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Dissertation

Controlling Tuberculosis Among High Risk Populations in Los Angeles

Three Essays

Jessica Yeats

RAND CORPORATION

Dissertation

Controlling Tuberculosis Among High Risk Populations in Los Angeles

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Jessica Yeats

This document was submitted as a dissertation in June 2015 in partial fulfillment of the requirements of the doctoral degree in public policy analysis at the Pardee RAND Graduate School. The faculty committee that supervised and approved the dissertation consisted of Emmett Keeler (Chair), Shanthi Nataraj, and Ricardo Basurto-Davila.

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Abstract

Tuberculosis disease (TD) is caused by the activation of latent TB infection (LTBI). LTBI is noninfectious and asymptomatic but can be treated to reduce the probability of progression to disease. With over 15 million persons in the United States infected with LTBI, prioritizing high risk groups for LTBI testing and treatment is essential to feasibly and cost effectively controlling the spread of TB. This dissertation comprises three essays that will help policymakers decide *who*, *how and why* to test and treat for LTBI.

Contents

Abstract iii

Introduction vii

Acknowledgments xi

Abbreviations xiii

The Cost of a Case of Drug-Susceptible Tuberculosis among the Homeless in Los Angeles County 1

Abstract 2

1 Introduction 3

2 Inpatient Length of Stay and Hospitalization Costs 6

3 Outpatient and Case Management Costs 16

4 Contact Investigations 18

5 Discounted Secondary Cases (Cost Category 4) 21

6 Quality Adjusted Life Years (Category 5) 25

7 Discussion 26

Appendix A: Cost of a Case Inputs and Supplemental Figures 28

The Cost Effectiveness of Mandatory Annual Screening for Latent Tuberculosis Infection in Los Angeles Homeless Shelters 30

Abstract 31

1 Quick Start User Guide 32

2 Background 42

3 Model 45

4 The Simulation Environment: Parameters, Mode Calibration and Output Monitors 47

5 Results and Policy Implications 73

Appendix: Supplemental Figures 81

Priorities for Targeted Testing for Latent Tuberculosis Infection among Foreign-Born Adults in the United States 85

Abstract 86

1 Introduction 87

2 LTBI Prevalence and Risk Factors 89

3 TB Progression Rate Overall and by Age 98

4 Risk Factors for TB Progression and TB Disease: Relative Risks and Population Prevalence 105

5 LTBI Testing and Treatment Parameters 114

6 Aggregate Risk of TB and Life Expectancy by Risk Group 119

7 Prioritization Tool: Cost Effectiveness of Testing and Treating Foreign Born Risk Groups 124

Appendix A: NHANES Analysis Technical Appendix 137

Appendix B: Meta-Analysis Synthesis and Error Estimation Methods 141

Appendix C: Relative Risk of Progression by Medical Risk Factor: Meta-Analyses 148

Appendix D: Medical Risk Factor Prevalence, Definitions and Associated Life Expectancy 174

