiary hospital Jan 2012 to Jan 2015	215
107	Singh	2016	Tuberculous lymphadenopathy: Experience from the referral center of Northern India	Madhya Pradesh	TB lymphadenopathy patients (>12 yo) treated at a tertiary hospital between Jul 2013 and Jun 2014	204
108	Sinha	2012	Early versus delayed initiation of antiretroviral therapy for Indian HIV-Infected individuals with tuberculosis on antituberculosis treatment	Delhi	Adult newly diagnosed HIV-TB patients in RCT on the timing of ART initiation relative to ATT, took only delayed ART control arm, treated as outpatients at govt tertiary hospital	150
109	Sinha	2013	Nevirapine versus efavirenz-based antiretroviral therapy regimens in antiretroviral-naive patients with HIV and tuberculosis infections in India: a pilot study	Delhi	Newly diagnosed HIV-TB patients at tertiary hospital ART clinic between Sep 2007 and Dec 2012	135
110	Sinha	2011	The antiretroviral efficacy of highly active antiretroviral therapy and plasma nevirapine concentrations in HIV-TB co-	Delhi	TB HIV patients at tertiary hospital diagnosed between Sep 2007 and Mar 2011	63

			infected Indian patients receiving rifampicin based antituberculosis treatment			
111	Soman	2014	*Successful Management of Highly Drug Resistant Tuberculosis with Individualised Drug Susceptibility Testing*	Maharashtra	MDR+ and XDR patients treated at a tertiary hospital	52
112	Swaminathan	2011	*Efficacy and Safety of Once-Daily Nevirapine- or Efavirenz-Based Antiretroviral Therapy in HIV- Associated Tuberculosis: A Randomized Clinical Trial*	Tamil Nadu	RCT of HIV drugs among adult newly diagnosed HIV/TB patients, took both arms	122
113	Thakor	2011	*Profile of paediatric TB cases in Ahmedabad Municipal Corporation area during year 2007 to 2009*	Gujarat	Ped patients treated at TU between 2007 and 2009	2253
114	Thomas	2011	*Extensively drug-resistant tuberculosis: experience at the Tuberculosis Research Centre, Chennai, India*	Tamil Nadu	MDR and XDR patients treated at , 2006-2007 cohort	38
115	Tiwari	2012	*Relationship Between Sputum Smear Grading And Smear Conversion Rate And Treatment Outcome In The Patients Of Pulmonary Tuberculosis Undergoing Dots- A Prospective Cohort Study*	Delhi	Cat I SSP TB patients treated at DOTS centres between Nov 2006 and Oct 2007	338
116	Tripathi	2015	*Treatment Outcome Of Tuberculosis In Hiv Seropositive Patients: An Experience Of Southeast Region Of Ahmedabad*	Gujarat	HIV TB patients starting ATT at a medical college between Jan 2012 and Dec 2013	120
117	Tripathy	2013	*Effectiveness of a community-based observation of anti-tuberculosis treatment in Bangalore City, India, 2010–2011*	Karnataka	New SSP RNTCP patients treated between Oct 2010 and Sep 2011	1864
118	Udwadia	2014	*Multidrug-resistant-tuberculosis treatment in the Indian private sector: Results from a tertiary referral private hospital in Mumbai*	Maharashtra	MDR TB patients treated at non-profit tertiary hospital between 2006 and 2010	78
119	Varshney	2011	*Incidence of various clinico-morphological variants of cutaneous tuberculosis and HIV concurrence: a study from the Indian subcontinent*	Uttar Pradesh	CTB patients treated at a private hospital between Oct 2007 and Nov 2009	131
120	Vashishtha	2013	*Efficacy and safety of thrice weekly DOTS in tuberculosis patients with and without HIV co-infection: an observational study*	Delhi	TB HIV patients initiating treatment at tertiary govt hospital between Apr 2006 and Oct 2010	305
121	Vasudevan	2014	*Smear Conversion, Treatment Outcomes and the Time of Default in Registered Tuberculosis Patients on RNTCP DOTS in Puducherry, Southern India*	Puducherry	TB patients at TU between Jan and Jun 2011	660
122	Veeramani	2016	*Study on outcome of the treatment of tuberculosis patients registered under Revised National Tuberculosis Control Programme – DOTS strategy*	Tamil Nadu	TB patients registered at DOTS centers in 2014	282

123	Velayutham	2016	*Factors associated with sputum culture conversion in multidrug-resistant pulmonary tuberculosis*	West Bengal, Delhi and Kerala	DR TB patients treated by RNTCP between Jan 2009 and Dec 2011	787
124	Vijay	2011	*Treatment Outcome and Mortality at One and Half Year Follow-Up of HIV Infected TB Patients Under TB Control Programme in a District of South India*	Karnataka	TB-HIV patients registered with the RNTCP between Jul 2007 and Jun 2008	281
125	Viswanathan	2014	*Effect of diabetes on treatment outcome of smear-positive pulmonary tuberculosis— A report from South India*	Tamil Nadu	TB patients registered at TUs between Jan and Mar 2011	245
126	Shibin	2014	*A CASE CONTROL STUDY ON CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES IN TUBERCULOSIS PATIENTS WITH DIABETES IN PALAKKAD DISTRICT*	Kerala	DTC TB patients	130
127	Patel	2017	*A Randomized, Controlled, Phase III Clinical Trial to Evaluate the Efficacy and Tolerability of Risorine with Conventional Rifampicin in the Treatment of Newly Diagnosed Pulmonary Tuberculosis Patients*	Jammu, Bangalore, Ahmedabhad	Control arm of RCT	117
128	Saini	2016	*A Retrospective Cohort Study of Treatment Outcome among HIV positive and HIV negative TB patients in Chandigarh, India*	Punjab	RNTCP treated adult DS patients	3551
129	Misra	2016	*A study of hyponatremia in tuberculous meningitis*	Uttar Pradesh	TBM patients treated at government hospital	76
130	Marskole	2018	*A Study of Impact of CD_4 and BMI on Effectiveness of DOTS in HIV-TB Cases Registered in Hamidia Hospital Bhopal*	Madhya Pradesh	TB and TB HIV patients in hospital DOTS and ART center	248
131	Das	2007	*A study of pulmonary tuberculosis in the elderly*	West Bengal	PTB patients at hospital	70
132	Nagpal	2015	*A Study of Sputum Conversion Rates Affecting the Treatment Outcome in Newly Diagnosed Smear Positive Cases under DOTS in Amritsar City*	Punjab	NSP patients at TUs	250
133	Nelliyanil	2012	*A STUDY OF THE SOCIO-DEMOGRAPHIC PROFILE AND TREATMENT OUTCOME OF PAEDIATRIC TUBERCULOSIS PATIENTS IN BANGALORE MAHANAGAR PALIKE AREA*	Karnataka	TU pediatric TB cases	209
134	Gharat	2017	*A Study on Socio-demographic Profile and Outcome of Tuberculosis in HIV-TB Co-infected Cases in Surat City, Western India*	Gujarat	RNTCP HIV-TB patients	204
135	Yerramilli	2017	*A study on the clinical outcomes and management of meningitis at a tertiary care centre*	Telangana	hospital TBM patients	41
136	Mukhopadhyay	2014	*Abdominal Tuberculosis with an Acute Abdomen: Our Clinical Experience*	West Bengal	Adult abdominal TB patients at govt tertiary hospital between Jan 2009 and Dec 2011	70

137	Bunkar	2016	*Add-on prednisolone in the management of cervical lymph node tuberculosis*	Rajasthan	Cervical TB treated at hospital - DOTS only arm	60
138	Alvarez-Uria	2015	*Adding Streptomycin to an Intensified Regimen for Tuberculous Meningitis Improves Survival in HIV-Infected Patients*	Andhra Pradesh	For this study, we included all HIV-infected patients diagnosed with tuberculous meningitis from 1 January 2011 to 1 October 2014 from the VFHCS database	79
139	Dela	2017	*Adverse drug reactions and treatment outcome analysis of DOTS plus therapy of MDRTB patients at district tuberculosis centre: A four year retrospective study*	Gujarat	MDR-TB patients treated by RNTCP, excluded natural causes deaths	125
140	Kumar	2017	*AN OVERVIEW OF ANTI-TUBERCULOSIS TREATMENT (ATT) IN CAT I NEWLY DIAGNOSED CASES OF TUBERCULOSIS IN RNTCP*	Madhya Pradesh	Hospital outpatients, new DS TB	360
141	Puri	2017	*Antitubercular therapy induced liver function tests abnormalities in human immunodeficiency virus infected individuals*	Maharashtra	TB-HIV ATT-naive adult patients diagnosed with TB at ART centre	100
142	Kondapaka	2012	*Are Tuberculosis Patients in a Tertiary Care Hospital in Hyderabad, India Being Managed According to National Guidelines?*	Telangana	TB inpatients	1132
143	Dhoble	2017	*Assessment of the Socio-Demographic Profile and Treatment Outcome of Pediatric Tuberculosis Patients*	Maharashtra	Pediatric patients from TU	69
144	Jaison	2018	*ASSESSMENT OF TREATMENT OUTCOME IN TUBERCULOSIS PATIENTS APPROACHING A TERTIARY CARE TEACHING HOSPITAL*	Kerala	TB patients treated at tertiary hospital	101
145	Datta	2015	*CAN VITAMIN D SUPPLEMENTATION HASTEN RECOVERY OF TUBERCULOSIS*	West Bengal	PTB hospital patients	271
146	Modi	2017	*Clinical and radiological predictors of outcome in tubercular meningitis: A prospective study of 209 patients*	Punjab	TBM patients at tertiary hospital	209
147	Synmon	2017	*Clinical and radiological spectrum of intracranial tuberculosis: A hospital based study in Northeast India*	Assam	Intracranial TB patients	93
148	Dole	2017	*Clinical Profile and Treatment Outcome of Drug Resistant Tuberculosis Patients of Western Maharashtra, India*	Maharashtra	DR TB patients treated at hospital	146
149	Mukherjee	2017	*Clinical Profile of Tubercular Empyema with Special Reference to Diagnostic Role of Cartridge Based Nucleic Acid Amplification test (CBNAAT)*	West Bengal	TB empyema patients at tertiary govt hospital	40
150	Mukherjee	2014	*Comparison between childhood and adult tuberculosis in a rural tuberculosis unit of West Bengal: A retrospective study*	West Bengal	Cases registered at TU between Jan 2008 and Dec 201, outcomes only for NSP	741

151	Parida	2014	Comparison of Directly Observed Treatment Short Course (DOTS) with Self-Administered Therapy in Pulmonary Tuberculosis in Udupi District of Southern India	Karnataka	Hospital DOTS records	75
152	Shukla	2016	Comparison of Outcome of Dots and Self Administered Therapy in Patients of Tuberculosis in Tertiary Care Hospital, Nainital	Uttarakhand	hospital TB patients - DOTS amr	60
153	Gopalan	2018	Daily vs Intermittent Antituberculosis Therapy for Pulmonary Tuberculosis in Patients With HIV A Randomized Clinical Trial	Tamil Nadu	HIV-TB patients in RCT	98
154	Kant	2017	Delay in initiation of treatment after diagnosis of pulmonary tuberculosis in primary health care setting: eight year cohort analysis from district Faridabad, Haryana, North India	Haryana	PTB patients at PHCs	662
155	Koul	2016	Demography and clinical outcome of pulmonary tuberculosis in Kashmir; 2 year prospective study	Kashmir	Adult PTB patients at public hospital	72
156	Siddiqui	2017	Diabetes prevalence and its impact on health-related quality of life in tuberculosis patients	Delhi	DOTS centre TB patients	316
157	Das	2014	Directly-Observed and Self-Administered Tuberculosis Treatment in a Chronic, Low-Intensity Conflict Setting in India	Andhra Pradesh, Odisha	DOT arm of MSF treated patients, community healthcare centre, initiated in 2012	55
158	Arockiaraj	2018	Drug resistant Skeletal Tuberculosis in a tertiary care centre in South India	Tamil Nadu	DR skeletal TB at tertiary centre	898
159	Mittal	2011	Effect of Disease Related Variables on Treatment Outcome Under DOTS	Uttar Pradesh	DOTS patients	900
160	Kadam	2017	EFFECTIVENESS OF DOTS THERAPY UNDER RNTCP-DOTS STRATEGY IN PAEDIATRIC TB- EXPERIENCE FROM WESTERN INDIA	Maharashtra	Pediatric patients at tertiary hospital	104
161	Chopra	2017	Efficacy of alternate day Directly Observed Treatment Short-course (DOTS) in skeletal tuberculosis – A retrospective study	Delhi	skeletal TB at RNTCP clinic	218
162	Lanjewar	2014	Evaluation of treatment outcome of tuberculosis patients in the urban field practice area of D. Y. Patil Medical College, Pimpri, Pune	Maharashtra	Urban DOTS patients	429
163	Jain	2016	Evaluation study of treatment outcome in Tuberculosis patients receiving DOTS under RNTCP	Madhya Pradesh	RNTCP treated TB patients	241
164	Anandaraj	2017	Factors influencing delay in sputum smear conversion among new smear-positive pulmonary tuberculosis patients of Davangere tuberculosis unit	Karnataka	Adult PTB treated at DMC	233
165	Bhattacharya	2017	Follow up of Drug-Resistant Pulmonary Tuberculosis	West Bengal	DR PTB patients at government hospital	142

			Patients in a DRTB Center in First Fifteen Months of Treatment			
166	Prasad	2016	Frequency of adverse events observed with second-line drugs among patients treated for multidrug-resistant tuberculosis	Uttar Pradesh	Pediatric TB cases	98
167	Taneja	2017	Home Based Care as an Approach to Improve the Efficiency of treatment for MDR Tuberculosis: A Quasi-Experimental Pilot Study	Delhi	Hospital chest clinic MDR patients	50
168	Mohammed	2018	Hypothalamic and pituitary dysfunction is common in tubercular meningitis: A prospective study from a tertiary care center in Northern India	Punjab	TBM patients at tertiary hospital	63
169	Mahmood	2018	IMPACT OF DIABETES MELLITUS ON TREATMENT OUTCOME OF MULTIDRUG RESISTANT PULMONARY TUBERCULOSIS	Uttar Pradesh	Hospital treated DOTS MDR patients	144
170	Bhatt	2018	Impact of integrated psycho-socio-economic support on treatment outcome in drug resistant tuberculosis – A retrospective cohort study	Delhi	Control arm in DOTS support trial at DTC	63
171	Iype	2011	In-hospital mortality of intermittent vs daily antitubercular regimen in patients with meningeal tuberculosis–a retrospective study	Kerala	TBM at tertiary hospital	55
172	Tutu	2017	INCIDENCE AND PATTERN OF ADVERSE DRUG REACTIONS (ADRs) IN PATIENTS TREATED FOR TUBERCULOSIS UNDER DOTS AT A TERTIARY CARE HOSPITAL OF NORTHERN INDIA	Uttar Pradesh	Hospital treated new TB DOTS patients	115
173	Shah	2018	Increasing Prevalence of Pediatric Drug-resistant Tuberculosis in Mumbai, India, and Its Outcome	Maharashtra	Pediatric DR-TB	110
174	Ranjkalkar	2018	Isoniazid and rifampicin concentrations in children with tuberculosis with either a daily or intermittent regimen: implications for the revised RNTCP 2012 doses in India	Tamil Nadu	Pediatric TB patients treated at tertiary hospital, intermittent DOTS arm	27
175	Mundra	2017	Magnitude and determinants of adverse treatment outcomes among tuberculosis patients registered under Revised National Tuberculosis Control Program in a Tuberculosis Unit, Wardha, Central India: A record-based cohort study	Maharashtra	Patients registered at TU in 2014	510
176	Jaryal	2011	Manifestations of tuberculosis in HIV/AIDS patients and its relationship with CD4 count	Himachal Pradesh	HIV-TB patients	87
177	Augustine	2015	Multidrug-resistant tuberculosis: Need for better diagnostic modalities and	Dehli	MDR culture confirmed patients at tertiary hospital	40

			clinical end points – Five-year tertiary care hospital experience			
178	Sinha	2017	Nevirapine- versus Efavirenz-based antiretroviral therapy regimens in antiretroviral-naive patients with HIV and Tuberculosis infections in India: a multi-centre study	Delhi, Maharashtra	Efavirenz arm of HIV-TB RCT	140
179	Latief	2016	Novel risk factors and early detection of anti tubercular treatment induced liver injury—Looking beyond American Thoracic Society Guidelines	Jammu and Kashmir	TB patients treated at tertiary hospital	200
180	Sinha	2017	Once Daily Dose of Nevirapine (400 mg) Versus Twice-Daily Dose (200 mg) of Nevirapine-Based Highly Active Antiretroviral Therapy Regimens in Antiretroviral Naïve Patients with HIV and Tuberculosis Infection in India	Delhi	Control arm of HAART trial in TB-HIV patients	31
181	Kunoor	2017	Outcomes of patients treated with individualised anti-tuberculosis regimens in a tertiary care centre in India	Kerala	Patients treated at private tertiary hospital	54
182	Gupta	2017	Predictors of adverse outcome in patients of tuberculous meningitis in a multi-centric study from India	Delhi	TBM patients treated at hospital	478
183	Barman	2017	PROFILE AND TREATMENT OUTCOME AMONG PULMONARY TUBERCULOSIS PATIENTS UNDER DOTS ATTENDING A TERTIARY CARE CENTRE IN DIBRUGARH DISTRICT, ASSAM	Assam	PTB patients diagnosed with PTB treated at tertiary hospital	661
184	More	2017	Profile of drug-resistant tuberculosis in Western Maharashtra	Maharashtra	Govt treated DR TB patients	96
185	Shah	2017	Profile of Tuberculous Cervical Lymphadenopathy in Children	Maharashtra	Pediatric cervical lymph TB	63
186	Velayutham	2018	Recurrence of tuberculosis among newly diagnosed sputum positive pulmonary tuberculosis patients treated under the Revised National Tuberculosis Control Programme, India: A multi-centric prospective study	Tamil Nadu, Karnataka, Delhi, Maharashtra, Madhya Pradesh, Kerala	RNTCP new SP adult PTB patients	1565
187	Anandaraj	2017	RELATIONSHIP BETWEEN PRE TREATMENT BACILLARY LOAD AND SMEAR CONVERSION AND TREATMENT OUTCOME OF PULMONARY TUBERCULOSIS PATIENTS IN A TB UNIT OF KARNATAKA	Karnataka	Adult PTB patients treated at DMC	313
188	Tiwari	2012	RELATIONSHIP BETWEEN SPUTUM SMEAR GRADING AND SMEAR CONVERSION RATE AND TREATMENT OUTCOME IN THE PATIENTS OF PULMONARY TUBERCULOSIS UNDERGOING DOTS- A	Delhi	Chest clinic DOTS patients	338

			PROSPECTIVE COHORT STUDY			
189	Kalita	2016	Safety and efficacy of additional levofloxacin in tuberculous meningitis: A randomized controlled pilot study	Uttar Pradesh	Control arm of TBM RCT	28
190	Sharma	2016	Six months versus nine months anti-tuberculous therapy for female genital tuberculosis: a randomized controlled trial	Delhi	Female genital TB with infertility	89
191	Rohit	2018	Socio-demographic profile and outcome of TB patients registered at DTC Rewa of Central India	Madhya Pradesh	DTC TB patients	133
192	Dhaked	2018	Socio-demographic profile and treatment outcomes in pediatric TB patients attending DOTS centers in urban areas of Delhi	Delhi	Pediatric TU patients in Delhi	140
193	Bagga	2017	SOCIO-EPIDEMIOLOGICAL CHARACTERISTICS AND TREATMENT OUTCOME OF ADULT TUBERCULOSIS PATIENTS UNDER DIRECTLY OBSERVED TREATMENT SHORT COURSE IN LUDHIANA CITY	Punjab	Adult TU patients	221
194	Lepcha	2017	Sociodemographic profile and treatment outcome of tuberculosis patients registered under Directly Observed Treatment Short course in East Sikkim with reference to defaulters	Sikkim	TU patients	2638
195	Banga	2018	Spinal Tuberculosis – Directly Observed Treatment and Short Course or Daily Anti Tubercular Therapy -Are We Over Treating?	Punjab	Spinal TB treated at hospital - DOTS arm	30
196	Patel	2018	Sputum Smear and Culture Conversion in Multidrug Resistance Tuberculosis Patients in Seven Districts of Central Gujarat, India: A Longitudinal Study	Gujarat	DOTS Plus DR patients	142
197	Brahmapurkar	2017	Sputum smear grading and treatment outcome among directly observed treatment short course patients of tuberculosis unit, Jagdalpur, Bastar	Chhattisgarh	TU patients, 2014	496
198	Yadav	2016	Study of factors influencing response and outcome of Cat-IV regimen in MDRTB patients	Rajasthan	MDR patients, hospital DOTS+ centre	115
199	Patil	2017	STUDY OF TREATMENT OUTCOME OF TUBERCULOSIS PATIENTS PLACED FOR TREATMENT UNDER DIRECTLY OBSERVED THERAPY SHORT COURSE (DOTS) AT A TUBERCULOSIS UNIT, KARAD, WESTERN MAHARASHTRA	Maharashtra	TU patients	319
200	Kumar	2017	STUDY OF WEIGHT VARIATION DURING ANTI-TUBERCULOSIS TREATMENT IN TUBERCULOSIS PATIENTS	Madhya Pradesh	RNTCP treated patients at tertiary hospital	453

			PUT ON DOTS IN RNTCP IN CENTRAL INDIA			
201	Singh	2018	Surgery for Abdominal Tuberculosis in the Present Era: Experience from a Tertiary-Care Center	Punjab	Abdominal TB at tertiary hospital	35
202	Kumar	2017	Thoracoscopic Decortication of Stage III Tuberculous Empyema Is Effective and Safe in Selected Cases	Delhi	TB empyema patients receiving surgery	135
203	Saharia	2015	Thyroid profile status of patients treated for multidrug-resistant tuberculosis in state of Meghalaya, India	Meghalaya	DTC MDR patients	114
204	Sarpal	2014	Treatment Outcome Among the Retreatment Tuberculosis (TB) Patients under RNTCP in Chandigarh, India	Punjab	RNTCP retreatment patients	545
205	Kumar	2018	TREATMENT OUTCOME AND EFFICACY OF ANTI-TUBERCULOSIS TREATMENT IN TUBERCULOSIS PATIENTS PUT ON DOTS IN RNTCP IN CENTRAL INDIA	Madhya Pradesh	Hospital outpatients starting DOTS	454
206	Cherian	2016	Treatment outcome of extrapulmonary tuberculosis under Revised National Tuberculosis Control Programme	NA	RNTCP EPTB patients in 3 districts	2046
207	Prajapati	2017	Treatment Outcome of Patients Having Extensively Drug-resistant Tuberculosis in Gujarat, India	Gujarat	XDR TB patients	112
208	Gupta	2018	Treatment Outcomes Associated with Multidrug-resistant Tuberculosis	Delhi	MDR TB patients at tertiary DOTS center	819
209	Ramesh	2012	Treatment outcomes of childhood tuberculosis with DOTS strategy in Kottayam, Kerala	Kerala	pediatric TU patients	155
210	Prakash	2017	Tuberculosis and human immunodeficiency virus co-infection: clinico-demographic determinants at an anti-retroviral therapy center in Northern India	Bihar	HIV-TB patients at ART center	508
211	Chadha	2018	Tuberculosis diagnostic and treatment practices in private sector: Implementation study in an Indian city	Karnataka	Privately treated TB patients	101
212	Puri	2013	Tuberculosis of the duodenum: clinical presentation, diagnosis and outcome	Delhi	TB of the duodenum patients at tertiary hospital	10
213	Jackson	2017	Tuberculosis treatment outcomes among disadvantaged patients in India	Jarkkhand, Odisha, Chhattisgarh, Rajasthan, Maharashtra, Madhya Pradesh, Delhi	Op ASHA treated patients	8415
214	Parmar	2018	Unacceptable treatment outcomes and associated factors among India's initial cohorts of multidrug-resistant tuberculosis (MDR-TB) patients under the	NA	all MDR patients registered with RNTCP 2007-2011	3712

			revised national TB control programme (2007–2011): Evidence leading to policy enhancement			
215	Suryawanshi	2017	*Unfavourable outcomes among patients with MDR-TB on the standard 24-month regimen in Maharashtra, India*	Maharashtra	RNTCP MDR TB patients	4024
216	Dhuria	2016	*Universal access to DOTS in Delhi prisons: Where do we stand?*	Delhi	TB patients treated by RNCTP in Delhi prison	603
217	Dangeti	2018	*Vitamin D deficiency in patients with tuberculous meningitis and its relationship with treatment outcome*	Puducherry	TBM patients at tertiary hospital	39
218	Karthika	2018	*Why are people dying due to tuberculosis? A study from Alappuzha District, Kerala*	Kerala	RNTCP treated patients	1618

Chapter 3: Case fatality and recurrent TB among privately treated TB patients in India

3.1 Preface

My systematic review in Chapter 2 highlighted a lack of high quality data on long term outcomes of TB patients treated in the Indian private sector. This group has been historically difficult to study due to a lack of feasible sampling frames. However, new quality of care interventions such as Private Provider Interface Agencies (PPIAs) allow for statistical sampling of privately treated TB patients. While patients treated by PPIAs likely receive better care than the average TB patient treated in the private sector, these cohorts still provide the first large datasets of privately treated TB patients. Additionally, PPIAs are becoming a popular means to improve quality of care in the private sector so establishing their efficacy has programmatic implications.

Here, I report the results of two 4,000 patient cohorts surveyed in Patna and Mumbai. These cohorts constitute the largest long-term outcome study of Indian privately treated TB patients ever conducted. As highlighted in my systematic review (Chapter 2), selection bias is not commonly addressed in the TB literature. In my cohort studies, I apply inverse probability selection weighting (IPSW) to correct for potential selection bias when estimating patient event rates. I estimate IPS weighted and unweighted treatment phase CFRs, post-treatment phase CFRs and recurrent rates for both cohorts. I additionally use survival modelling to explore patient demographic characteristics associated with poor outcomes.

This work is being prepared for submission to Lancet Global Health.

3.2 Title Page

Case fatality and recurrent TB among privately treated TB patients in India

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3.3 Abstract

Background and Objectives: A key component of the WHO End TB Strategy is quality of care, for which case fatality is a critical marker. India accounts for 38% of global tuberculosis (TB) deaths and half of India's TB patients are treated in the highly unregulated private sector. This study estimated the case fatality ratio (CFR) and the rate of recurrent TB among privately treated Indian TB patients.

Methods: Private Provider Interface Agencies (PPIA) pilot projects in Patna (World Health Partners) and Mumbai (PATH) treated over 80,000 private sector TB patients since 2014. Two random samples of 4,000 patients from each city treated from 2014 to 2016 were surveyed for case fatality and recurrent TB. CFR is defined as the proportion of patients who die during the period of interest. Treatment CFRs, post-treatment CFRs and rates of recurrent TB were calculated. Predictors for fatality and recurrence were identified using Cox proportional hazards modelling. Selection bias due to unreachable patients was adjusted for using inverse probability selection weighting (IPSW).

Results: Survey response rates were 56.0% in Patna and 54.6% in Mumbai. The selection bias-adjusted treatment CFR was 7.27% (5.97%, 8.49%) in Patna and 7.09% (5.99%, 8.23%) in Mumbai. The adjusted 24 month post-treatment phase CFR was 3.32% (2.36%, 4.42%) in Patna and 2.36% (1.67%, 3.04%) in Mumbai. The adjusted 24 month post-treatment phase rate of recurrent TB was 3.56% (2.54%, 4.79%) in Patna and 1.86% (1.25%, 2.46%) in Mumbai. Age was a significant predictor of treatment fatality in both cohorts (Patna – HR: 1.03 [1.02, 1.04], Mumbai – HR: 1.02 [1.02,1.03]).

Conclusions: In order to improve patient outcomes they must first be reliably measured, yet much of the Indian TB literature carries a high risk of selection bias. This work represents the first robust estimates of TB patient outcomes in the Indian private sector. PPIA-treated patients in Patna and Mumbai experienced a moderate treatment CFR but rates of recurrent TB and post-treatment CFRs were low.

3.4 Introduction

India has the largest TB epidemic in the world, accounting for 27% of cases and 38% of global deaths.[1] In line with the WHO End TB strategy[2], the Indian national tuberculosis program has paid increasing attention to the quality of TB care in the country, especially in the largely unregulated private sector. However, as highlighted in the preceding systematic review[3], a reliable estimate of a key measure of the quality of care, the case fatality ratio (CFR), remains unclear for privately treated TB patients in India. Private healthcare dominates the Indian medical sector and it's engagement is critical for ending TB in the country.

Private sector TB care in India and private provider interface agencies

Half of all Indian TB patients are treated in the private sector where quality of care is generally low.[4,5] Unlike in the public sector, there is no systematic monitoring of privately treated TB patient and very few studies have addressed case fatality among Indian private sector TB patients.[3] One solution for improved quality of care in the private sector lies in Private Provider Interface Agencies (PPIAs) which have been successfully implemented in multiple regions in India.[6] Early evidence suggests that PPIAs have been effective in increasing TB case notifications, increasing rates of TB testing, and improving treatment completion rates.[7,8]

PPIAs recognize that private physicians have little incentive to refer their patients to the public sector as this means lost income. Additionally, patients may prefer to receive treatment with their family physician, despite the freely available care in public facilities, to avoid over-crowded conditions and impersonal treatment. PPIAs provide a suite of interventions to improve patients' care, including physician training on TB, free TB diagnostics, medicines, and treatment monitoring, in a manner that aligns with private physician incentives to retain their patients.[9]

Measuring quality of TB care

Two critical measures of quality of TB care are the CFR and the rate of recurrent TB after treatment completion. At the country level, CFRs are estimated as the "number of TB deaths divided by the estimated number of incident cases in the same years" and is expressed as a percentage.[1] In cohort studies such as this work, the CFR can be exactly calculated because the number of incident cases in the cohorts is fixed by design. The End TB strategy called for a global TB CFR below 6.5% with an ideal CFR below 5%. Elevated CFRs suggest failures in the patient pathway of care such as treatment delay, diagnostics delay, incorrect treatment regimens, unaddressed comorbid conditions, or poor treatment adherence.

A TB recurrence is defined as an instance when a patient who had completed treatment is later diagnosed with another TB episode.[10] TB recurrence can occur under two scenarios: 1) when the initial treatment has failed and the patient has a relapse with the same TB strain or 2) when a patient is successfully cured only to be later re-infected. Without

molecular epidemiology studies, it is difficult to separate failure-to-cure relapse from true re-infections, though both are markers of failures in TB care.

Failure to cure is due to either ineffective treatment or loss to follow-up during treatment. Re-infections indicate that patients were cured but that the medical or social conditions such as malnutrition, HIV co-infection, and overcrowding that led to the first TB infection have not been addressed. In India, there is currently no routine long-term monitoring of TB patients for recurrence, but previous studies have estimated the recurrence rate as 10% with most recurrent episodes occurring within 6 months of treatment cessation.[11]

Loss to follow-up and selection bias

A major methodological concern when estimating patient outcomes is patient loss to follow-up.[12] Patients who are lost to follow-up may systematically differ from those retained in follow-up because they were sicker, more transient, received less social support, etc. Excluding these patients from analyses can induce selection bias and lead to inaccurate estimates. As noted in my systematic review (Chapter 2), the Indian TB literature has underutilized modern epidemiological corrections for selection bias induced by loss to follow-up.[3]

Table 3-1, Selected common approaches to missing data

Method	Description	Strengths	Limitations
Non-regression imputation	Includes mean value imputation, last value carried forward, etc.	-Simple to implement	-Ignores relationship between missing values and other variables -Can alter distribution of imputed variables
Regression imputation	A regression is used to predict missing values based on observed relationships in the data.	-Maintains relationships between other variables and imputed values	-Ignores additional uncertainty around imputed values
Multiple imputation	Multiple datasets are created with missing values imputed using regression. Results are pooled across analyses from each dataset.	-More appropriately handles uncertainty around imputed values	-More complex to implement
Inverse Probability Selection Weighting	Observed individuals are re-weighted to represent the full dataset. Theoretically equivalent to multiple imputation.	-Utilizes available baseline data. -Can inspect weights for highly influential individuals	-More complex to implement -Can be less efficient than multiple imputation
Double sampling	A random sample of missing individuals is subjected to intensive follow-up. This second sampled is re-weighted to represent all missing individuals.	-Conceptually simple	-Unrealistic assumptions about independence of loss-to-follow-up

Inverse probability selection weighting (IPSW)[13] is a causal inference based method that reweights observed patients to represent the full cohort, including unobserved patients. This method takes advantage of baseline data available on the cohort and provides straightforward-to-interpret marginal rather than conditional estimates, as compared to older epidemiological techniques such as regression-based corrections (Table 3-1).[12] It does, however, require that all variables related to the probability of response and the probability of the outcome event are included in the model used to estimate the patient weights. To investigate the robustness of my results to certain unmeasured variables not included in the IPSW model, I conduct a probabilistic bias analysis simulation study in Chapter 4.

IPSW can be less efficient than multiple imputation but it is also less opaque, allowing for inspection of the weights to identify any highly influential individuals.[13] IPSW also has advantages over non-parametric double sampling or two stage sampling methods more commonly used in econometric literature, but occasionally applied in epidemiology.[14–16] In double sampling corrections, a random sample of patients lost to follow-up is subjected to a more intensive second stage of follow-up. Based on the sampling fraction for the random sample, a weight is calculated and the patients found in the second stage sample are re-weighted to represent themselves and the lost to follow-up patients not selected for the second stage sample. While double sampling is a methodologically simple correction, it ignores available patient data and is only effective under an unrealistic set of assumptions about the independence of patient loss to follow-up.[17]

My earlier systematic review[3] estimated a treatment phase CFR among all Indian TB patients of 5.16% (4.20%, 6.34%), but too few high-quality studies were available concerning case fatality among TB patients managed in the private healthcare sector. To explore quality of care and patient outcomes in the Indian private sector, I conducted two retrospective cohort surveys in two Indian cities, Mumbai and Patna. In each city a cohort of 4,000 patients who had completed treatment for TB in the private sector through either the World Health Partners (WHP) PPIA in Patna or the PATH PPIA in Mumbai was re-contacted to assess recurrence and fatality. I estimated treatment phase and post-treatment phase CFRs as well as the rate of recurrent TB for each cohort. Additionally, I assessed patient demographics associated with the risk of fatality and recurrence using survival modelling. Loss-to-follow up was corrected for using IPSW.

3.5 Methods

Parent Studies

World Health Partners Private Provider Interface Agency - Patna

In 2013, WHP established a PPIA in Patna, Bihar, India (Figure 3-1). Between 2013 and 2020, the WHP PPIA has treated 54,538 TB patients and continues to enroll patients. This program is not a research activity – it is a service delivery program providing quality TB services to private sector patients in the city with the engagement of the local government and various partners. Private sector physicians recruited to the program are

trained on the diagnosis and treatment of TB. Patients enrolled by their physician with the PPIA are provided with vouchers for free chest X-rays, molecular diagnostics and treatment. A WHP call center provides biweekly treatment adherence monitoring calls and counselling. Patients who are not reachable by phone or who require additional counselling are visited at home by field officers. Patients diagnosed with drug-resistant TB are referred to the public sector.

At enrollment, patient contact information, date of enrollment, age and sex are recorded. The PPIA database also captures whether patients have pulmonary (PTB) or extrapulmonary TB (EPTB), whether the patient was a new or re-treatment case, and patient reported adherence to treatment.

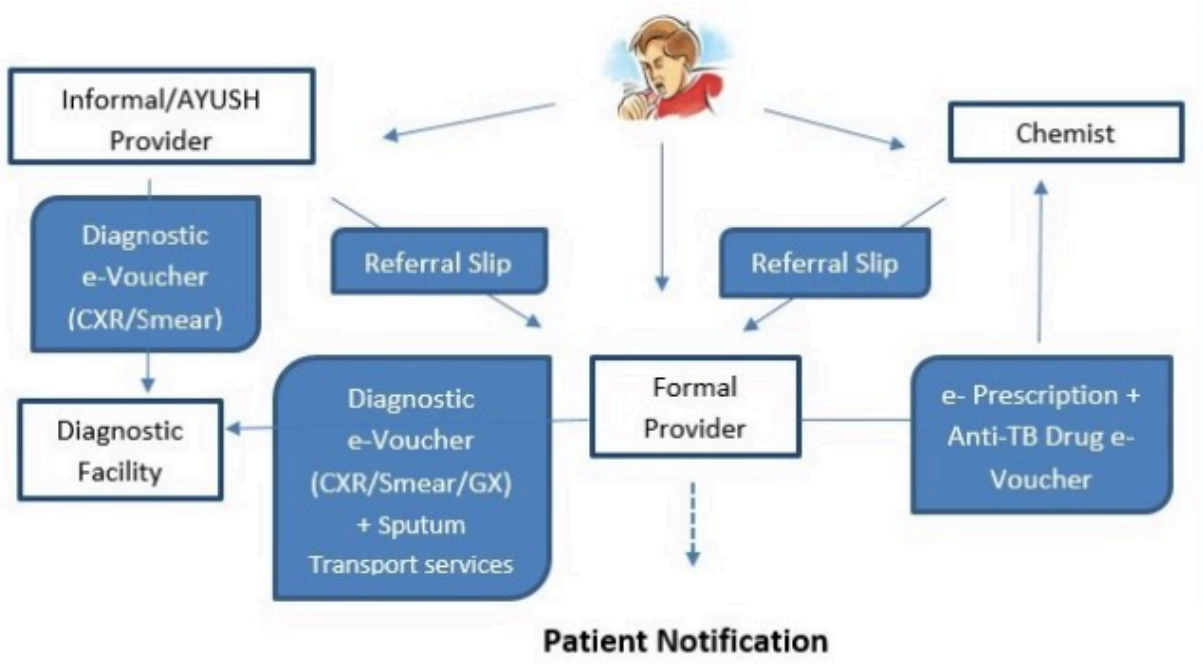

Figure 3-1, Schematic of WHP's Patna PPIA project.
Abbreviations: CXR – chest X-ray; AYUSH – Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy; GX – GeneXpert, Smear – Sputum smear test

PATH Private Provider Interface Agency - Mumbai

Between 2014 and 2017, PATH managed a PPIA in Mumbai, Maharashtra, India, treating 44,125 patients before transitioning the program to government control (Figure 3-2). This program sought to improve service delivery and was not a research activity. The provider training was similar to the WHP PPIA. The PATH PPIA also provided call center treatment monitoring. Drug-resistant patients were also referred to the public sector. At enrollment, contact information, age, and sex were recorded. The PPIA database also captured whether the patients had PTB or EPTB, whether they were clinically or microbiologically diagnosed, whether they were new, retreatment or transferred cases, and patient reported treatment adherence.

Figure 3-2, Schematic of PATH's Mumbai PPIA project.
Abbreviations: CBNAAT – cartridge based nucleic acid amplification test; FDC – fixed dose combination; RNTCP – Revised National TB Control Program, MCGM – Municipal Corporation of Greater Mumbai

The results from these cohorts are presented separately because, while the PPIA programs in each city are fairly similar, the exact interventions, incentives to providers, and target populations differ. In addition, Mumbai's public healthcare system is substantially stronger than Patna's; consequently trust in public healthcare is stronger in Mumbai. This could mean that patients seeking care in the private sector in Mumbai differ systematically from analogous patients in Patna, where many patients will preferentially seek private healthcare over the weak public healthcare system. Further, Mumbai is the epicenter of the drug-resistant TB epidemic in India. Even though both PPIAs treated only drug sensitive TB patients, drug-sensitive Mumbai patients may again represent a more selected group than drug-sensitive patients in Patna

Patient sampling and survey

A random sample of 4,000 patients was drawn from all adult patients treated by the WHP Patna PPIA (n=54,538) and from all adult patients treated by the PATH Mumbai PPIA (n=44,125). The WHP sample was drawn in July 2018 and the PATH sample was drawn in November 2019. Surveys were conducted between July 2018 and April 2019 in Patna for a maximum possible follow-up time for patients of 5 years. Surveys were conducted between November 2019 and January 2020 in Mumbai with a maximum possible follow-up time for patients of 5 years. Patients were contacted by up to three phone calls in Mumbai and Patna. For the Patna cohort, if all phone calls were unanswered, a field officer visited the address recorded at PPIA enrollment (Figure 3-3). These home visits yielded very few additional surveys and were thus not conducted in Mumbai. Patients or

their next of kin who provided oral consent were administered a short survey asking if the patient had died and/or initiated another round of TB treatment and the date of either event. Patients or their next of kin were also asked if the patient had continued treatment after the 6-9 months provided by the PPIA. Survey responses were collected on paper forms before digital data entry using EpiCollect 5 (*Oxford Big Data Institute*). Local research assistants also coded patient addresses as being "slum" or "non-slum" as a proxy for economic status.