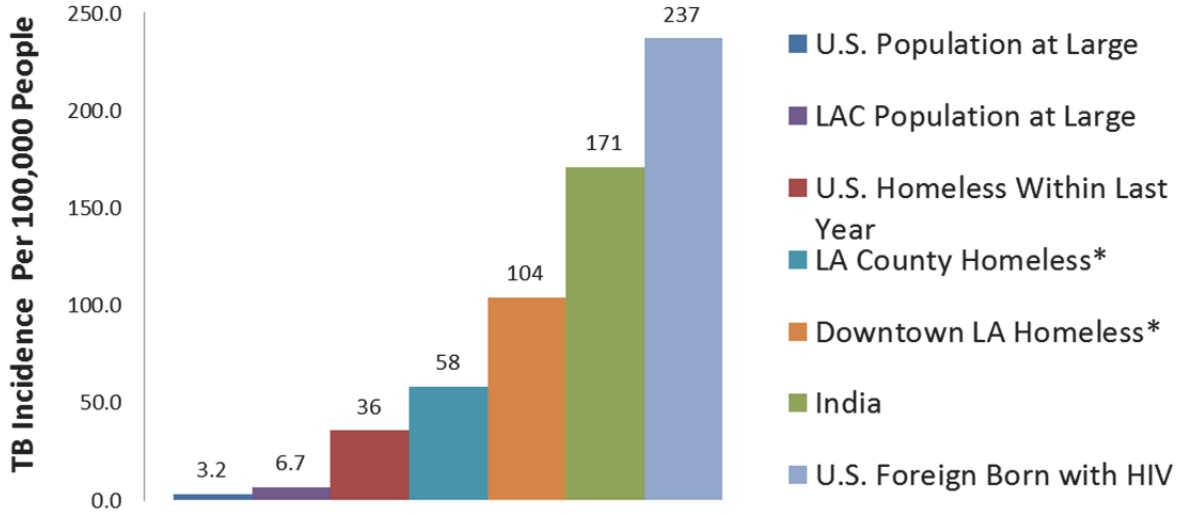
Appendix E: LTBI Testing and Treatment Parameters 194

References 196

Introduction

Tuberculosis (TB) is a disease disproportionately afflicting poor and immunocompromised populations. Globally, it is the second most deadly infectious disease among adults [1]. While the majority of TB cases are concentrated in developing countries, at-risk populations in the United States such as the homeless or the immunocompromised foreign-born can experience incidence rates rivaling the developing world (Figure S.1).

Figure S.1: Incident TB Cases, 2013



*Incidence for LAC homeless derived using the adjusted annualized homeless population documented the Cost of a Case paper.

TB disease, or "active TB disease," is caused by the progression of recently or previously acquired *Mycobacterium tuberculosis (Mtb)* infection (Figure S.1). Mtb is transmitted from persons with active TB disease to uninfected hosts via airborne particles, primarily invading the lungs. When Mtb enters an uninfected, immunocompetent person they become *infected* with Mtb but do not typically develop TB disease. Five to ten percent of persons infected with Mtb will progress to TB disease during their lifetime, with approximately half of their lifetime risk of disease occuring within the first two years following exposure [2]. In the remaining 90-95% of infected persons, Mtb infection remains dormant or *latent* [3]. Globally, about a third of the world's population is infected with *latent TB infection (LTBI)* [4]. Overall rates in the United States are lower, closer to 5%, but vary considerably by risk factor [5].

Overall risk for TB disease is a function of the risk of infection (LTBI) and the risk that infection will progress to TB disease. While infection risk is assumed to primarily depend on exposure to infectious cases, the risk of progression is influenced by immune function status, the host's

primary defense against the activation of disease [6, 7]. An individual's lifetime risk of TB disease is therefore the product of social and demographic factors that predispose them to infection (foreign birth, age, race, poverty, etc.), and the presence of medical risk factors that compromise the host's immune function, the primary defense against the activation of disease. This dissertation addresses two high-risk populations at the intersection of these risk dimensions: the h*omeless* (high risk of exposure due to congregate living environments as well as a high prevalence of immune-compromising comorbidities) and *foreign born persons with medical risk factors for progression*.

Figure S.2: Transmission of Mycobacterium Tuberculosis Infection Progression to Tuberculosis Disease

Red denotes active TB disease; yellow denotes Mtb or latent TB infection (LTBI); green denotes TB disease recovery.

LTBI is noninfectious and asymptomatic but can be treated to reduce the probability of progression to disease. In high-burden countries, treating LTBI is difficult to rationalize due to its high prevalence. In the United States, TB control policy priorities have shifted to the detection and treatment of LTBI as the incidence of TB disease has fallen [8]. However, with over 15 million persons in the United States infected with LTBI, prioritizing high risk groups for LTBI testing and treatment is essential to feasibly and cost effectively controlling the spread of TB. This dissertation comprises three essays that will help policymakers decide *who*, *how and why* to test and treat for LTBI.