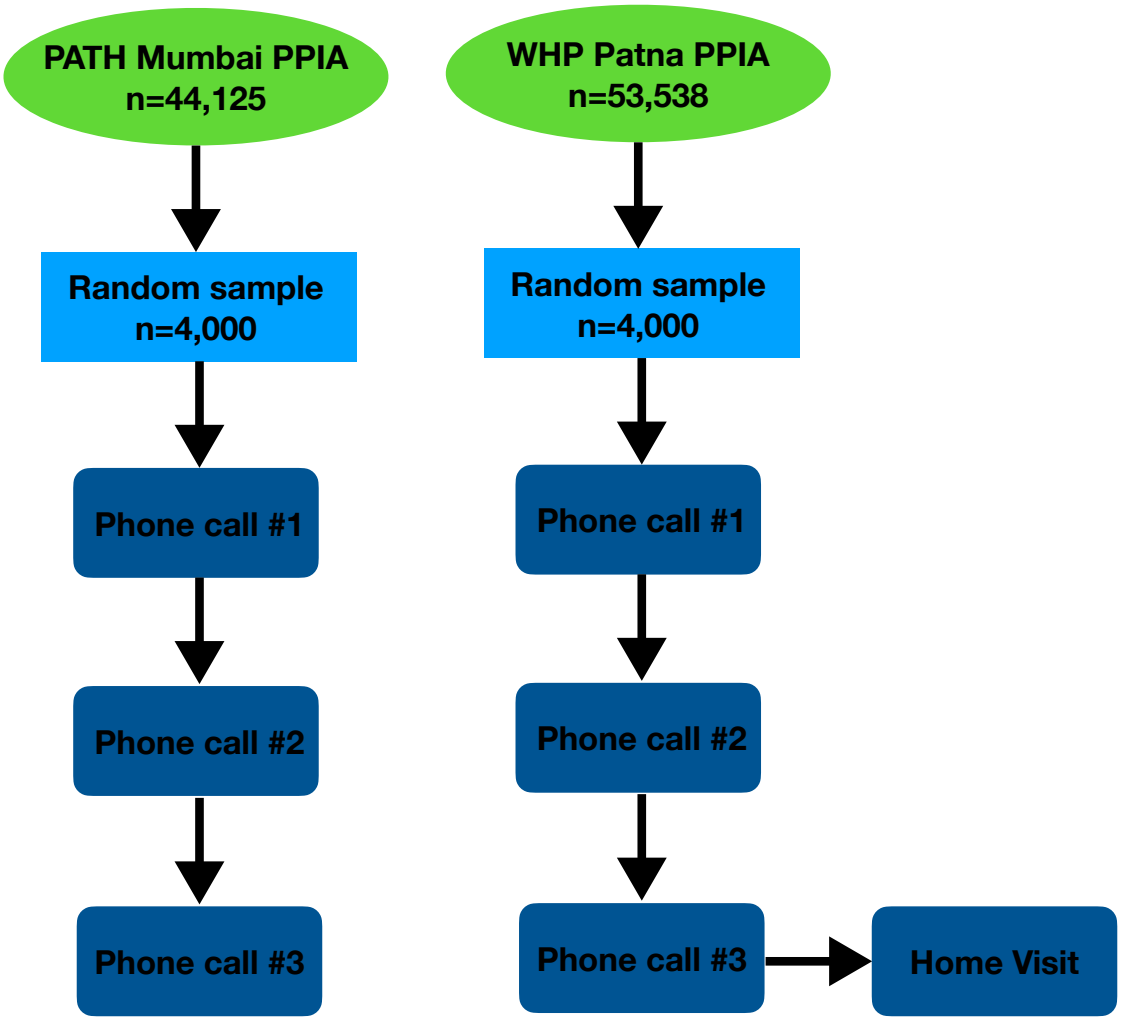

Figure 3-3, Schematic of study sampling and patient contact attempts

Definitions

We defined the treatment phase as the period between the treatment initiation month recorded at cohort entry and the database-recorded month of treatment completion unless the patient reported continuing treatment outside the PPIA program, in which case the end of the treatment phase was defined as the self-reported month of treatment cessation. We defined the post-treatment phase as the period between the end of the

treatment phase and the month that the patient completed the survey. The end of the post-treatment phase is also the point of censoring from end of follow-up. Thus, the post-treatment phase duration for each patient is variable. Patients who completed treatment earlier will have had potentially more time in the post-treatment phase before being censored at the survey date than patients who finished treatment more recently. To account for this, time spent in the post-treatment phase is accounted for in all analyses. Patients could experience fatality either during the treatment or post-treatment phase (Figure 3-4). Patients could only experience recurrence during the post-treatment phase. Patients could experience recurrence before experiencing post-treatment fatality. As only patients who responded to the survey are used our IPS weighted analysis, censoring only occurred due to end of follow-up at the time of responding to the survey.

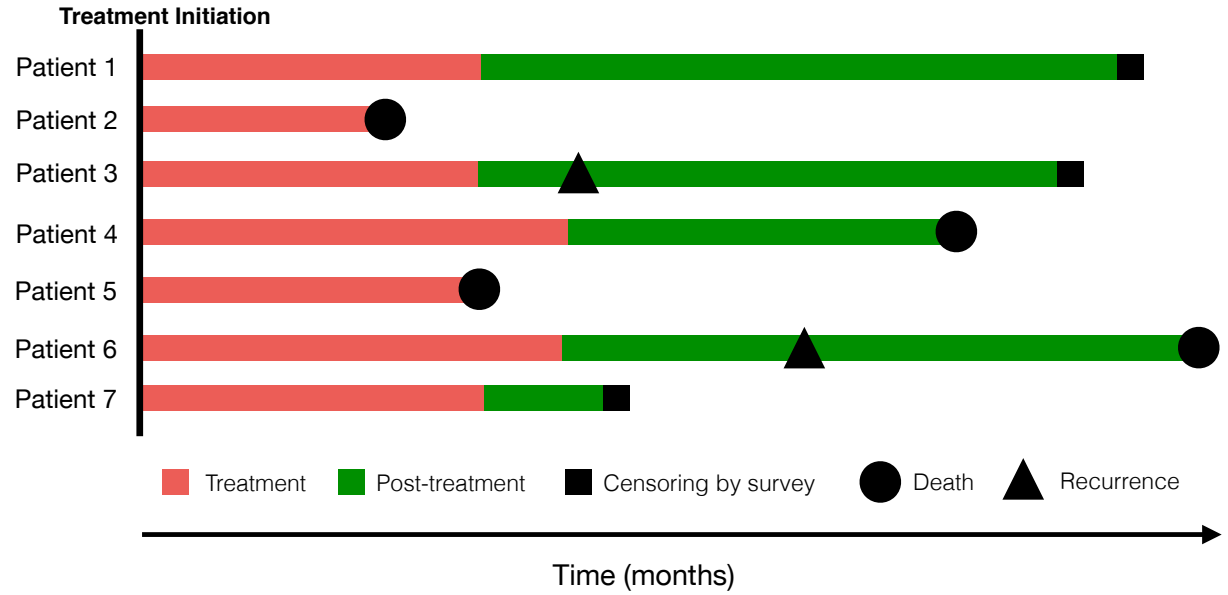

Figure 3-4, Diagram of hypothetical patient follow-up periods.
Red indicates the treatment phase, which is defined from treatment initiation to PPIA-reported or patient-reported treatment cessation, whichever is longer. Green indicates the post-treatment phase, which is defined from treatment cessation to the date of survey or fatality or recurrence.

We defined the case fatality ratio, a measure of all-cause mortality, as the proportion of patients who died from any cause during the treatment or post-treatment phase divided by the number of patients starting the relevant phase (Equation 3-1). We defined the recurrence rate as the proportion of patients in the post-treatment phase who reported initiating another round of TB treatment.

$$\text{CFR} = \frac{\text{Number of deaths from any cause during specified time period}}{\text{Number of patients in cohort at beginning of specified time period}}$$

Equation 3-1, CFR definition

In the Patna data, adherence proportion was defined as the average proportion of doses reported taken by the patient during biweekly adherence monitoring calls. In the Mumbai data, adherence proportion was defined as the proportion of monthly

medication boxes picked up by the patient. Adherence proportion was categorized in some analyses into patients who received less than one month of doses ("<1 month Adherence"), patients who received between one month and 80% of doses ("Poor Adherence"), and patients who received more than 80% of doses ("Good Adherence").

Sample size calculation

Sample size was calculated to give adequate precision to the phase-specific event rates. The same assumptions were used for each cohort.
A 4,000 patient sample assuming a 5% CFR during treatment (based on reports from the Indian national TB program[18]) and independent observations, would give a treatment CFR with a margin of error of 0.68%. Conservatively assuming that 3,000 of these patients enter the post-treatment phase, at a 5% event rate, the post-treatment CFR and recurrence proportion would have a margin of error of 0.78%.

These margins of error were deemed sufficiently precise for the meaningful estimation of the CFRs and recurrence rate.

Missing baseline data and imputation

The rate of missingness in the data collected at enrollment in both PPIA cohorts was low. In the Patna cohort, data were missing from the slum address classification (n=259, 6.5%) and in the PPIA reported treatment phase duration (n=21, 0.5%). In the Mumbai cohort, data were missing from gender (n=1, 0.03%), age (n=29, 0.7%), slum address classification (n=40, 1.0 %) and adherence proportion (n=7, 0.2%). When missingness is this low, the choice of imputation method is unlikely to substantially influence the results; thus, a single chained imputation[19] was performed. The raw demographics are summarized in Table 3-2 and Table 3-10. In all models, the imputed data were used.

Loss to follow up and inverse probability selection weighting

Despite best efforts to contact patients, some could not be reached. It is possible that patients who could not be surveyed experienced differential rates of fatality or recurrence, thus excluding nonresponsive patients from analyses would bias the resulting event rates. To correct for this selection bias, IPSW was applied.[13] This method takes advantage of the baseline demographic variables recorded at cohort entry. Demographic variables theorized to be related to the risk of fatality and/or recurrence and the probability of completing the survey were used to construct a model predicting the probability of competing the survey. This predicted probability was inverted to create a weight. By applying these selection weights, observed patients were re-weighted to represent themselves and unobserved patients allowing for selection bias-corrected analyses.

The following baseline variables were available in the Patna PPIA database and were hypothesized, based on prior research, to be related to both the likelihood of response and risk of fatality and/or recurrence: age, gender, PTB/EPTB, new/retreatment case,

slum/non-slum address, urban/rural/out-of-Patna address, PPIA reported treatment duration, treatment adherence and date of treatment initiation.[3,20–23]

The following baseline variables were available in the Mumbai PPIA database and were hypothesized to be related to both the likelihood of response and risk of fatality and/or recurrence: age, gender, PTB/EPTB, clinical/microbiological diagnosis, new/retreatment/transferred-in case, slum/non-slum address and treatment adherence.[3,20–23]

Sensitivity analysis: Truncated weights

Rare combinations of demographics among observed patients can result in large IPS weights creating highly influential patients. To assess the sensitivity of our results to outlier weights, the primary analysis was recalculated after truncating the weights to fall within the 1st and 99th percentile.

Case fatality ratios and recurrence rates

A case fatality ratio for the entire treatment phase weighted by IPSW was estimated. Case fatality ratios and recurrence rates also weighted by IPSW were calculated at 3, 6, 9, 12, 18, and 24 months in the post-treatment phase. Corresponding unweighted CFRs and recurrence rates were also estimated. All proportion confidence intervals were empirically bootstrapped one thousand times for both the weighted and un-weighted proportions. Confidence intervals were taken as the 2.5th and 97.5th percentile of the resulting proportion distribution.[24]

Survival curves and Survival modelling

Stratified Kaplan-Meir curves were created for treatment and post-treatment phase fatality and post-treatment phase TB recurrence, all weighted using IPSW.

Multivariable Cox proportional hazards models[25] were used to estimate adjusted hazard ratios (HRs) for fatality from any cause during the treatment and post-treatment phases weighted with IPSW. For the treatment phase fatality model, patients were followed from the month of treatment initiation until fatality or censoring due to treatment completion (the defined end of the treatment phase). In the post-treatment phase fatality model, patients were followed from the month of treatment completion to fatality or censoring at the survey date. The proportionality assumptions were verified using Schoenfeld residuals.[26] In the multivariable Cox proportional hazard models, treatment adherence was modelled flexibly using penalized splines[27,28] with four degrees of freedom, except in the Mumbai post-treatment phase fatality model where the spline induced convergence issues. In this model, categorical adherence groups ("<1 month adherence", "poor adherence", "good adherence") were used instead. If required to maintain proportionality, treatment phase fatality models included a time term, either linearly, as an interaction with a coefficient or using penalized splines (df=4).

As death is a competing risk for recurrence which can bias standard Cox proportional hazards models, a Fine and Gray sub-distributional hazard model[29] was estimated for post-treatment phase recurrence weighted with IPSW. In this model, patients were followed from the month of treatment completion to either 1) recurrence, 2) the competing event, fatality, or 3) censoring at the survey date. Adherence was modelled categorically ("<1 month adherence", "poor adherence", "good adherence") as the introduction of splines created convergence issues.

All models used months as the time scale. In the WHP Patna cohort, models were adjusted for gender, age, PTB/EPTB, new/retreatment case, region (Patna urban/Patna rural/out of Patna), slum/non-slum address and treatment adherence. Post-treatment models additionally adjusted for duration of treatment. In the PATH Mumbai cohort models were adjusted for gender, age, clinical/microbiological diagnosis, PTB/EPTB, new/retreatment/transferred case, slum/non-slum address and treatment adherence. Post-treatment models additionally adjusted for duration of treatment. Data on measures of disease severity or comorbid conditions were not available.

Unweighted models of identical forms are also presented for comparison.

All coefficient confidence intervals for all survival models were empirically bootstrapped one thousand times. Confidence intervals were taken as the 2.5^{th} and 97.5^{th} percentile of the resulting coefficient distribution.[30]

Ethics

Approval for secondary data analysis of this survey data was obtained from McGill University (A02-M05-18B). World Health Partners collected the patient follow-up surveys as part of their ongoing PPIA management with approval from local national tuberculosis program authorities. Approval for the PATH survey was received from the Seattle-based PATH Research Ethics committee (#1406207-02), the Delhi-based Emmanuel Hospital Association Institutional Ethics Committee (#210) and local TB program authorities.

3.6 Results from Patna

Of the 4,000 patients in the sample, 2,128 (2,128/4000, 53.2%) patients were contacted and consented to the survey. Because of linkage errors (n=28) or impossible dates (n=4), 32 (32/2128, 1.5%) patient records were discarded. Including deaths recorded in the PPIA database (n=144), 2,240 (2240/4000, 56.0%) of patients had complete records and form the observed cohort (Figure 3-5).

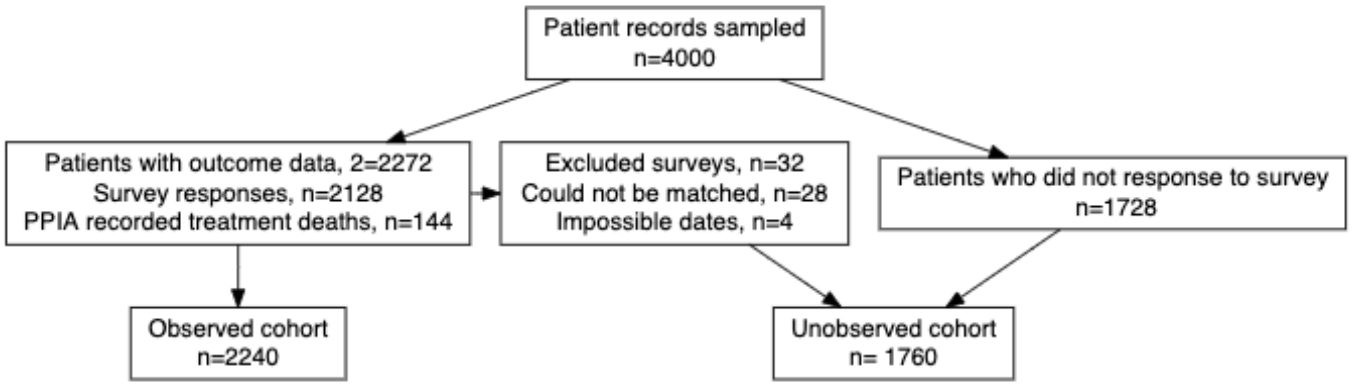

Figure 3-5, Flow chart of patient sampling and surveying.

Cohort characteristics

A summary of the baseline characteristics of the total 4,000 patient sample as well as the observed and unobserved patient subsets is presented in Table 3-2. The average age in the total patient sample was 30.4 years and 40.4% of patients were female. A third of patients had EPTB (n=1,256, 31.4%) and 10.7% were retreatment cases. Almost half of the cohort resided in a slum (n=1,800, 45.0%). Patient reported treatment adherence was low with 21.7% reporting less than a month of treatment adherence to the call center, and 46.0% reporting less than 80% of doses. Half of the cohort lived in urban Patna (n=2,023, 50.6%), 18.0% lived in rural Patna, and 31.4% resided outside of Patna city limits.

In total, 2,240 patients were included in the observed cohort (Figure 3-5). Unobserved patients were less likely to have EPTB compared to observed patients (27.6% vs. 34.4%), suggesting that unobserved patients may have experienced more severe disease. Unobserved patients were more likely to report less than one month of treatment adherence (32.0% vs. 13.5%) and more likely to live in rural Patna (21.9% vs. 15.0%).

Table 3-2, Summary of baseline cohort demographics, n=4000

	Total Cohort (n=4000)		**Observed (n=2240)**		**Unobserved (n=1760)**	
	n	**%**	**n**	**%**	**n**	**%**
Female	1615	40.4	915	40.8	700	39.8
Mean age	30.4, SD=18.8		30.8 SD=19		29.9 SD=18.5	
EPTB	1256	31.4	770	34.4	486	27.6
Retreatment	427	10.7	229	10.2	198	11.2
Resides in slum	1800	45.0	1023	45.7	777	44.1
< 1 month of treatment adherence	867	21.7	303	13.5	564	32.0
Poor adherence	1840	46.0	1016	45.4	824	46.8
Urban Patna	2023	50.6	1191	53.2	832	47.3
Rural Patna	720	18.0	335	15.0	385	21.9
Out of Patna	1257	31.4	714	31.9	543	30.9

Abbreviations: SD – standard deviation, EPTB – extrapulmonary TB

Inverse probability selection weights

The IPS weights from the selection model (Equation 3-2) had a median of 1.49 and ranged from 1.05 to 8.61. The 10th and 90th percentiles were 1.27 and 2.54 respectively, meaning there were very few highly influential patient weights (Figure 3-6). The weights produced excellent covariate balance between the observed and full cohort (

Table 3-3).

$$S \sim gender_{imp} + spline(age) + TB\ site + Case\ type + slum_{imp} + spline(adherence_{imp}) + spline(time\ since\ initiation) + spline(PPIA\ treatment\ duration) + region$$

Equation 3-2, where S is observation status, "imp" indicates imputed, TB site refers to PTB/EPTB, case type refers to new/retreatment cases, time since initiation was the number of calendar months since the patient initiated treatment and June 2019, PPIA treatment duration is the number of months of treatment recorded in the PPIA database and region refers to out of Patna/Patna urban/Patna rural . All categorical variables were modelled using dummy variables. Splines were penalized splines with df=4

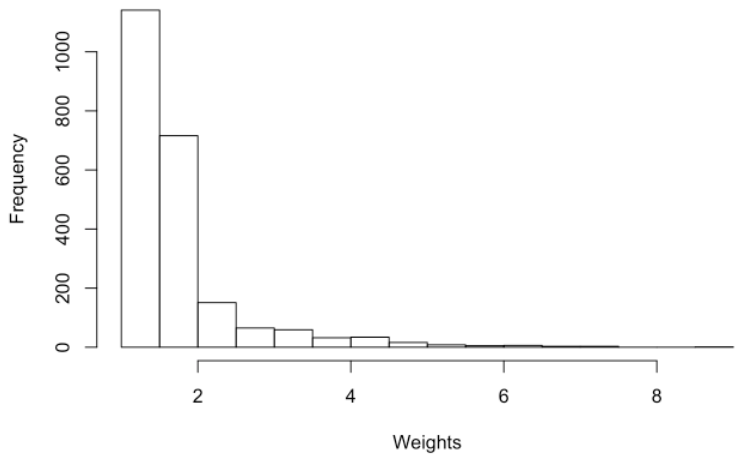

Figure 3-6, Histogram of IPS weight distribution

Table 3-3, Covariate balance between full cohort and the IPS weighted observed cohort

	Full cohort		IPS weighted observed cohort	
	Mean	**Variance**	**Mean**	**Variance**
Age	30.38	352.76	30.47	353.73
% Female	0.40	0.24	0.40	0.24
% PTB	0.69	0.22	0.68	0.22
% New	0.89	0.10	0.89	0.10
% Patna Urban	0.51	0.25	0.51	0.25
% Out of Patna	0.31	0.22	0.30	0.21
% Slum, imputed	0.48	0.25	0.48	0.25
Treatment months (PPIA reported), imputed	7.61	17.03	7.39	15.72
Average % Adherence	0.51	0.14	0.53	0.13

Treatment phase case fatality

The weighted average patient-reported treatment duration was 8.7 months (8.6 months unweighted average).

Case fatality ratio

The unweighted treatment phase CFR was 4.15% (3.56%, 4.83%) and the weighted treatment phase CFR was 7.27% (5.97%, 8.49%).

Survival curve and modelling

Case fatality occurred fairly linearly through the treatment phase (Figure 3-7). Some patients had treatment phases that outlasted the standard 6-9 month treatment duration for drug-sensitive TB as some private providers advised patients to continue treatment past what was provided for free by the PPIA. Older patients were significantly more likely to die with a hazard ratio (HR) of 1.03 (1.02, 1.04) for each additional year in age (Table 3-4). Adherence exhibited a complex relationship with the risk of fatality (Figure 3-8A).

The risk for fatality was significantly elevated around 40% adherence. The risk of fatality was significantly lowered for adherence between 70% and 90%. Paradoxically, near perfect adherence was associated with increased hazard; this may be driven by confounding by indication, where the sickest patients were more likely to be highly adherent to treatment or given more support by the care providers. The risk of fatality decreased substantially with time (Figure 3-8B).

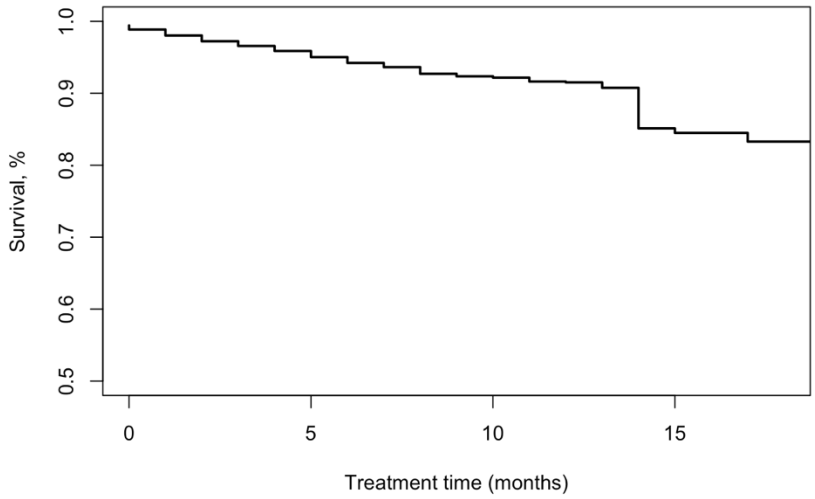

Figure 3-7, Treatment phase Kaplan-Meir survival curve weighted using IPSW.
Follow-up period begins at treatment initiation and continues until fatality or censoring by self-reported treatment completion. Treatment time refers to the months of treatment reported by the patient.

Table 3-4, Weighted and unweighted treatment phase case fatality Cox proportional hazards model hazard ratios

	Unweighted model hazard ratio (95% CI)	**Weighted model hazard ratio (95% CI)**
Male	Ref	Ref
Female	0.75 (0.54, 1.02)	0.71 (0.47, 1.05)
Age (per year)	**1.03 (1.02, 1.03)**	**1.03 (1.02, 1.04)**
New	Ref	Ref
Retreatment	1.37 (0.86, 2.14)	1.34 (0.74, 2.26)
Out of Patna	Ref	Ref
Patna Rural	0.90 (0.57, 1.33)	0.99 (0.58, 1.56)
Patna Urban	0.72 (0.51, 1.08)	0.79 (0.53, 1.15)
PTB	Ref	Ref
EPTB	0.95 (0.68, 1.31)	0.84 (0.57, 1.19)
Non-slum	Ref	Ref
Slum	0.81 (0.60, 1.07)	0.72 (0.51, 1.00)

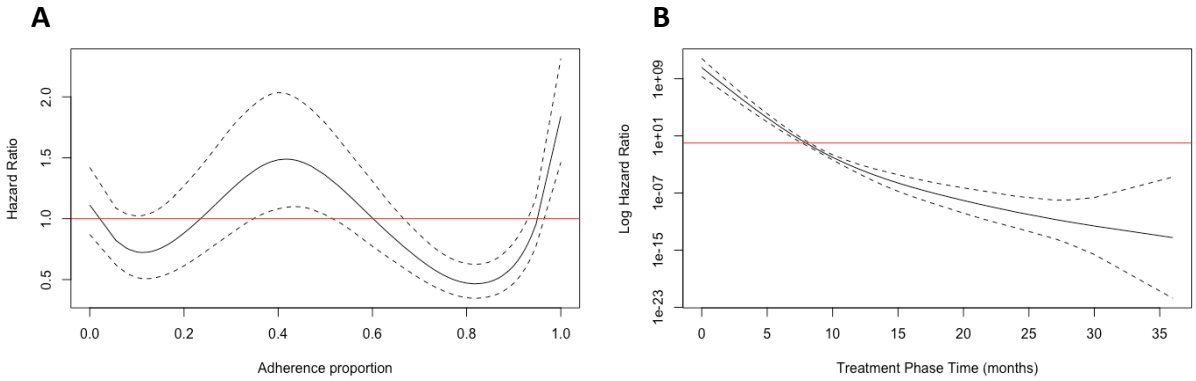

Figure 3-8, Penalized spline functions (df=4) from the treatment phase fatality model.
(A) The solid black line is the estimated hazard ratio (y-axis) for adherence proportion (x-axis) with all other variables in the model held constant. (B) The solid black line is the estimated log hazard ratio (y-axis) for treatment phase time in months (x-axis) with all other variables in the model held constant. Dashed black lines are the non-bootstrapped confidence intervals. Red lines indicate the null HR of one.

Post-treatment phase outcomes

A total of 2,078 surveyed patients entered the post-treatment phase, after weighting they represent 3,642 patients. The weighted average post-treatment phase duration was 26.4 months (25.8 months unweighted average).

Case fatality ratio

Unweighted and weighted post-treatment CFRs are available in Table 3-5. At 24 months into the post-treatment phase, the unweighted post-treatment phase CFR was 3.53% (2.59%, 4.78%) and the weighted post-treatment phase CFR was 3.32% (2.36%, 4.42%).

Table 3-5, Unweighted and weighted post-treatment CFRs.

Months post-treatment	Unweighted Post-treatment CFR % (95% CI)	Weighted Post-Treatment CFR % (95% CI)
3	0.44 (0.21, 0.86)	0.39 (0.15, 0.65)
6	0.83 (0.50, 1.35)	0.76 (0.42, 1.18)
9	1.04 (0.66, 1.62)	0.92 (0.54, 1.35)
12	1.34 (0.90, 1.99)	1.23 (0.75, 1.73)
18	2.16 (1.53, 3.03)	2.03 (1.39, 2.69)
24	3.53 (2.59, 4.78)	3.32 (2.36, 4.42)

Survival model

Post-treatment phase case fatality occurred fairly linearly throughout the post-treatment phase (S3-1).

Older patients were more likely to die during the post-treatment phase with a HR of 1.06 (1.05, 1.08) per year of age. Patients living in rural Patna were less likely to die compared to patients who lived outside city bounds (HR: 0.39, [0.11, 0.88], Table 3-6). The risk of

fatality during the post-treatment phase trended downwards with increasing treatment adherence, but the only significant increase in hazard occurred at extremely low adherence (Figure 3-9).

Table 3-6, Unweighted and weighted post-treatment phase case fatality Cox proportional hazards model hazard ratios

	Unweighted model hazard ratio (95% CI)	**Weighted model hazard ratio (95% CI)**
Male	Ref	Ref
Female	0.96 (0.49, 1.74)	0.96 (0.52, 1.79)
Age (per year)	**1.06 (1.05, 1.07)**	**1.06 (1.05, 1.08)**
New	Ref	Ref
Retreatment	1.38 (0.39, 3.07)	1.70 (0.51, 3.68)
Out of Patna	Ref	Ref
Patna Rural	**0.39 (0.10, 0.86)**	**0.39 (0.11, 0.88)**
Patna Urban	0.60 (0.33, 1.10)	0.61 (0.32, 1.14)
PTB	Ref	Ref
EPTB	0.85 (0.35, 1.61)	0.97 (0.44, 1.88)
Non-slum	Ref	Ref
Slum	1.45 (0.82, 2/73)	1.29 (0.69, 2.50)
Months of treatment	1.00 (0.92, 1.07)	0.98 (0.90, 1.05)

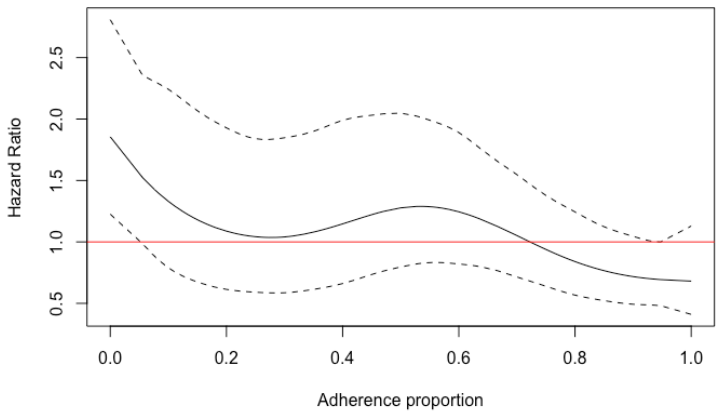

Figure 3-9, Penalized spline functions (df=4) from the post- treatment phase fatality model. The solid black line is the estimated hazard ratio (y-axis) for adherence proportion (x-axis) with all other variables in the model held constant. Dashed black lines are the non-bootstrapped confidence intervals. Red lines indicate the null HR of one.

Recurrence rate

Unweighted and weighted post-treatment recurrence rates are available in Table 3-7. At 24 months into the post-treatment phase, the unweighted post-treatment phase

recurrence rate was 3.73% (2.77%, 5.01%) and the weighted post-treatment phase recurrence rate was 3.56% (2.54%, 4.79%).

Table 3-7, Unweighted and weighted post-treatment recurrence rates

Months post-treatment	Unweighted Post-treatment recurrence rate % (95% CI)	Weighted Post-Treatment recurrence rate % (95% CI)
3	0.29 (0.12, 0.66)	0.29 (0.08, 0.55)
6	0.59 (0.32, 1.05)	0.56 (0.23, 0.91)
9	0.74 (0.43, 1.25)	0.73 (0.36, 1.14)
12	1.19 (0.77, 1.81)	1.23 (0.72, 1.80)
18	1.96 (1.37, 2.79)	1.89 (1.27, 2.62)
24	3.73 (2.77, 5.01)	3.56 (2.54, 4.79)

Recurrence survival model

The risk of a recurrent episode of TB occurred linearly throughout the post-treatment phase (S3-1). No significant associations with the risk of recurrence in the presence of death as a competing risk were found in the weighted sub-distributional hazard models (Table 3-8).

Table 3-8, Post-treatment phase recurrence Fine and Gray survival model sub-distribution hazard ratios

	Unweighted sub-distribution Hazard Ratio (95% CI)	Weighted sub-distribution Hazard Ratio (95% CI)
Male	Ref	Ref
Female	1.02 (0.63, 1.59)	1.03 (0.61, 1.67)
Age (per year)	0.99 (0.98, 1.01)	1.00 (0.99, 1.01)
New	Ref	Ref
Retreatment	1.41 (0.61, 2.54)	1.27 (0.54, 2.57)
Out of Patna	Ref	Ref
Patna Rural	1.97 (0.93, 3.83)	1.82 (0.86, 3.81)
Patna Urban	0.96 (0.62, 2.02)	0.91 (0.55, 1.57)
PTB	Ref	Ref
EPTB	0.96 (0.56, 1.68)	1.01 (0.58, 1.63)
Non-slum	Ref	Ref
Slum	0.71 (0.45, 1.10)	0.68 (0.40, 1.14)
Good Adherence (>80% of doses)	Ref	Ref
< 1 month of treatment adherence	0.86 (0.33, 1.63)	0.71 (0.23, 1.42)
Poor Adherence (<80% of doses)	1.14 (0.72, 1.89)	1.07 (0.64, 1.80)
Months of treatment	1.05 (0.97, 1.09)	1.05 (0.97, 1.10)

Truncated weights sensitivity analysis

The 1st and 99th percentile IPW weights were 1.10 and 5.19, respectively. As a sensitivity analysis, the primary outcomes were recalculated with the weights truncated to within this range (Table 3-9). The results after truncating the weights are nearly identical indicating that this analysis is not sensitive to outlier IPS weights.

Table 3-9, Comparison of primary analysis and truncated weight sensitivity analysis

Treatment Phase		Post-treatment Phase				
Full weights CFR % (95% CI)	**Truncated weights CFR % (95% CI)**	**Months post-treatment**	**Full weights CFR % (95% CI)**	**Truncated weights CFR % (95% CI)**	**Full weights recurrence rate % (95% CI)**	**Truncated weights recurrence rate % (95% CI)**
7.27 (5.97, 8.49)	7.18 (6.90, 8.40)	3	0.39 (0.15, 0.65)	0.39 (0.16, 0.67)	0.29 (0.08, 0.55)	0.29 (0.07, 0.55)
		6	0.76 (0.42, 1.18)	0.76 (0.42, 1.13)	0.56 (0.23, 0.91)	0.56 (0.26, 0.92)
		9	0.92 (0.54, 1.35)	0.93 (0.52, 1.38)	0.73 (0.36, 1.14)	0.74 (0.38, 1.16)
		12	1.23 (0.75, 1.73)	1.23 (0.75, 1.74)	1.23 (0.72, 1.80)	1.23 (0.71, 1.80)
		18	2.03 (1.39, 2.69)	2.04 (1.4, 2.77)	1.89 (1.27, 2.62)	1.90 (1.20, 2.66)
		24	3.32 (2.36, 4.42)	3.34 (2.38, 4.44)	3.56 (2.54, 4.79)	3.58 (2.52, 4.64)

3.7 Results from Mumbai

Of the 4,000 patient records sampled, 3,999 patients were eligible for inclusion (one record was excluded because the patient was less than 18 years old). A total of 2,087 (2087/3999, 52.2%) patients were surveyed. Ten surveys (10/2087, 0.4%) were excluded due to non-response in critical questions (n=8) and impossible dates (n=2). Including deaths recorded in the PPIA database (n=108), 2,184 (2184/3999, 54.6%) patients had complete records and form the observed cohort (Figure 3-10).

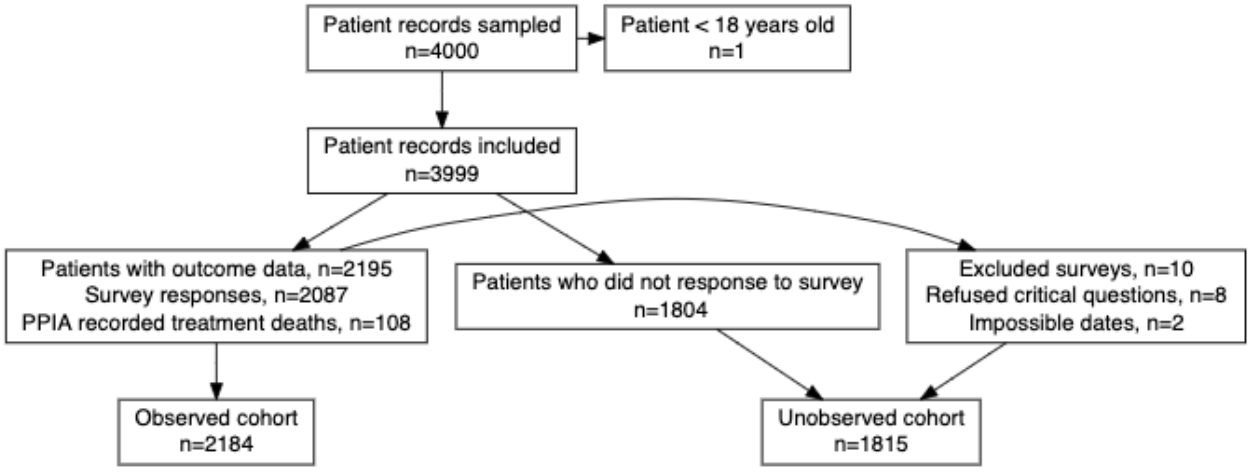

Figure 3-10, Flow chart of patient sampling and surveying

Cohort characteristics

A summary of the Mumbai patient cohort baseline demographics is presented in Table 3-10. Patients had a mean age of 34.2 years. Clinical diagnoses predominated with 29.1% (27.7%, 30.6%) of patients receiving a microbiological diagnosis and 10.3% (9.4%, 11.3%) had EPTB. Retreatment cases accounted for 12.3% (11.3%, 13.3%) of patients, while 15.0% (13.9%, 16.2%) transferred into the PPIA from treatment elsewhere. Almost two-thirds (63.8%, [61.3%,64.3%]) of patients lived in slums. Most patients reported at least some adherence to treatment with only 3.4% (2.8%, 4.0%) reporting less than one month of adherence. However, 34.4% (33.0, 35.9%) reported poor adherence, meaning fewer than 80% of doses taken.

Observed patients were more likely to be female (53.3% vs. 47.2%) and have a microbiological diagnosis (30.9% vs. 27.0%) compared to un-observed patients. Observed patients had a higher rate of EPTB (11.2% vs. 9.3%), were less likely to have transferred into the PPIA (13.2% vs. 17.2%), and less likely to live in a slum (57.5% vs. 69.3%). Rates of poor adherence were lower in the observed cohort (31.1% vs. 38.4%).

Table 3-10, Summary of baseline cohort demographics, n=4000

	Total Cohort (n=4000)		Observed (n=2184)		Unobserved (n=1815)	
	n	**%**	**n**	**%**	**n**	**%**
Female	2020	50.5	1163	53.3	857	47.2
Mean age	34.2, SD=14.7		34.7, SD=15		33.6, SD=14.3	
Microbiological Diagnosis	1165	29.1	675	30.9	490	27.0
EPTB	412	10.3	244	11.2	168	9.3
Retreatment	490	12.3	268	12.3	222	12.2
Transferred in	601	15.0	289	13.2	312	17.2
Resides in slum	2512	62.8	1255	57.5	1257	69.3
< 1 month of treatment adherence	134	3.4	71	3.3	63	3.5
Poor adherence	1377	34.4	680	31.1	697	38.4

Abbreviations: SD – standard deviation, EPTB - extrapulmonary TB

Inverse probability selection weights

The IPS weights from the selection model (Equation 3-3) had a median of 1.78 and ranged from 1.28 to 3.25. The 10th and 90th percentiles are 1.47 and 2.24 respectively, meaning there are no highly influential patient weights (Figure 3-11). The weights produced excellent covariate balance between the observed and full cohort (
Table 3-11).

$$S \sim gender_{imp} + spline(age_{imp}) + TB\ site + Case\ type + slum_{imp} + spline(adherence_{imp})$$

Equation 3-3, where S is observation status, "imp" indicates imputed, TB site refers to PTB/EPTB, and case type refers to new/retreatment/transferred cases. All categorical variables were modelled using dummy variables. Splines were penalized splines with df=4

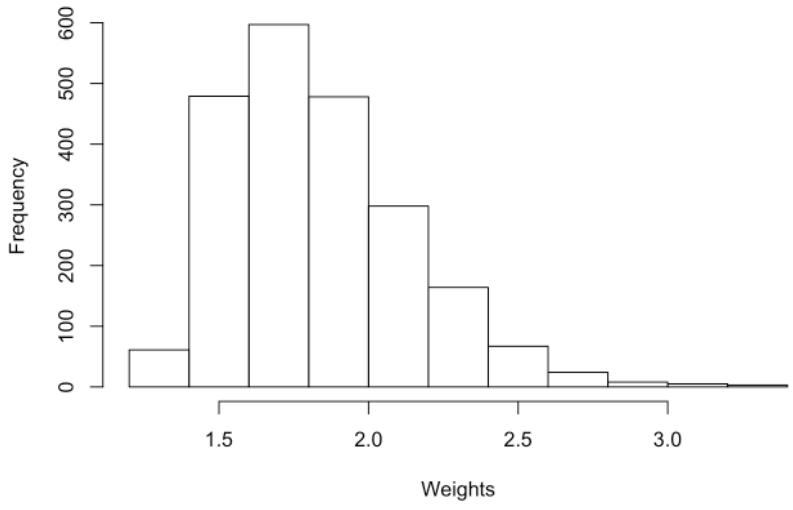

Figure 3-11, Histogram of IPS weight distribution

Table 3-11, Covariate balance between full cohort and the IPS weighted observed cohort

	Actual mean	Actual variance	Weighted mean	Weighted variance
Age	34.22	216.14	34.16	219.19
% Female	0.51	0.25	0.51	0.25
% PTB	0.90	0.09	0.90	0.09
% New	0.73	0.20	0.73	0.20
% Transferred in	0.15	0.13	0.15	0.13
% Micro Dx	0.29	0.21	0.29	0.21
% Slum	0.63	0.23	0.63	0.23
Avg % Adherence	0.74	0.04	0.74	0.04
Age	34.22	216.14	34.16	219.19

Treatment phase case fatality

The average adjusted patient reported treatment phase duration was 8.8 months (9.1 months unweighted average).

Case fatality ratio

The unweighted treatment phase CFR was 3.68% (3.12%, 4.32%) and the weighted treatment phase CFR was 7.09% (5.99%, 8.23%).

Survival curves and model

Fatality occurred linearly throughout the treatment phase (Figure 3-12).

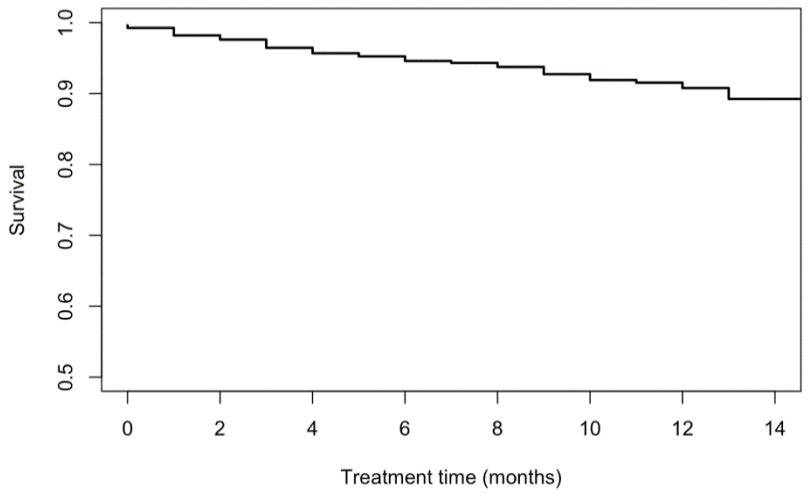

Figure 3-12, Treatment phase Kaplan-Meir survival curve weighted using IPSW.
Follow-up period begins at treatment initiation and continues until fatality or censoring by self-reported treatment completion.

Fatality during the treatment phase was significantly associated with age with an HR of 1.02 (1.02, 1.03) per year (Table 3-12). Patients with a clinical diagnosis were less likely to

die during treatment, possibly because they had been misdiagnosed and did not actually have TB (HR: 0.61, [0.45, 0.84]). Fatality also decreased significantly with time on treatment (HR: 0.09, [0.06, 0.10], per month). The penalized spline term for adherence proportion (Figure 3-13) shows a significantly elevated hazard of fatality below 80% adherence and a significantly lower hazard above this threshold.

Table 3-12, Weighted and unweighted treatment phase case fatality Cox proportional hazards model hazard ratios

	Unweighted model hazard ratio (95% CI)	**Weighted model hazard ratio (95% CI)**
Male	Ref	Ref
Female	1.27 (0.96, 1.83)	1.27 (0.94, 1.77)
Age (per year)	**1.02 (1.02, 1.03)**	**1.02 (1.02, 1.03)**
Microbiological diagnosis	Ref	Ref
Clinical Diagnosis	**0.61 (0.47, 0.86)**	**0.61 (0.45, 0.84)**
New	Ref	Ref
Retreatment	1.18 (0.74, 1.77)	1.19 (0.76, 1.78)
Transferred in	1.35 (0.79, 2.08)	1.42 (0.86, 2.16)
PTB	Ref	Ref
EPTB	0.56 (0.17, 1.05)	0.58 (0.21, 1.09)
Non-slum	Ref	Ref
Slum	1.12 (0.83, 1.56)	1.15 (0.84, 1.59)
Months of treatment	**0.09 (0.06, 0.10)**	**0.09 (0.06, 0.10)**

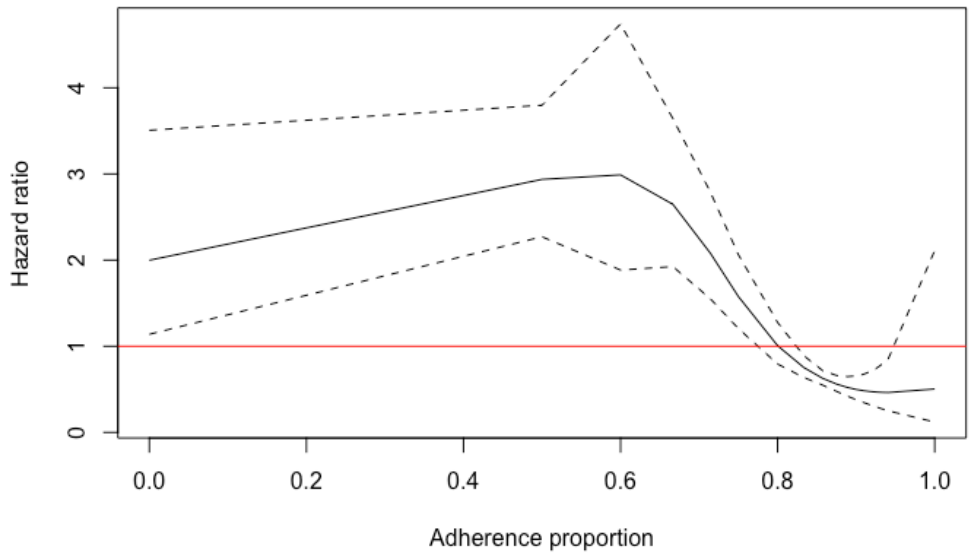

Figure 3-13, Penalized spline functions (df=4) from the treatment phase fatality model.
The solid black line is the estimated hazard ratio (y-axis) for adherence proportion (x-axis) with all other variables in the model held constant. Dashed black lines are the non-bootstrapped confidence intervals. Red lines indicate the null HR of one.Post-treatment phase outcomes.

Post-treatment phase case fatality

A total of 2,037 surveyed patients entered the post-treatment phase, after weighting they represent 3,713 patients. The weighted average post-treatment phase duration was 42.6 months (unweighted average 42.5 months).

Case fatality ratio

Unweighted and weighted post-treatment CFRs are available in Table 3-13. At 24 months into the post-treatment phase, the unweighted post-treatment phase CFR was 2.34% (1.75%, 3.13%) and the weighted post-treatment phase CFR was 2.36% (1.67%, 3.04%).

Table 3-13, Unweighted and weighted post-treatment CFRs.

Months post-treatment	Unweighted Post-treatment CFR % (95% CI)	Weighted Post-Treatment CFR % (95% CI)
3	0.59 (0.32, 1.06)	0.61 (0.27, 0.96)
6	0.98 (0.62, 1.54)	1.03 (0.58, 1.53)
9	1.38 (0.93, 2.01)	1.42 (0.96, 1.98)
12	1.62 (1.14, 2.30)	1.65 (1.10, 2.23)
18	2.07 (1.51, 2.81)	2.07 (1.48, 2.71)
24	2.34 (1.75, 3.13)	2.36 (1.67, 3.04)

Survival model

Post-treatment fatality also occurred fairly linearly throughout the post-treatment phase (S3-1). Patients who had transferred in during treatment were significantly more likely to die in the post-treatment phase compared to new TB patients (HR 2.07, [1.07, 9.59]). Patients who had less than one month of recorded adherence were more likely to die in the post-treatment phase (HR 0.11, [0.00, 0.25]) perhaps because patients who survived to post-treatment without needing to take medication had their treatment stopped due to suspicion of having an infection other than TB. Finally, every month of treatment received was associated with a protective HR of 0.87 (0.79, 0.91) (Table 3-14).

Table 3-14, Weighted and unweighted post-treatment phase case fatality Cox proportional hazards model hazard ratios

	Unweighted model hazard ratio (95% CI)	**Weighted model hazard ratio (95% CI)**
Male	Ref	Ref
Female	0.62 (0.26, 1.04)	0.59 (0.26, 1.00)
Age (per year)	0.99 (0.97, 1.04)	0.99 (0.97, 1.05)
Time (per month)	<0.00 (<0.00, <0.00)	<0.00 (<0.00, <0.00)
Age:Time (per 10 months) Interaction	1.02 (1.00, 1.03)	1.02 (1.00, 1.03)
Microbiological diagnosis	Ref	Ref
Clinical Diagnosis	0.79 (0.35, 1.29)	0.79 (0.36, 1.29)
New	Ref	Ref
Retreatment	1.65 (0.75, 3.82)	1.75 (0.75, 4.27)
Transferred in	**2.04 (1.01, 9.63)**	**2.07 (1.07, 9.59)**
PTB	Ref	Ref
EPTB	0.56 (0.00, 2.27)	0.56 (0.00, 2.27)
Non-slum	Ref	Ref
Slum	1.24 (0.73, 2.58)	1.24 (0.73, 2.58)
Good Adherence (>80% of doses)	Ref	Ref
< 1 month of treatment adherence	**0.10 (0.00, 0.26)**	**0.11 (0.00, 0.25)**
Poor Adherence (<80% of doses)	0.85 (0.44, 1.42)	0.84 (0.41, 1.35)
Months of treatment	**0.87 (0.78, 0.92)**	**0.87 (0.79, 0.91)**

Recurrence rate

Unweighted and weighted post-treatment recurrence rates are available in Table 3-15. At 24 months into the post-treatment phase, the unweighted post-treatment phase recurrence rate was 1.84% (1.31%, 2.56%) and the weighted post-treatment phase recurrence rate was 1.86% (1.25%, 2.46%).

Table 3-15, Unweighted and weighted post-treatment recurrence rates

Months post-treatment	**Unweighted Post-treatment recurrence rate % (95% CI)**	**Weighted Post-Treatment recurrence rate % (95% CI)**
3	0.35 (0.15, 0.74)	0.32 (0.09, 0.60)
6	0.40 (0.18, 0.81)	0.38 (0.14, 0.67)
9	0.70 (0.4, 1.19)	0.69 (0.35, 1.10)
12	0.80 (0.47, 1.33)	0.81 (0.43, 1.23)
18	1.31 (0.87, 1.94)	1.31 (0.80, 1.84)
24	1.84 (1.31, 2.56)	1.86 (1.25, 2.46)

Recurrence survival model

Recurrence again occurred evenly throughout the post-treatment phase (S3-1). Risk factors for recurrent TB were estimated with death as a competing risk (Table 3-16). Females were less likely to report beginning treatment for a recurrent episode (HR: 0.40, [0.21, 0.67]) as were patients who had transferred into the PPIA during treatment (HR: 0.34, (0.00, 0.89).

Table 3-16, Post-treatment phase recurrence Fine and Gray survival model sub-distribution hazard ratios

	Unweighted sub-distribution Hazard Ratio (95% CI)	**Weighted sub-distribution Hazard Ratio (95% CI)**
Male	Ref	Ref
Female	**0.41 (0.23, 0.71)**	**0.40 (0.21, 0.67)**
Age (per year)	1.00 (0.98, 1.01)	1.00 (0.98, 1.01)
Microbiological diagnosis	Ref	Ref
Clinical Diagnosis	1.42 (0.85, 2.75)	1.37 (0.77, 2.72)
New	Ref	Ref
Retreatment	1.64 (0.79, 2.91)	1.72 (0.76, 3.19)
Transferred in	**0.30 (0.00, 0.73)**	**0.34 (0.00, 0.89)**
PTB	Ref	Ref
EPTB	0.68 (0.14, 1.47)	0.60 (0.14, 1.32)
Non-slum	Ref	Ref
Slum	1.10 (0.66, 1.93)	1.11 (0.66, 2.01)
Good Adherence (>80% of doses)	Ref	Ref
< 1 month of treatment adherence	1.14 (0.00, 3.19)	0.94 (0.00, 2.79)
Poor Adherence (<80% of doses)	1.84 (1.10, 3.03)	1.90 (1.11, 3.11)
Months of treatment	1.00 (0.94, 1.05)	1.01 (0.93, 1.07)

Truncated weights sensitivity analysis

The 1st and 99th percentile IPW weights were 1.36 and 2.77 respectively. As a sensitivity analysis, the primary outcomes were recalculated with the weights truncated to within this range (Table 3-17). The results after truncating the weights are minimally changed indicating that this analysis is not sensitive to outlier IPS weights.

Table 3-17, Comparison of primary analysis and truncated weight sensitivity analysis

Treatment Phase		Post-treatment Phase				
Full Weights CFR % (95% CI)	**Truncated Weights CFR % (95% CI)**	**Months post-treatment**	**Full Weights CFR % (95% CI)**	**Truncated Weights CFR % (95% CI)**	**Full Weights recurrence rate % (95% CI)**	**Truncated Weights recurrence rate % (95% CI)**
7.09 (5.99, 8.23)	7.09 (5.96, 8.25)	3	0.61 (0.27, 0.96)	0.61 (0.30, 0.94)	0.32 (0.09, 0.60)	0.29 (0.07, 0.55)
		6	1.03 (0.58, 1.53)	1.04 (0.62, 1.50)	0.38 (0.14, 0.67)	0.56 (0.26, 0.92)
		9	1.42 (0.96, 1.98)	1.42 (0.89, 1.92)	0.69 (0.35, 1.10)	0.74 (0.38, 1.16)
		12	1.65 (1.10, 2.23)	1.66 (1.10, 2.25)	0.81 (0.43, 1.23)	1.23 (0.71, 1.80)
		18	2.07 (1.48, 2.71)	2.08 (1.50, 2.70)	1.31 (0.80, 1.84)	1.90 (1.20, 2.66)
		24	2.36 (1.67, 3.04)	2.37 (1.76, 3.08)	1.86 (1.25, 2.46)	3.58 (2.52, 4.64)

3.8 Discussion

Table 3-18, Summary of key weighted estimates for each cohort

	Patna Cohort % (95% CI)	**Mumbai Cohort** % (95% CI)
Treatment Phase CFR	7.27 (5.97, 8.49)	7.09 (5.99, 8.23)
24 month post-treatment phase CFR	3.32 (2.36, 4.42)	2.36 (1.67, 3.04)
24 month post-treatment phase recurrence rate	3.56 (2.54, 4.79)	1.86 (1.25, 2.46)
Systematic review [3] overall treatment phase CFR	5.16 (4.20 to 6.34)	

Similar patient outcomes were observed between the Patna and Mumbai cohorts. In both cohorts, the IPS weighted average patient reported treatment duration was almost nine months (Patna: 8.7 months, Mumbai: 8.8 months) as many patients continued treatment with their physician after using the 6 months provided for free by the PPIAs. In Patna, the weighted treatment phase CFR was 7.27% (5.97%, 8.49%) and in Mumbai it was 7.09% (5.99%, 8.23%). Both CFRs are nearly two-fold higher than crude unweighted CFRs (4.15% [3.56%, 4.83%] and 3.68% [3.12%, 4.32%] in Patna and Mumbai respectively) suggesting that patient loss to follow-up severely biased the crude estimates. The Patna and Mumbai weighted treatment phase CFRs are also higher than the CFR found in my Chapter 2 systematic review, again suggesting that the pooled literature estimate is biased downwards by patient loss to follow-up. Patna patients lost to follow-up were much more likely to have minimal treatment adherence and Mumbai patients lost to follow-up were much more likely to live in slums, both of which are major risk factors for poor

outcomes. The corrected CFRs are also higher than the target CFR identified in the WHO End TB Strategy.[2] Treatment phase fatality was predicted by age in both cohorts (Patna HR: 1.03 [1.02, 1.04], Mumbai HR: 1.02 [1.02, 1.03]) and was associated low treatment adherence (Figure 3-9 and Figure 3-13). In Mumbai, patients who received a clinical diagnosis compared to a microbiological diagnosis were less likely to die (HR: 0.61, [0.45, 0.84]). It may be that microbiologically confirmed patients were sicker and therefore more likely to test positive on smear stains or GeneXpert testing; it could also be that clinically diagnosed TB patients actually may not have had TB.

Our study benefited from a long post-treatment follow-up period; the average weighted post-treatment phase duration was 26.4 months in Patna and 42.6 months in Mumbai. In Patna, the CFR at 24 months into the post-treatment phase was 3.32% (2.36%, 4.42%) while it was slightly lower in Mumbai at 2.36% (1.67%, 3.04%). The difference between the weighted and unweighted post-treatment phase CFRs was less than that observed in the treatment phase CFRs. This suggests that loss to follow-up was related to risk of death during the treatment phase but that missingness in the post-treatment phase was closer to missingness at random.

Different covariates were associated with post-treatment fatality in Patna and Mumbai. In Patna, post-treatment fatality was associated with age (HR: 1.06 [1.05, 1.08]) and poor adherence (Figure 3-9). Living in rural Patna was associated with a lower hazard of post-treatment fatality (HR: 0.39 [0.11, 0.88]). In Mumbai, post-treatment fatality was associated with being a transfer case compared to a new case (HR: 2.07 [1.07, 9.59]). Increasing treatment duration was associated with a lower hazard of post-treatment fatality (HR: 0.87 [0.79, 0.91]), and, paradoxically, less than one month of treatment adherence (HR: 0.11 [0.00, 0.25]). This last result may be an artifact of the data, only 64 of 2037 (3.1%) patients in the post-treatment phase had less than one month of reported treatment adherence.

As observed with post-treatment case fatality, the 24 months recurrence rate was notably higher in Patna (3.56% [2.54%, 4.79%], than in Mumbai (1.86% [1.25%, 2.46%]). This trend of improved long term patient outcomes in Mumbai may reflect the higher average economic status in Mumbai versus Patna.[31] Very few studies have investigated post-treatment recurrence rates but previous literature estimates were as high as 10%.[11] The relatively low recurrence rates observed here suggest that the PPIA treatment regimens were effective, however any number of patients suffering a second bout of TB highlights the failure to correct socioeconomic conditions that leave patients vulnerable to TB infection. Improving food security and reducing overcrowded housing conditions are critical in addition to improving economic status. Recurrence occurred evenly throughout the post-treatment period (S3-1), suggesting that most recurrences were not a relapse, which we would expect early in the post-treatment phase.

Strengths and limitations

This work represents the largest patient outcome study of privately treated Indian TB patients to date; a group historically difficult to study because of the fragmented nature of the private healthcare sector. Additionally, this work benefits from the application of IPSW to adjust for loss to follow-up; selection bias correction methods are underutilized in the TB literature.[3] However, there are important limitations to this work. First, we could not assess cause of death through our phone surveys, meaning that our CFRs reflect all-cause mortality. The WHO defines any death that occurs during TB treatment as a TB-related death[1] but in future work it would be useful to investigate cause-specific death rates. If patient deaths were investigated prospectively, verbal autopsy[32] could be used to assign cause of death, as many Indians die at home and do not receive death certificates.[33] Other studies have suggested that TB patients are more susceptible to cardiovascular disease after treatment completion than the general population.[34] Another limitation to this work is that PPIAs likely represent the best-case scenario for treatment quality in India's largely unregulated private healthcare sector. Many patients in the private sector do not receive the standard WHO TB treatment regimen[5] or may receive substandard drugs,[35] thus the PPIA patient experience is not universal. Additionally, it is possible that some patients were treated by the same physician and that these clustered patients may have correlated data. We did not account for this clustering because provider codes were not provided in the de-identified data used for these analyses. We do not anticipate this potential clustering to meaningfully impact results as regardless of provider, each patient received the same standard drug regimen and treatment adherence monitoring. If the intra-cluster correlation within provider group was substantial, our estimated standard errors may be smaller than the true standard errors. Our study was limited to patient self-report for both treatment adherence and recurrence of TB. Patients may have felt pressure to report higher than actual treatment adherence to the call center counsellor. The ideal measure of recurrent TB would involve symptom screening and TB testing, however because of our design we were restricted to asking if patients had initiated another round of TB treatment. This definition means we may have missed patients who had begun to show TB symptoms but had not yet been diagnosed. We may also have included patients who had received medication for a disease other than TB, but erroneously reported this as a recurrent TB episode. Data on TB disease severity or comorbid conditions were not collected in the PPIA databases, thus the influence of these factors on fatality and recurrence could not be assessed.

Finally, in order for IPSW to provide unbiased weighted estimates, the probability of selection model must contain all variables that are related to the probability of response and the probability of experiencing the outcome events. There are variables known to influence the risk of TB fatality – like smoking[36], HIV status[37] and malnutrition[38] – that were not available in the PPIA database. It is possible that these variable also influenced the probability of responding to our surveys. In order to investigate the magnitude of the potential bias induced by these unmeasured variables, I conducted a probabilistic bias analysis simulation study, presented in Chapter 4.

Implications

PPIAs are an increasingly common response to ensuring even and high-quality TB care in the large Indian private healthcare sector. In Mumbai- and Patna-based PPIAs, we observed near ideal treatment phase CFRs and moderately low rates of post-treatment phase fatality and recurrence. This favorable evaluation supports the continued roll-out of PPIAs to improve private sector TB care. However, PPIAs would benefit from incorporating systematic routine quality assessment and cascade of care analysis.[39] Given that PPIAs already use call centers to provide adherence counselling, it would be straightforward to include post-treatment monitoring for long-term outcomes. Patient outcomes both during and after treatment could be monitored and reported through "dashboards" that could highlight where improvements could be made in the cascade of care.

Methodologically rigorous studies of Indian TB patient outcomes are too rare, indeed this work is the first in the literature to apply a correction for selection bias induced by loss to follow-up.[3] This correction substantially elevated the estimate for treatment phase case fatality, demonstrating that TB patient cohort studies, like most cohort studies, are susceptible to selection bias. To make accurate evaluations of TB program effectiveness, researchers and TB programs alike must account for missing data. To make the best decisions to improve patient quality of care, we must first accurately measure the current state of affairs.

Finally, this work highlights that TB patients are still at risk after their treatment ends. Up to 3% of patients had died only two years after treatment; almost 4% had started another round of TB treatment. These fatality and recurrence rates could be reduced with continuing contact with the healthcare system and efforts to improve the socioeconomic status of TB patients. Future work will include relative survival analysis comparing post-treatment TB patient fatality rates to the general population rates and verbal autopsy studies to assess causes of death.

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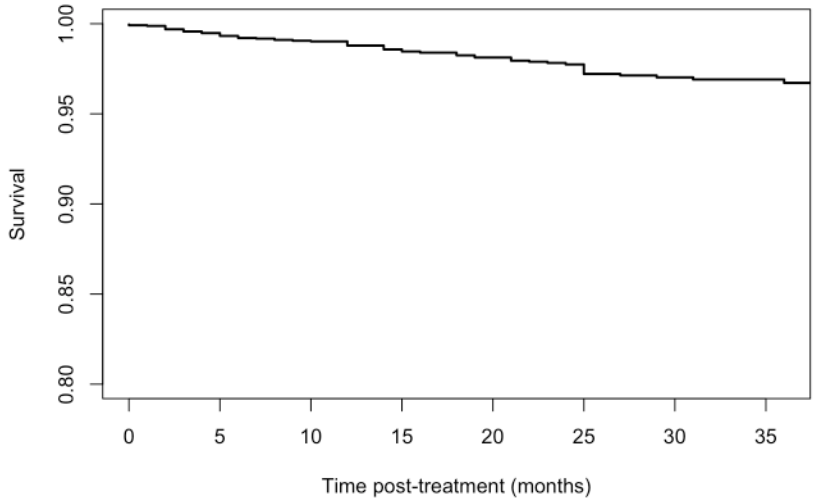
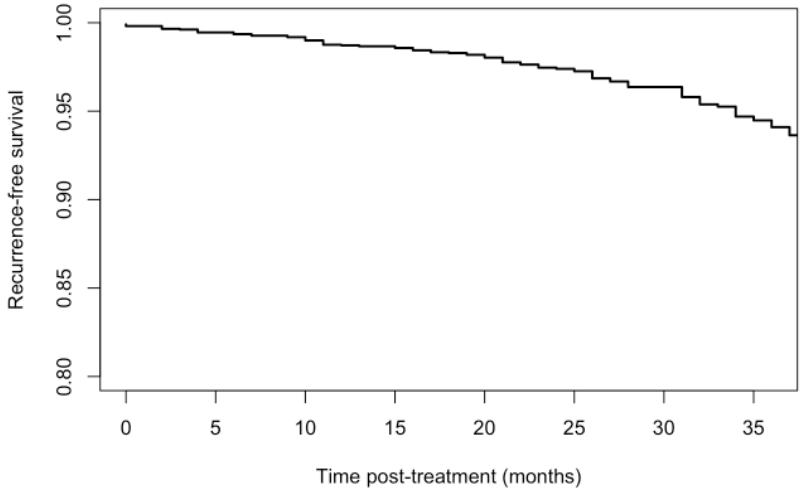
S3-1 Post-treatment phase survival curves

WHP PPIA – Patna

Survival curve

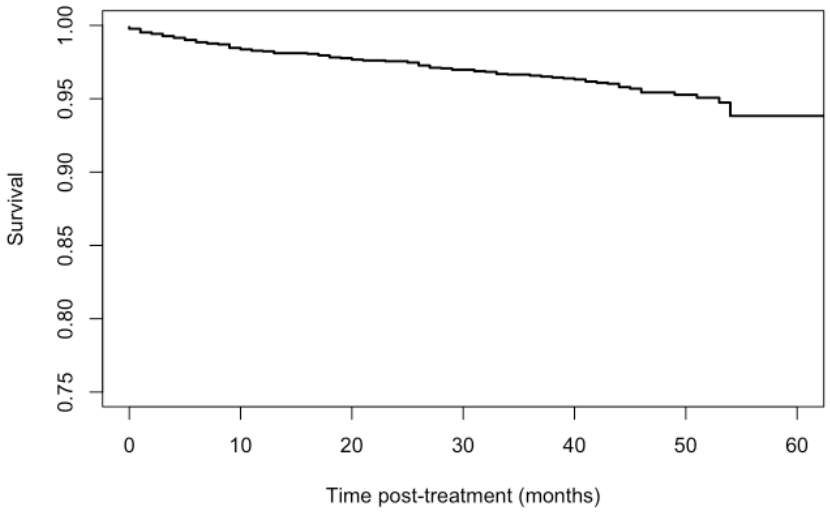


Recurrence-free survival curve

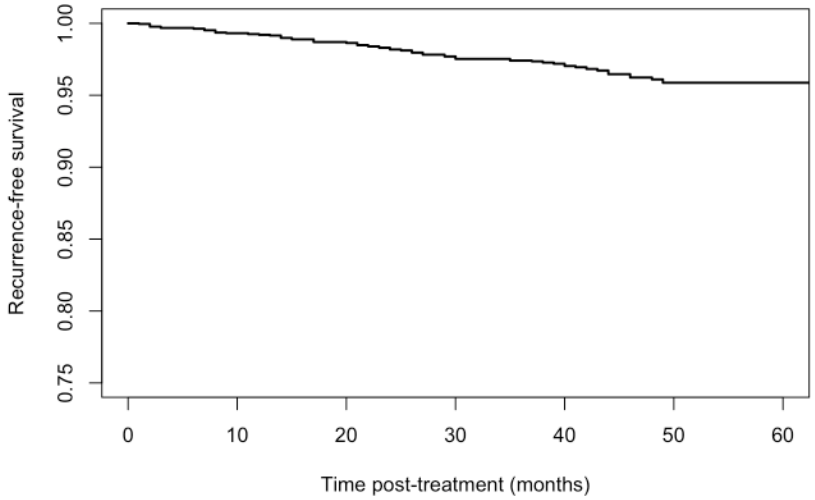


PATH PPIA – Mumbai

Survival curve



Recurrence-free survival curve



Chapter 4: Unmeasured confounding and inverse probability selection weighting in a tuberculosis patient cohort study: A probabilistic bias analysis

4.1 Preface

Inverse probability selection weighting (IPSW) is an effective correction for selection bias provided that all covariates related to both the probability of being observed and the probability of experiencing the outcome of interest are included in the observation status prediction model. Failure to do so may leave residual bias in the weighted estimates. As there are several patient variates not available in the PPIA patient database which are known to be strongly associated with TB fatality and recurrence, and which could also be related to the probability of being observed, it was possible that my IPSW-based adjustment was incomplete.

To assess the robustness of my results to unmeasured confounders of the observation-outcome relationship, I designed a probabilistic bias analysis. Using the WHP Patna cohort as a reference, I simulated a TB patient cohort of 4,000 patients and assigned them fatality, recurrence and observation statuses according to relationships observed in Chapter 3. I identified smoking, HIV and malnutrition status as potentially biasing unmeasured confounders of the observation-outcome relationship and simulated these variables in the patient cohort with levels appropriate to age, sex, and outcome strata based on literature estimates. I also simulated both weak and moderate relationships between the simulated confounders and the probability of being observed. I then compared my Chapter 3 IPSW analysis to the true values as well as to an IPSW model which contained the full set of confounders.

This work is being prepared for submission to Statistical Methods in Biomedical Research.

4.2 Title Page

Unmeasured confounding and inverse probability selection weighting in a tuberculosis patient cohort study: A probabilistic bias analysis

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4.3Abstract

Background: Unmeasured confounding of the observation-outcome relationship can result in an incomplete adjustment for selection bias when applying Inverse Probability Selection Weighting (IPSW).

Methods: A probabilistic bias analysis was conducted to establish the robustness of IPSW-corrected patient event rates in a survey of 4,000 privately treated tuberculosis (TB) patients in Patna, India. Patient outcomes and observation status were simulated based on relationships observed in the parent study. Three confounders of the observation-outcome relationship – smoking, HIV, and malnutrition status – were simulated to be related to patient demographics and patient outcomes and to have realistic age and sex specific prevalences. The confounders were also simulated to have a 1) weak and 2) moderate association with observation status in two simulation scenarios. Parameters for the relationships between variables were drawn from trapezoidal distributions within each of the 5,000 iterations in each simulation scenario. The true patient event rates were compared to the original IPSW model adjusted estimates and estimates adjusted using an IPSW model that also included the simulated confounders.

Results: The median proportions of patients observed were in line with the parent study with 54.4% observed in the weak association scenario and 51.7% observed in the moderate association scenario. Appropriate median rates of smoking, HIV and malnutrition were achieved for Indian TB patient populations at 20%, 7%, and 83% respectively. The inclusion of these simulated confounders in the IPSW model did not substantially change results with the median difference in estimates between the two IPSW models all below 0.25%.

Conclusions: In this instance, smoking, HIV and malnutrition appear unlikely to have substantially confounded the observation-outcome relationship and their addition to the IPSW model did not substantively change the resulting estimates. This is likely due to the limited variability of these confounders in Indian TB patients.

4.4 Introduction

Patient loss to follow-up is a major concern in cohort studies because of the potential for selection bias. The patients most likely to be lost may also be those most likely to experience poor outcomes, biasing event rates.[1]

Inverse probability selection weighting

Cohort studies have a unique advantage when researchers attempt to correct for selection bias: patient demographic information and other social determinants are usually collected upon enrollment in the cohort. This information can be used to "match" observed patients with those lost to follow-up using inverse probability selection weighting (IPSW)[2] to correct for potential selection bias in the resulting event rates.

IPSW is a selection bias correction method grounded in epidemiological counterfactual theory.[2] It assumes that the relationship between patient observation status and patient outcomes is confounded by some set of patient characteristics (U, Figure 4-1).These patient characteristics are used as independent variables in a logistic regression model with observation status as the dependent variable. In this manner, a probability of being observed is estimated for each patient, regardless of actual observation status. When this probability is inverted, a selection weight is created. Using these weights, the observed patients are reweighted to represent the full cohort of observed and unobserved patients. Analyses done using these weights are thus adjusted for selection bias by essentially analyzing the "full" cohort.

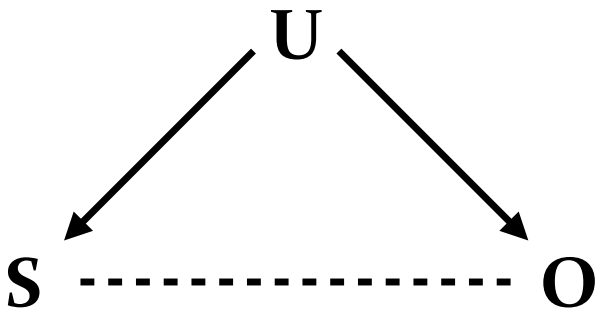

Figure 4-1, Directed Acyclic Graphic (DAG) of the confounders (U) of the observation (S) – outcome (O) relationship.

Unmeasured confounding of the observation-outcome relationship

In Chapter 3, I employed IPSW to correct for patient loss to follow-up when estimating patient case fatality and recurrence rates. The central assumption of IPSW is that all confounders of the observation-outcome relationship are available for inclusion in the observation status prediction model. Failure to include such variables (i.e. because they were not collected at cohort enrollment) could lead to residual confounding of the observation-outcome relationship and the resulting selection weights would fail to fully adjust for selection bias. As discussed in Chapter 3, it is possible that smoking, HIV and malnutrition status, which are not available in the baseline patient data, may be confounders of the observation-outcome relationship. These variables are of concern

because they are known to have a strong relationship with patient outcomes[5,8,9,10-13] and are likely to have a relationship with the probability of being observed in the survey. Patients with these comorbidities are likely sicker and poorer than patients without these comorbidities. This may make them more likely than others to change their phone number or to have it disconnected, impacting the probability of being contacted for the survey. Diabetes, another major TB comorbidity in India, is known to impact patient outcomes but because many diabetics are asymptomatic until late in the disease, it is less likely that diabetics would behave differently from non-diabetics in a way that would alter the probability of being observed in the survey.

Simulation and probabilistic bias analysis

In analyses of real world data, we cannot be certain that our estimates are equal to, or even close to, the true unknowable values. However, through simulation, we can create data where the truth is known. In this work, I simulate a dataset where some patients are observed and some are not, however, the outcomes for all patients are known regardless of observation status. In this way, I can compare analyses of observed patients (mimicking a real world analysis) to the true values.

In order to create a realistic simulation, the relationships between the simulated variables must be similar to those observed in the real world. The relationships between simulated variables are defined by a parameter or multiple parameters. Probabilistic bias analysis[3] (PBA) is a type of simulation which assumes these parameters to belong to distributions, rather than being single fixed values.[42] We refer to this type of simulation as probabilistic because within each simulation iteration, each of the parameters is drawn from its respective distribution. With each new iteration, new combinations of parameters are assigned. This probabilistic sampling creates many realistic combinations of parameters increasing the realism of simulation results. This technique has been used in bias analyses in multiple fields.[43–45]

To assess the results of Chapter 3 for robustness to unmeasured confounding of the observation-outcome relationship by smoking, HIV and malnutrition, I conducted a probabilistic bias analysis. In a hypothetical TB patient population based on the World Health Partners (WHP) Patna cohort, realistic levels of smoking, HIV and malnutrition were simulated. In two simulation scenarios, these confounders were created with either a weak or moderate association with the probability of being observed. The IPSW analysis was then repeated using a) the IPSW model used in Chapter 3 and b) the previous model with additional terms for smoking, HIV and malnutrition status. The patient outcome rates estimated using the two IPSW models were compared to each other and the true values to assess the potential magnitude of the bias introduced by unmeasured confounding of the observation-outcome relationship in the primary analysis.

4.5 Methods

Primary analysis

This bias analysis seeks to estimate the robustness of key results from Chapter 3: the treatment phase case fatality rate (CFR), the six month post-treatment phase CFR, and the six month post-treatment phase recurrence rate. In brief, the primary analysis examined two cohorts of 4,000 Indian TB patients treated in the private sector in Patna and Mumbai, India through Private Provider Interface Agencies (PPIAs). These cohorts were surveyed up to five years after initiating TB treatment in order to estimate the treatment phase case fatality ratio, post-treatment case fatality ratios and recurrence rates. Patient loss to follow-up was adjusted for using IPSW. Because the results from the Patna WHP and Mumbai PATH cohorts were similar as were the patient cohorts, I have arbitrarily chosen the Patna WHP patient cohort to use as the reference population for this bias analysis. The demographic and treatment phase data from the n=4,000 patient World Health Partners Patna cohort was used to create a reference population used in the current simulation. Imputed variables were taken to ensure a complete base of data.

Simulation

Two simulation scenarios were conducted. The first assumed a weak relationship between the simulated confounders and the probability of being observed (i.e. successfully contacted and consented to participate). In the second scenario a moderate relationship was assumed. For each scenario, 5,000 iterations were run. Within each simulation iteration, 4,000 patients were drawn with replacement from the reference population and this sample was used as the patient cohort for that iteration.

Simulation overview

The demographics of the iteration-specific patient cohort, D_{obs}, were used as the starting point for the simulation (Figure 4-2). The first step taken was to simulate patient outcomes, O_{sim}, based on relationships observed between patient demographics and outcomes observed in Chapter 3. Second, the unmeasured confounders, U_{sim}, of the observation-outcome relationship were simulated based on literature estimates of their relationship to patient demographics and outcomes. Third, patient observation status, S_{sim}, was simulated in relation to patient demographics, using relationships observed in Chapter 3, and in relation to the unmeasured confounders, using simulation scenario assumptions. Details of each simulation step are described in the following sections.

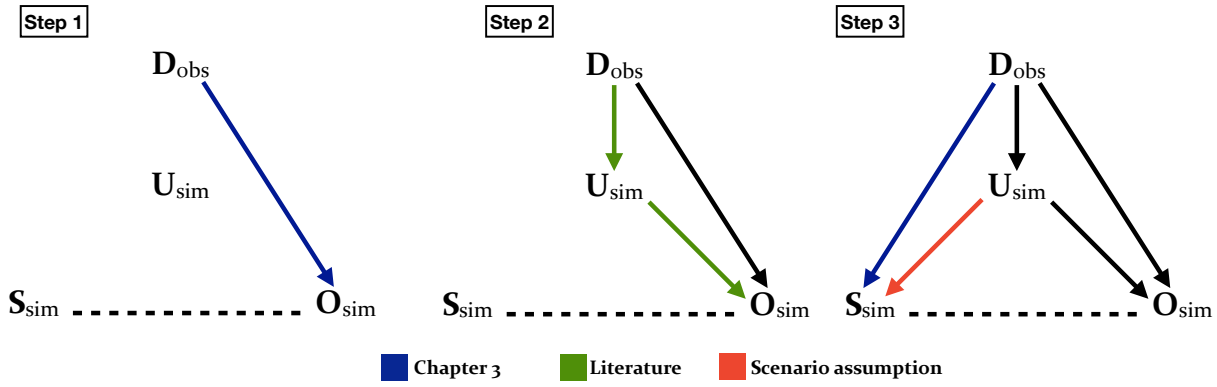

Figure 4-2, Diagrammatic overview of the simulation
Relationships were based on those observed in Chapter 3 (blue), the literature (green) and scenario assumptions (red). D_{obs} – Patient demographic data taken from the iteration specific cohort drawn from the reference population. U_{sim} – simulated unmeasured confounders of the observation-outcome relationship: smoking, HIV and malnutrition status. O_{sim} – simulated patient outcomes: treatment phase fatality, 6 month post-treatment phase fatality, and 6 month post-treatment phase recurrence. S_{sim} – simulated observation status.

Step 1: simulating patient outcomes

I simulated binary outcomes for treatment phase case fatality, six month post-treatment phase case fatality and six month post-treatment phase recurrence. To predict these binary outcomes, a logistic equation was constructed relating patient characteristics to a probability of experiencing a given patient outcome, based on relationships observed in the analysis of the Patna WHP cohort. The form of the patient outcome predictions equations were as follows:

$$logit\,(P_{Trt\ death}) = \beta_{baseline} + \beta_{female}X_{female} + \beta_{age}X_{age} + \beta_{retrt}X_{retrt} + \beta_{rural}X_{rural} + \beta_{urban}X_{urban} + \beta_{EPTB}X_{EPTB} + \beta_{poor\ adh}X_{poor\ adh} + \beta_{<1\ mo.\ adh}X_{<1\ mo.\ adh} + \beta_{slum}X_{slum}$$

*Equation 4-1, Prediction equation for treatment phase death ($P_{Trt\ death}$), where **X** are patient variables and β are iteration specific model coefficients drawn from the distributions described in Table 6-1. Age is a linear term. "Retrt" refers to retreatment cases (vs. new cases). Patients had either rural, urban or outside of Patna (reference value) addresses. "EPTB" refers to extrapulmonary TB cases (vs. pulmonary TB cases). "Poor adh" refers to poor adherence, defined as between 1 month and 80% of doses, "<1 mo. adh" refers to patients who had less than one month of adherence, good adherence, defined as >80% of doses was the reference value. Patients with non-slum addresses were the reference value for the slum coefficient.*

$$logit\,(P_{Ptrt\ death}) = \beta_{baseline} + \beta_{female}X_{female} + \beta_{age}X_{age} + \beta_{retrt}X_{retrt} + \beta_{rural}X_{rural} + \beta_{urban}X_{urban} + \beta_{EPTB}X_{EPTB} + \beta_{poor\ adh}X_{poor\ adh} + \beta_{<1\ mo.\ adh}X_{<1\ mo.\ adh} + \beta_{slum}X_{slum} + \beta_{Trt\ months}X_{Trt\ months}$$

*Equation 4-2, Prediction equation for post- treatment phase death ($P_{Ptrt\ death}$), where **X** are patient variables and β are iteration specific model coefficients drawn from the distributions described in Table 6-1. Age is a linear term. "Retrt" refers to retreatment cases (vs. new cases). Patients had either rural, urban or outside of Patna (reference value) addresses. "EPTB" refers to extrapulmonary TB cases (vs. pulmonary TB cases). "Poor adh" refers to poor adherence, defined as between 1 month and 80% of doses, "<1 mo. adh" refers to patients who had less than one month of adherence, good adherence, defined as >80% of doses was the reference value. Patients with non-slum addresses were the reference value for the slum coefficient. "Trt months" refers to the duration of the patients treatment phase and was modeled linearly.*

$$logit\,(P_{Rec}) = \beta_{baseline} + \beta_{female}X_{female} + \beta_{age}X_{age} + \beta_{retrt}X_{retrt} + \beta_{rural}X_{rural} + \beta_{urban}X_{urban} + \beta_{EPTB}X_{EPTB} + \beta_{poor\ adh}X_{poor\ adh} + \beta_{<1\ mo.\ adh}X_{<1\ mo.\ adh} + \beta_{slum}X_{slum} + \beta_{Trt\ months}X_{Trt\ months}$$

*Equation 4-3, Prediction equation for post- treatment phase recurrence (P_{Rec}), where **X** are patient variables and β are iteration specific model coefficients drawn from the distributions described in Table 6-1. Age is a linear term. "Retrt" refers to retreatment cases (vs. new cases). Patients had either rural, urban or outside of Patna (reference value) addresses. "EPTB" refers to extrapulmonary TB cases (vs. pulmonary TB cases). "Poor adh" refers to poor adherence, defined as between 1 month and 80% of doses, "<1 mo. adh" refers to patients who had less than one month of adherence, good adherence, defined as >80% of doses was the reference value. Patients with non-slum addresses were the reference value for the slum coefficient. "Trt months" refers to the duration of the patients treatment phase and was modeled linearly.*

The odds ratios (ORs) for the prediction equations were drawn within each simulation iteration from trapezoidal distributions based on the ORs and their confidence intervals (CIs) from models of the same form as Equation 4-1, Equation 4-2, and Equation 4-3 run on the original WHP Patna cohort weighted with the Chapter 3 IPS weights.

The lower limit of the trapezoidal distribution was defined as the lower confidence interval (CI) value minus half the margin of error (MOE, half the width of the confidence interval[†]). The first and second modes were the lower and upper CI values and the upper limit of the distribution was defined by the upper CI value plus half the MOE. For the intercept term, a similar distribution was constructed around the baseline odds value. The OR distributions are described in Table 4-1. The natural log of the OR (or baseline odds for the intercept) was used as the coefficient in the prediction equations above.

[†] The confidence intervals calculated here are Wald intervals which are not perfectly symmetric on the OR scale, thus the difference of the central estimate and the lower confidence interval limit was taken as the MOE.

Table 4-1, Distributions for OR draws for patient outcome prediction models

	Term	Distribution	OR scale distribution parameters	Reference
Treatment phase death prediction equation	$\beta_{baseline}$	Trapezoidal	(0.01, 0.02, 0.04, 0.05)	Chapter 3
	β_{female}	Trapezoidal	(0.47, 0.56, 0.96, 1.04	
	β_{age}	Trapezoidal	(1.02, 1.03, 1.04, 1.04)	
	β_{retrt}	Trapezoidal	(0.65, 0.84, 1.76, 1.94)	
	β_{rural}	Trapezoidal	(0.70, 0.88, 1.75, 1.93)	
	β_{urban}	Trapezoidal	(0.43, 0.53, 0.97, 1.07)	
	β_{EPTB}	Trapezoidal	(0.51, 0.62, 1.13, 1.24)	
	$\beta_{poor\ adh}$	Trapezoidal	(0.57, 0.70, 1.33, 1.47)	
	$\beta_{<1\ mo.\ adh}$	Trapezoidal	(1.53, 1.89, 3.58, 3.94)	
	β_{slum}	Trapezoidal	(0.45, 0.53, 0.88, 0.96)	
Post-treatment phase death prediction equation	$\beta_{baseline}$	Trapezoidal	(0.00, 0.00, 0.01, 0.01)	
	β_{female}	Trapezoidal	(0.15, 0.40, 2.04, 2.30)	
	β_{age}	Trapezoidal	(1.03, 1.04, 1.08, 1.09)	
	β_{retrt}	Trapezoidal	(0.00, 0.49, 4.40, 4.89)	
	β_{rural}	Trapezoidal	(0.00, 0.03, 0.94, 1.01)	
	β_{urban}	Trapezoidal	(0.10, 0.29, 1.52, 1.71)	
	β_{EPTB}	Trapezoidal	(0.13, 0.45, 2.63, 2.95)	
	$\beta_{poor\ adh}$	Trapezoidal	(0.09, 0.34, 2.08, 2.33)	
	$\beta_{<1\ mo.\ adh}$	Trapezoidal	(0.05, 0.46, 3.59, 4.00)	
	β_{slum}	Trapezoidal	(0.29, 0.69, 3.28, 3.69)	
	$\beta_{Trt\ months}$	Trapezoidal	(0.81, 0.85, 1.03, 1.08)	
Recurrence prediction equation	$\beta_{baseline}$	Trapezoidal	(0.00, 0.00, 0.03, 0.03)	
	β_{female}	Trapezoidal	(0.12, 0.47, 2.90, 3.25)	
	β_{age}	Trapezoidal	(0.97, 0.98, 1.03, 1.04)	
	β_{retrt}	Trapezoidal	(0.00, 0.00, 10.0, 10.0)	
	β_{rural}	Trapezoidal	(0.02, 0.55, 4.72, 5.25)	
	β_{urban}	Trapezoidal	(0.00, 0.16, 1.48, 1.64)	
	β_{EPTB}	Trapezoidal	(0.20, 0.82, 5.15, 5.76)	
	$\beta_{poor\ adh}$	Trapezoidal	(0.00, 0.72, 7.11, 7.88)	
	$\beta_{<1\ mo.\ adh}$	Trapezoidal	(0.00, 0.24, 5.50, 5.96)	
	β_{slum}	Trapezoidal	(0.10, 0.35, 2.10, 2.35)	
	$\beta_{Trt\ months}$	Trapezoidal	(0.80, 0.85, 1.07, 1.12)	

Using these equations with iteration-specific coefficients, a probability of experiencing a given patient outcome was predicted. Individual patient outcome status was then drawn from a binomial distribution defined by the patients' assigned probability of experiencing the outcome. Post-treatment phase outcomes were only predicted for patients who had been simulated to have survived the treatment phase.

Step 2: simulating unmeasured confounders

Smoking, HIV and malnutrition status were simulated such that they were related both to patient characteristics and outcomes. These relationships were based on literature estimates.[6-13] Whenever possible, literature estimates from Indian tuberculosis patients were used. However, if relevant studies on Indian TB patients were not available, data from the Indian general population or non-Indian TB patients were used. Smoking, HIV and malnutrition were simulated independently from each other as creating joint distributions would dramatically increase simulation complexity. Linear equations were again constructed to assign probabilities of confounder status. The form of the confounder prediction equations were as follows:

$$logit\,(P_{smo}) = \beta_{baseline} + \beta_{male} + \beta_{gender_j age_k} X_{gender_j age_k} + \beta_{trt\ death} X_{trt\ death} + \beta_{ptrt\ death_j} X_{ptrt\ death_j} + \beta_{rec} X_{rec}$$

$$j \in \{male, female\}, k \in \{[20,25), [25,30), \ldots, [60,65), [65,\infty)\}$$

*Equation 4-4, Prediction equation for current smoker status (P_{smo}), where **X** are patient variables and β are iteration specific model coefficients drawn from the distributions described in Table 6-2. "Trt death" refers to treatment phase death, "ptrt death" refers to post-treatment phase death, and "rec" refers to post-treatment phase recurrence.*

$$logit\,(P_{HIV}) = \beta_{baseline} + \beta_{Male} X_{Male} + \beta_{15 \le age < 45} X_{15 \le age < 45} + \beta_{trt\ death} X_{trt\ death} + \beta_{ptrt\ death} X_{ptrt\ death} + \beta_{rec} X_{rec}$$

*Equation 4-5, Prediction equation for HIV status (P_{HIV}), where **X** are patient variables and β are iteration specific model coefficients drawn from the distributions described in Table 6-2. "Trt death" refers to treatment phase death, "ptrt death" refers to post-treatment phase death, and "rec" refers to post-treatment phase recurrence.*

$$logit\,(P_{mal}) = \beta_{baseline} + \beta_{Male} X_{Male} + \beta_{age \ge 25} X_{age \ge 25} + \beta_{trt\ death} X_{trt\ death} + \beta_{ptrt\ death} X_{ptrt\ death} + \beta_{rec} X_{rec}$$

*Equation 4-6, Prediction equation for malnutrition status (P_{mal}), where **X** are patient variables and β are iteration specific model coefficients drawn from the distributions described in Table 6-2. "Trt death" refers to treatment phase death, "ptrt death" refers to post-treatment phase death, and "rec" refers to post-treatment phase recurrence.*

ORs were drawn within each simulation iteration from trapezoidal distributions constructed as described previously, and the natural log of these values were used as the coefficient in the confounder prediction equations. Baseline odds were drawn from

uniform distributions constructed based on literature prevalences and calibrated to ensure realistic confounder prevalences. The log baseline odds were used as the intercept in the prediction equation. The coefficient distributions and their sources are described in Table 4-2. Confounder status for each patient was drawn from a binomial distribution centered on their predicted probability.

Table 4-2, Distributions for OR draws for confounder prediction models

	Term	Distribution	OR scale distribution parameters	Reference
Smoking prediction equation	$\beta_{baseline}$	Uniform	(0.0005, 0.007)	4
	β_{male}	Trapezoidal	(0.00, 4.50, 44.04, 48.83)	
	$\beta_{male,20-25}$	Trapezoidal	(0.06, 0.82, 6.70, 7.46)	5
	$\beta_{male,25-30}$	Trapezoidal	(0.30, 1.82, 12.93, 14.44)	
	$\beta_{male,30-35}$	Trapezoidal	(0.50, 2.61, 17.94, 20.06)	
	$\beta_{male,35-40}$	Trapezoidal	(0.73, 3.57, 23.99, 26.83)	
	$\beta_{male,40-45}$	Trapezoidal	(0.76, 3.73, 25.03, 28.00)	
	$\beta_{male,45-50}$	Trapezoidal	(0.80, 3.90, 26.11, 29.21)	
	$\beta_{male,50-55}$	Trapezoidal	(0.93, 4.44, 29.57, 33.07)	
	$\beta_{male,55-60}$	Trapezoidal	(0.89, 4.25, 28.38, 31.74)	
	$\beta_{male,60-65}$	Trapezoidal	(0.89, 4.25, 28.38, 31.74)	
	$\beta_{male,65+}$	Trapezoidal	(0.73, 3.57, 23.99, 26.83)	
	$\beta_{female,20-25}$	Trapezoidal	(0.00, 0.10, 9.78, 10.23)	
	$\beta_{female,25-30}$	Trapezoidal	(0.00, 0.16, 11.34, 11.93)	
	$\beta_{female,30-35}$	Trapezoidal	(0.00, 0.28, 14.71, 15.58)	
	$\beta_{female,35-40}$	Trapezoidal	(0.00, 0.22, 12.99, 13.73)	
	$\beta_{female,40-45}$	Trapezoidal	(0.00, 0.34, 16.46, 17.48)	
	$\beta_{female,45-50}$	Trapezoidal	(0.00, 0.41, 18.25, 19.41)	
	$\beta_{female,50-55}$	Trapezoidal	(0.00, 0.34, 16.46, 17.48)	
	$\beta_{female,55-60}$	Trapezoidal	(0.00, 0.55, 21.9, 23.35)	
	$\beta_{female,60-65}$	Trapezoidal	(0.00, 0.69, 25.65, 27.4)	
	$\beta_{female,65+}$	Trapezoidal	(0.00, 0.61, 23.76, 25.36)	
	$\beta_{trt\ death}$	Trapezoidal	(0.13, 0.88, 6.44, 7.19)	8
	$\beta_{ptrt\ death,male}$	Trapezoidal	(0.76, 1.24, 3.93, 4.41)	5
	$\beta_{ptrt\ death,female}$	Trapezoidal	(0.00, 0.71, 7.98, 8.81)	
	β_{rec}	Trapezoidal	(0.59, 1.17, 4.66, 5.24)	9
HIV prediction equation	$\beta_{baseline}$	Uniform	(0.00001, 0.005)	6
	β_{male}	Trapezoidal	(0.00, 0.85, 11.46, 12.6)	
	$\beta_{15\leq age<45}$	Trapezoidal	(0.00, 0.21, 13.17, 13.9)	
	$\beta_{trt\ death}$	Trapezoidal	(0.00, 1.57, 34.32, 37.21)	10
	$\beta_{ptrt\ death}$	Trapezoidal	(0.00, 0.39, 378.56, 384.44)	
	β_{rec}	Trapezoidal	(0.00, 3.64, 56.52, 61.87)	11
Malnutrition prediction equation	$\beta_{baseline}$	Uniform	(0.85, 1.00)	7
	β_{male}	Trapezoidal	(0.25, 0.33, 0.73, 0.81)	7
	$\beta_{age\geq 25}$	Trapezoidal	(0.25, 0.29, 0.47, 0.51)	
	$\beta_{trt\ death}$	Trapezoidal	(0.00, 1.26, 26.98, 29.27)	12
	$\beta_{ptrt\ death}$	Trapezoidal	(0.00, 0.32, 6.75, 7.32)	*
	β_{rec}	Trapezoidal	(0.89, 1.16, 2.49, 2.76)	13

Step 3: simulating observation status

Observation status was simulated such that it was related to patient characteristics and the simulated confounders. Observation status was not simulated with an explicit relationship to patient outcomes but because both observation status and patient outcomes are related to patient characteristics, an association between observation status and patient outcomes did exist. The observation status and patient characteristic relationships were based on those observed in the primary analysis. The form of the observation status prediction equation is as follows:

$$logit\,(P_{Obs}) = \beta_{baseline} + \beta_{female}X_{female} + \beta_{age}X_{age} + \beta_{retrt}X_{retrt} + \beta_{rural}X_{rural} + \beta_{urban}X_{urban} + \beta_{EPTB}X_{EPTB} + \beta_{poor\ adh}X_{poor\ adh} + \beta_{<1\ mo.\ adh}X_{<1\ mo.\ adh} + \beta_{slum}X_{slum} + \beta_{smo}X_{smo} + \beta_{HIV}X_{HIV} + \beta_{mal}X_{mal}$$

*Equation 4-7, Prediction equation for observation status (P_{Obs}), where **X** are patient variables and β are iteration specific model coefficients drawn from the distributions described in Table 6-3. Age is a linear term. "Retrt" refers to retreatment cases (vs. new cases). Patients had either rural, urban or outside of Patna (reference value) addresses. "EPTB" refers to extrapulmonary TB cases (vs. pulmonary TB cases). "Poor adh" refers to poor adherence, defined as between 1 month and 80% of doses, "<1 mo. adh" refers to patients who had less than one month of adherence, good adherence, defined as >80% of doses was the reference value. Patients with non-slum addresses were the reference value for the slum coefficient. "smo" refers to current smoker status, "HIV" refers to HIV status and "mal" refers to malnutrition status.*

Again, the ORs for this prediction equations were drawn within each simulation iteration from trapezoidal distributions based on the ORs and their CIs from models of the same form as Equation 4-7 run on the original WHP Patna cohort weighted with the Chapter 2 IPS weights. The distributions of these ORs are described in Table 4-3.

The relationships between observation status and the simulated confounders were defined as part of each scenario assumption. Because patients with HIV are more likely to have on-going contact with the healthcare system in order to treat their HIV, patients with HIV were simulated to have higher odds of being retained in care than patients who smoked or were malnourished. In the weak association scenario, the OR for observation status based on smoking, HIV and malnutrition status were drawn from the following uniform distributions: U(0.85, 0.95), U(0.90, 1.0) and U(0.85, 0.95) respectively. In the moderate association scenario, the adjusted OR for observation status based on smoking, HIV and malnutrition status were drawn from the following uniform distributions: U(0.75, 0.85), U(0.85, 0.95) and U(0.75, 0.85) respectively. The natural log of these ORs and baseline odds were then used as the coefficients in the observation status prediction equation. Observation status for each patient was drawn from a binomial distribution centered on their predicted observation probability.

Table 4-3, Distributions for OR draws for observation status prediction model

	Term	Distribution	OR scale distribution parameters	Reference
Observation status prediction equation	$\beta_{baseline}$	Trapezoidal	(1.87, 2.13, 3.33, 3.6)	Chapter 3
	β_{female}	Trapezoidal	(0.77, 0.83, 1.09, 1.15)	
	β_{age}	Trapezoidal	(1.00, 1.00, 1.01, 1.01)	
	β_{retrt}	Trapezoidal	(0.59, 0.64, 0.85, 0.90)	
	β_{rural}	Trapezoidal	(0.63, 0.71, 1.09, 1.17)	
	β_{urban}	Trapezoidal	(0.86, 0.92, 1.19, 1.26)	
	β_{EPTB}	Trapezoidal	(0.16, 0.18, 0.27, 0.28)	
	$\beta_{poor\ adh}$	Trapezoidal	(0.40, 0.43, 0.59, 0.62)	
	$\beta_{<1\ mo.\ adh}$	Trapezoidal	(0.54, 0.60, 0.89, 0.95)	
	β_{slum}	Trapezoidal	(0.88, 0.95, 1.29, 1.37)	
	β_{smo}	Uniform	Weak: (0.85, 0.95) Moderate: (0.75, 0.85)	
	β_{HIV}	Uniform	Weak: U(0.90, 1.00) Moderate: (0.85, 0.95)	
	β_{mal}	Uniform	Weak: (0.85, 0.95) Moderate: (0.75, 0.85)	

Estimating key patient outcome metrics

The IPSW-adjusted patient outcomes, treatment phase CFR, six month post-treatment phase CFR and six month post-treatment phase recurrence rate, were estimated in the same manner as in Chapter 3.

The reduced IPSW model was of the same form as in Chapter 3:

$$S \sim gender_{imp} + spline(age) + TB\ site + Case\ type + slum_{imp} + spline(adherence_{imp}) + spline(time\ since\ initiation) + spline(PPIA\ treatment\ duration) + region$$

Equation 4-8, where S is observation status, "imp" indicates imputed, TB site refers to PTB/EPTB, case type refers to new/retreatment cases, time since initiation was the number of calendar months since the patient initiated treatment and June 2019, PPIA treatment duration is the number of months of treatment recorded in the PPIA database and region refers to out of Patna/Patna urban/Patna rural . All categorical variables were modelled using dummy variables. Splines were penalized splines with df=4

The full IPSW model was of the same form as Equation 4-8 but with additional terms for the simulated confounders:

$$S \sim gender_{imp} + spline(age) + TB\ site + Case\ type + slum_{imp} + spline(adherence_{imp}) + spline(time\ since\ initiation) + spline(PPIA\ treatment\ duration) + region + smoking + HIV + malnutrition$$

Equation 4-9, where S is observation status, "imp" indicates imputed, TB site refers to PTB/EPTB, case type refers to new/retreatment cases, time since initiation was the number of calendar months since the patient initiated treatment and June 2019, PPIA treatment duration is the number of months of treatment recorded in the PPIA database and region refers to out of Patna/Patna urban/Patna rural. All categorical variables were modelled using dummy variables. Splines were penalized splines with df=4

For both the full and reduced models, the fitted observation status model was used to predict the probability of being observed for all patients and this probability was inverted to create the selection weights. These weights were then applied to the observed patients to estimate the IPSW-adjusted event rates for both reduced and full model calculations. The true event rates were calculated using all patients regardless of observation status and were not weighted.

Iteration demographics

For each iteration, key summary measures were stored. These included the proportion of patients observed and the overall and age/sex specific prevalence proportions of the simulated confounders. Additionally, the true patient outcome rates and the estimated reduced and full model weighted estimates were stored.

The summary measures presented here are the median values of the respective distribution. The accompanying CIs are defined as the 2.5th percentile and 97.5th percentile values of the distribution.

4.6 Results

The distributions of simulated treatment phase CFRs are consistent with the CFRs observed in Chapter 3 (7.27% in the Patna WHP cohort and 7.09% in the Mumbai PATH cohort) for both the weak association scenario (median 8.4%, [3.8%, 14.8%]) and the moderate association scenario (median 8.3%, [3.9%, 14.8%], Table 4-4). The median simulated post-treatment phase CFR was 4.2% (0.3%, 20.8%) in the weak association scenario and 4.2% (0.3%, 20.3%) in the moderate association scenario. The median simulated post-treatment phase recurrence rate was 6.7% (0.4%, 32.8%) in the weak association scenario and 6.7% (0.3%, 33.8%) in the moderate association scenario. Both of these median simulated values are higher than the respective values in Chapter 3 though this may be driven by the zero truncation of these distributions (Figure 4-3). The Chapter 3 six month post-treatment CFR (0.76% in the Patna WHP cohort and 1.03% in the Mumbai PATH cohort) and recurrence rate (0.56% in the Patna WHP cohort and 0.38%

in the Mumbai PATH cohort) still fall within the confidence intervals of the simulated values.

Table 4-4, Summary of simulated patient outcomes for the weak and moderate association scenarios

	Weak association scenario Median % (CI)	**Moderate association scenario Median % (CI)**
Treatment phase CFR	8.4 (3.8, 14.8)	8.3 (3.9, 14.8)
Post-treatment phase CFR	4.2 (0.3, 20.8)	4.2 (0.3, 20.3)
Post-treatment phase recurrence rate	6.7 (0.4, 32.8)	6.7 (0.3, 33.8)

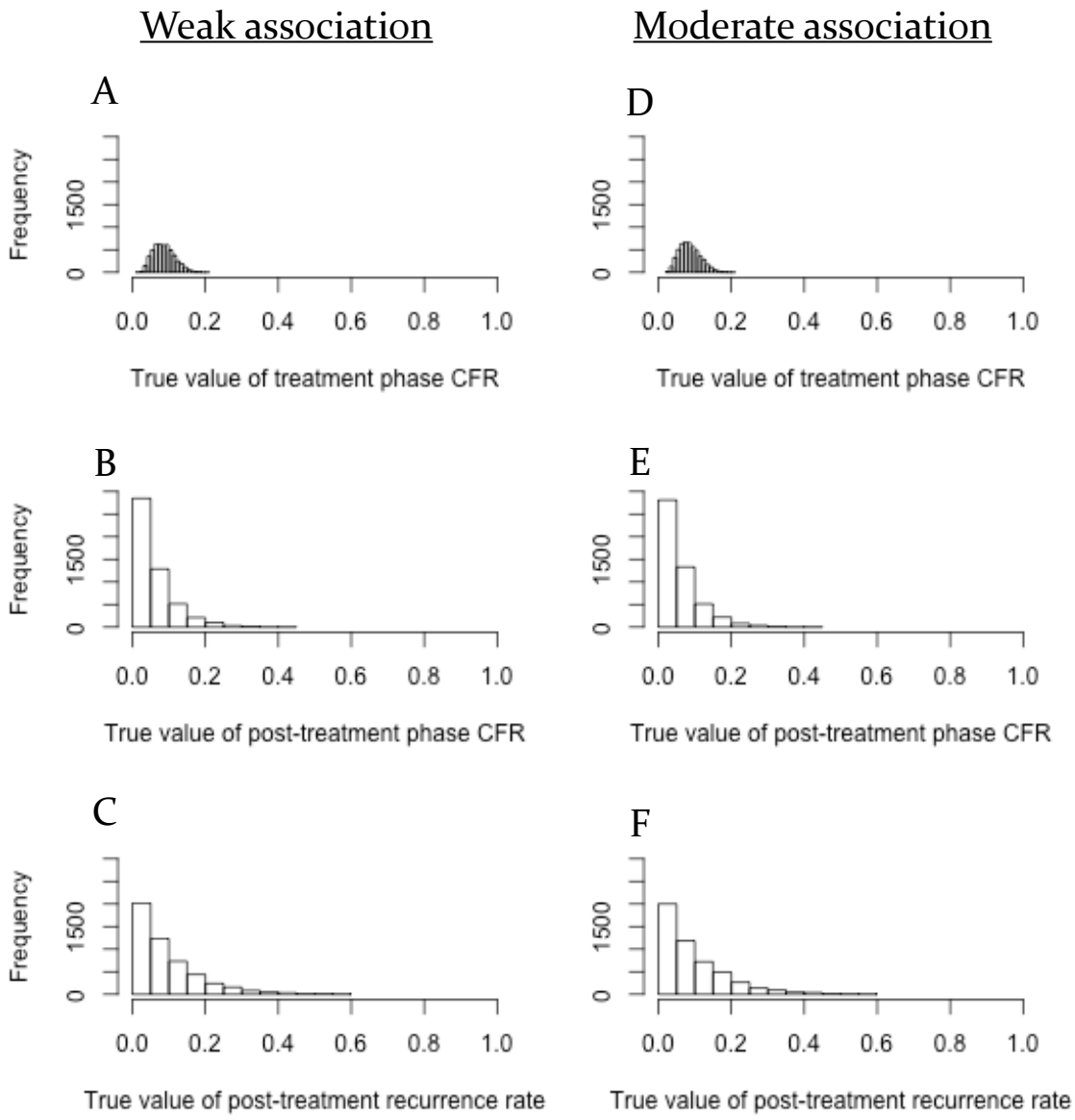

Figure 4-3, Histograms of patient outcome rates for weak association (A, B, C) and moderate association (D, E, F) simulation scenarios.

The simulated proportion of patients observed was consistent with that observed in Chapter 3 (56.0% in the Patna WHP cohort and 54.6% in the Mumbai PATH cohort) with a median response rate of 54.4% (45.0%, 63.1%) in the weak association scenario and 51.7% (42.3%, 60.4%) in the moderate association scenario. The lower median response rate in the moderate association scenario is consistent with the stronger relationship dictated in the scenario assumptions between the simulated confounders and non-response in the observation prediction model.

Simulated confounders were calibrated to match overall and age and sex specific prevalences in addition to having literature based relationships to patient outcomes. Each

of the target values for the simulated confounders are close to the median simulated prevalences. The simulated overall prevalence of current smokers had a median value of 20.6% (4.2%, 35.1%) in the weak association scenario and 20.7% (3.8%, 35.2%) in the moderate association scenario (Table 4-5, Figure 4-4). The confidence intervals include the target overall prevalence of 16% observed in Indian TB patients.[4] The age and sex distribution of simulated smoking also closely followed Indian population age and sex smoking rates[5] used to inform the smoking prediction equation (Figure 4-5).

The simulated overall prevalence of HIV had a median value of 7.0% (0.5%, 21.2%) in the weak association scenario and 7.1% (0.6%, 21.1%) in the moderate association scenario. HIV is relatively rare among Indian TB patients so these confidence intervals contain the target value of 2.5%.[6]

Finally, malnutrition is almost universal among Indian TB patients thus the target value was 90%.[7] In the weak association scenario the median prevalence of malnutrition was 83.4% (67.4%, 99.0%) and in the moderate association scenario it was 83.9% (68.0%, 99.1%).

Table 4-5, Summary of simulated confounders and observation status for the weak and moderate association scenarios

	Weak association scenario Median % (CI)	**Moderate association scenario Median % (CI)**
Proportion of patients observed	54.4 (45.0, 63.1)	51.7 (42.3, 60.4)
Current smoker prevalence	20.6 (4.2, 35.1)	20.7 (3.8, 35.2)
HIV prevalence	7.0 (0.5, 21.1)	7.1 (0.6, 21.1)
Malnutrition prevalence	83.4 (67.4, 99.0)	83.9 (68.0, 99.1)

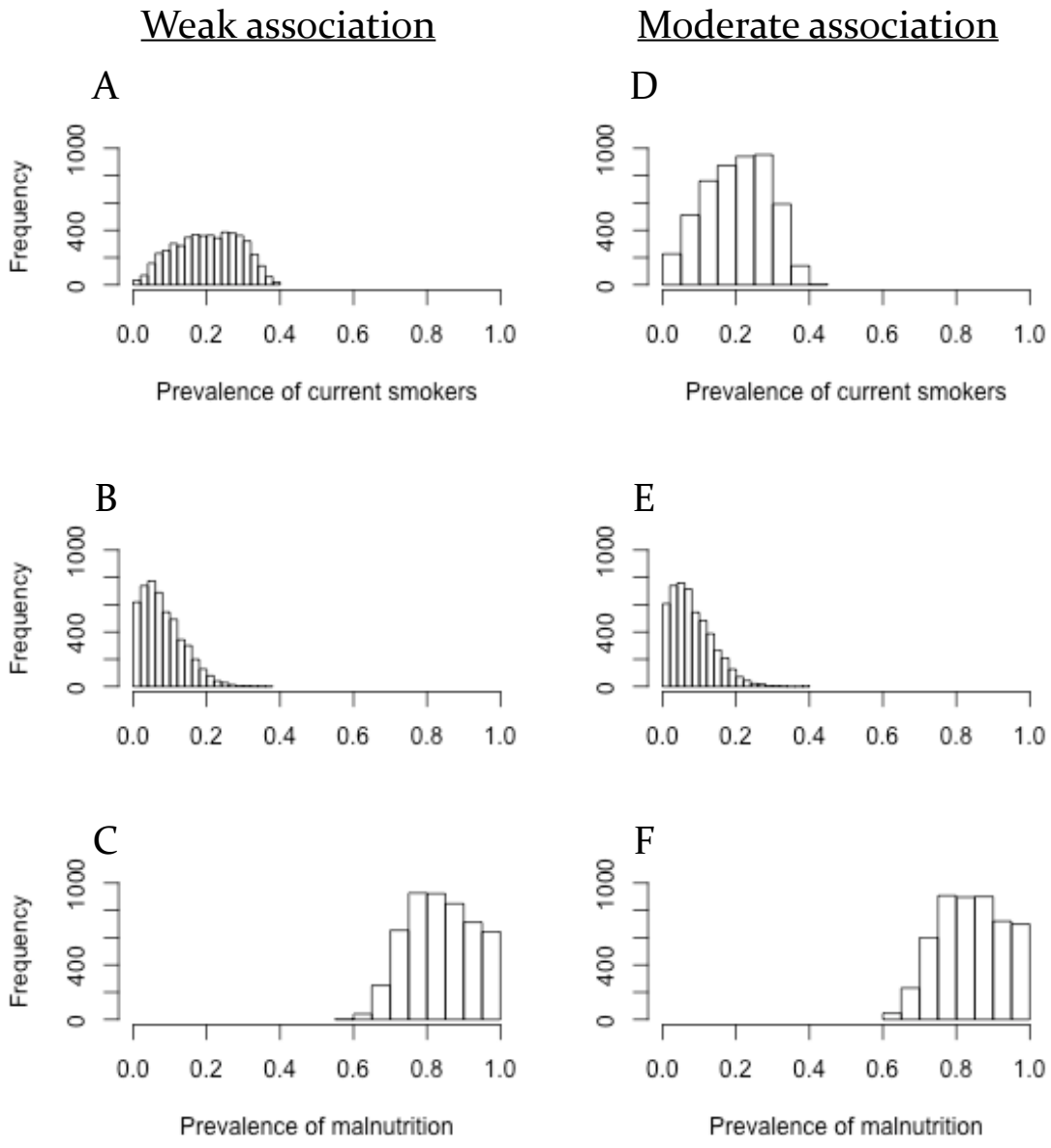

Figure 4-4, Histograms of simulated confounders overall prevalence for weak association (A, B, C) and moderate association (D, E, F) simulation scenarios.

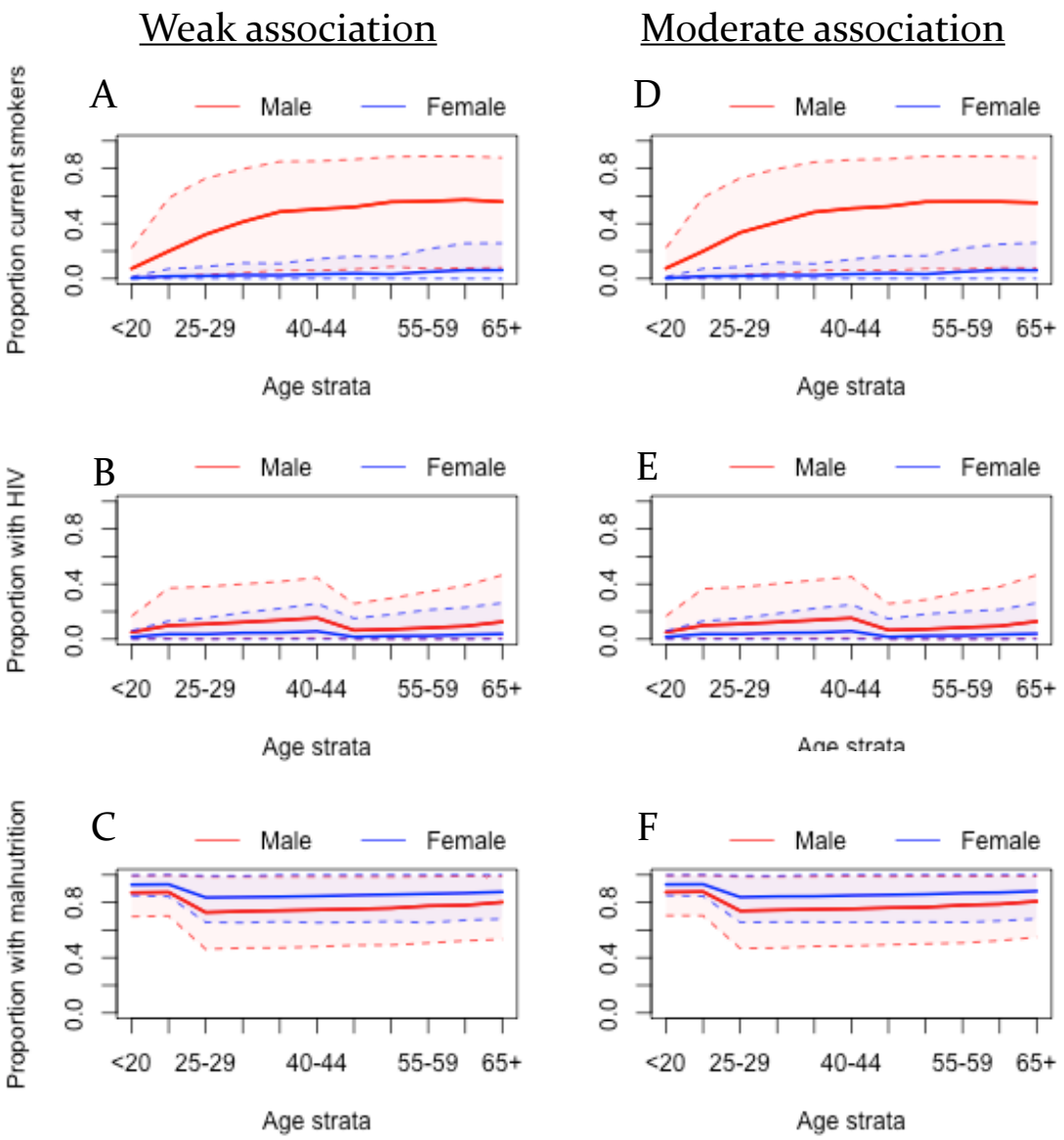

Figure 4-5, Age and sex strata specific prevalences for simulated confounders for weak association (A, B, C) and moderate association (D, E, F) simulation scenarios.
Red indicates male 5-year age strata specific prevalences and blue indicates female 5-year age strata specific prevalences. Solid line indicates median age and sex specific confounder prevalence and dashed lines indicate 2.5th and 97.5th percentiles.

In the weak association scenario, both the reduced IPSW model identical to that used in Chapter 3 and the full IPSW model incorporating the simulated confounders produced estimates of patient outcome measures very close to the true values (Table 4-6). For example, the reduced IPSW model treatment phase CFR estimate had a median absolute bias of 0.29% while the full IPSW model produced a similar median absolute bias of 0.28%. Consequently, the median absolute difference between the estimates produced under the reduced and full IPSW models were also small. For the treatment phase CFR

estimates, the median absolute difference between the two models' estimates was only 0.11%. The median absolute difference between the two models was smaller for the post-treatment phase CFR (0.08%) and close to null for the recurrence rate (0.02%)

As expected, the bias observed in the moderate association scenario is higher but still not large enough to meaningfully alter the interpretation of the outcome measures. For the treatment phase CFR, the median absolute bias for the reduced IPSW model estimate was 0.34% while it was 0.30% for the full IPSW model. The median absolute difference between the full and reduced model estimates was 0.24% for the treatment phase CFR, 0.14% for the post-treatment phase CFR and 0.03% for the recurrence rate.

Table 4-6, Comparison of key event rates under reduced and full IPSW to each other and the true values. NB that the median absolute bias is expressed on the outcome scale, which is a percentage. These bias measures are not expressed as a proportion of the outcome metrics. IQR – interquartile range.

	Median true value, % (IQR)	**Median reduced IPSW model value, % (IQR)**	**Median full IPSW model value, % (IQR)**	**Median absolute bias, reduced vs. true, % (IQR)**	**Median absolute bias, full vs. true, % (IQR)**	**Median absolute difference between full and reduced, % (IQR)**
Weak association scenario						
Treatment phase CFR	8.4 (4.1)	8.3 (4.1)	8.5 (4.2)	0.29 (0.36)	0.28 (0.35)	0.11 (0.15)
Post-treatment phase CFR	4.2 (6.1)	4.1 (6.0)	4.1 (6.1)	0.21 (0.32)	0.19 (0.27)	0.08 (0.16)
Post-treatment phase recurrence rate	6.7 (10.2)	6.6 (10.1)	6.7 (10.1)	0.31 (0.47)	0.32 (0.46)	0.02 (0.03)
Moderate association scenario						
Treatment phase CFR	8.4 (4.0)	8.1 (4.0)	8.4 (4.1)	0.34 (0.45)	0.30 (0.38)	0.24 (0.23)
Post-treatment phase CFR	4.2 (6.1)	4.1 (5.9)	4.2 (6.1)	0.25 (0.38)	0.21 (0.30)	0.14 (0.26)
Post-treatment phase recurrence rate	6.7 (10.5)	6.7 (10.5)	6.7 (10.5)	0.33 (0.49)	0.33 (0.50)	0.03 (0.05)

4.7 Discussion

It remains important to consider and account for selection bias, especially in cohort studies. IPSW is a straightforward correction for patient loss to follow-up, however it is also important to be aware of the necessary assumptions this method requires.

Probabilistic bias analysis is an effective tool to investigate the potential magnitude of the impact of unmeasured confounding of the observation-outcome relationship in IPSW analyses on resulting event rates. In this case, these simulations suggest that the unmeasured confounders – smoking, HIV and malnutrition status – are unlikely to produce sufficient bias such that the interpretation of the primary results would change. Indeed, the median differences between the reduced and full model estimates were all below 0.25%. This suggests that the confounders present in the database and in the primary IPSW model sufficiently control for confounding of the observation-outcome relationship.

How can strong predictors of patient outcomes, like smoking, HIV and malnutrition, even when simulated to have ORs for observation status between 0.75 and 0.90, not meaningfully impact IPSW performance? One component of the answer may be that some of the confounding by these variables is adjusted for through their relationship to other patient characteristics. For instance, because gender and smoking were strongly correlated, then controlling for gender in the IPSW model would indirectly control for some of the confounding by smoking. Additionally, there is limited variation in these confounders among Indian TB patients. HIV is quite rare in Indian TB populations[6] while rates of malnutrition are very high.[7] Similarly, smoking is very common among male Indian TB patients but remains quite rare among female patients which again reduces its ability to drive observation status. While together these confounders have a strong relationship to patient outcomes, they cannot have a substantial impact on observation thus are not able to produce a large selection bias. However, in other TB populations with differing prevalences of these confounders the results could be quite different, thus it would benefit PPIA schemes and other cohort studies to consider routinely collecting data on all potential confounders of the observation-outcome relationship at enrollment.

This simulation was strengthened by the effort to produce realistic confounder rates within age and sex strata that closely align with literature estimates. Additionally, variation was introduced into the simulation in as many parameters as possible, including through bootstrap-style sampling of a reference population, stochastic coefficient selection, and weak and moderate scenarios. However, some concessions had to be made to computational simplicity. The confounders were simulated independently of each other when in reality they are likely dependent, i.e. someone who has HIV is more likely to be malnourished than someone who does not. Additionally, detailed age and sex specific prevalences were only available for Indian smoking rates thus the HIV and malnutrition prediction equations had to use coarse age strata.

In conclusion, these simulations support the robustness of the primary results described in Chapter 3 to unmeasured confounding in the ISPW model. This work also provides a template for other similar bias analyses in TB populations.

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Chapter 5: Summary and conclusions

5.1 Summary of results

The results of my systematic review show that the pooled literature estimate for the Indian TB CFR, 5.16% (4.20%, 6.34%), is in line with WHO recommendations, but the literature largely reflects publicly treated patients and serious quality concerns existed for the majority of the included papers. This review also highlighted that privately treated Indian TB patients are underrepresented in the literature despite representing half of all Indian TB patients.[1.] It is also noteworthy that out of 212 identified papers, zero adjusted for patients lost to follow-up even though rates of lost patients were often high.

In my cohort survey of private sector PPIA-treated patients, I established the selection-bias corrected estimates of patient outcome rates during and after treatment. The treatment phase CFRs (Patna: 7.27%, Mumbai: 7.09%) were higher than ideal, but likely represent a much higher treatment success rate than privately treated patients outside of PPIA programs. I also showed that the crude treatment phase CFRs were substantially biased by patient loss to follow-up. Post-treatment case fatality (Patna: 3.32%, Mumbai: 2.36%) and recurrence rates (Patna: 3.56%, Mumbai: 1.86%) were moderate at two years post-treatment and highlight that the risks for TB patients do not end with the last dose of anti-TB medication.

Finally, I showed that my cohort results are likely robust to the unmeasured confounders of the observation-outcome relationship that were not included in the IPSW model. This is likely due to the limited variability of smoking, HIV and malnutrition status in Indian TB populations.

5.2 Strengths and Limitations

This work is strengthened by its scale. More than 200 papers were identified in my systematic review and my cohort studies are the largest of their kind. However, it is important to note the limitations of this work. First, the CFR is a measure of all-cause mortality and thus this work cannot help understand the specific fatal risks to TB patients. Secondly, although PPIAs are an increasingly common intervention in the Indian private sector, these patients currently do not represent the average private sector TB patient experience. In addition, the definition of recurrence used in this work was limited to patient self-report of additional rounds of TB treatment. In a prospective study, recurrence could be assessed more accurately with diagnostic testing of symptomatic people and genetic epidemiology could be used to assess whether a recurrent episode was due to the original TB strain or a new infection. Finally, my simulation work suggests that my cohort study results are robust to unmeasured confounding of the observation-outcome relationship, however this simulation is only as accurate as my assumptions about real-world relationships. Great care was taken to ensure that the relationships between the simulated variables were realistic, but if the confounders are stronger predictors of observation status or more variable than simulated, my results are likely to be overly optimistic.

5.3 Implications

In order to properly benchmark progress towards global goals, we must have accurate measurements. Thus, the TB field and the greater global health community must adopt and implement modern selection bias adjustment techniques as a matter of course in the analysis of cohort studies. The field should also consider more frequently using simulation studies to explore the implications of the unique data challenges encountered in global health research.

This work also supports the use of PPIAs as an effective means of improving the quality of care for TB patients in the Indian private sector. PPIAs could improve their understanding of the rates and risk factors of poor patient outcomes during and after treatment by implementing routine selection bias correction and programmatic post-treatment monitoring.

In the current COVID-19 epidemic, delivery of TB services in India and around the world has been hampered and this is projected to cause a 20% increase in TB mortality worldwide.[2] Repeating this analysis in the coming years would help to assess how the TB CFR has been impacted by COVID-19 and inform efforts to regain ground in the fight against TB.

5.4 Directions for future research

Weak vital records data, including death certificates, continue to make it difficult to study cause-specific morality among Indian TB patients after treatment completion. However, there is evidence from other countries, that TB patients are at an elevated risk of cardiovascular disease deaths post-treatment.[3] In future work with prospectively followed TB patient cohorts, verbal autopsies could be used to establish cause-specific mortality rates which could inform interventions to prevent these deaths. Additionally, post-treatment case fatality could be compared to the expected fatality rate for the general population using relative survival modelling,[4] a technique developed in cancer epidemiology.

5.5 Conclusion

To improve TB patient outcomes, India must first accurately measure them. This work is a step forward in understanding the experiences and outcomes of TB patients in the understudied Indian private sector and promotes the use of modern epidemiological techniques to minimize bias when estimating longitudinal patient outcomes. Through accurate measurement of patient outcomes and consistent efforts to improve quality of care, India can succeed in curbing its TB epidemic.

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B. Doctoral training publication list

*indicates authors contributed equally

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