Broadly, there are two LTBI risk profiles and associated testing and treatment approaches considered throughout this dissertation manuscript. First, *populations at risk of recently transmitted LTBI,* such as the homeless exposed to an outbreak, for whom annual or routine screening may be needed to combat transmission (paper #1 and paper #2). Second, *populations with high prevalence of previously acquired LTBI*, such as the foreign born, for whom *one-time testing and treatment* is likely sufficient to mitigate the majority of their lifetime risk of progression to disease (paper #3).

The Los Angeles County (LAC) Department of Public Health (DPH) is currently combatting the largest outbreak of Tuberculosis (TB) among the homeless to have been reported in the United States. Since 2007, over 330 cases of active TB have been identified among homeless persons. Among them, over a quarter have been epidemiologically linked by genetic markers to a single chain of transmission. The persistent transmission of TB within this high at-risk population coupled with a high mortality rate underscore the need for cost-effective interventions to reduce the ongoing spread of disease.

To inform the design of cost-effective interventions aimed at controlling the outbreaks of TB among the homeless in LAC and in other urban homeless populations, the first paper, entitled *The Cost of a*

*Case of Drug-Susceptible Tuberculosis among the Homeless in Los Angele*s, estimates the total direct and indirect costs and the determinants of inpatient lengths of stay (LOS) among homeless and non-homeless cases of TB reported to LAC-DPH during 1998-2014. Including the discounted costs of secondary cases, this study finds that each case of TB costs the health system an average of $365,000 for a homeless patient and $69,000 for a non-homeless patient. When considering only the direct costs of inpatient and outpatient care, each case costs $175,000 and $50,000 for a homeless and non-homeless patient, respectively. The direct cost margin associated with homelessness is driven by significantly longer LOS, with homeless patients spending on average 25 more days in the hospital.

These results suggest that studies examining TB control interventions targeting the homeless may underestimate cost effectiveness of the intervention if cost inputs are based on the costs of a case among the general population. The high cost of averted cases among the homeless suggests that even expensive interventions may generate cost savings, particularly when accounting for transmission. There are fewer significant predictors of hospitalization at diagnosis and of cumulative LOS among the homeless, suggesting that the excess hospitalizations are due to the patient's housing status rather than the burden of disease.

In response to the *outbreak,* LAC-DPH is considering an intervention that would require homeless shelter operators to screen all clients at least once annually for LTBI and refer positive cases to treatment. This second paper in this dissertation series, *The Cost Effectiveness of Mandatory Annual Shelter Screening for LTBI in LAC Homeless Shelters,* proposes a discrete time-driven stochastic microsimulation that compares costs and outcomes associated with mandatory, annual LTBI screening to those associated with no mandatory screening in a hypothetical cohort of 20,000 persons experiencing homelessness in downtown LA.

Model outcomes demonstrate that the intervention would generate cost savings between the fifth and ninth year following adoption and would be cost-saving under a wide range of shelter participation, compliance and treatment initiation parameters *if LAC-DPH were able to initiate treatment for at least 600 new homeless clients* per year. However, local experts believe that only about 200 additional patients can initiate treatment per year out of an LTBI positive population of more than 3,000 in downtown LA. Subject to this constraint, the intervention is conceptually equivalent to randomly screening 7% of the population per year, which, while potentially cost-effective after 10 years, may be a less effective use of limited treatment capacity than targeting subgroups at higher risk of progression to disease. DPH should expand treatment capacity before requiring additional shelters to adopt the recommendation.

Over half of all TB cases in the U.S. are attributable to reactivation of previously acquired LTBI among the foreign-born (FB). Detecting and treating LTBI in FB populations has thus become a centerpiece of TB control policy in the United States. Recent studies have found that testing and treating all FB persons (the "universal approach") would be cost effective. However, with limited treatment resources and an estimated 7.5 million FB persons living with LTBI this approach may not be feasible. To assist resource-constrained local health jurisdictions in optimally allocating finite LTBI treatment

resources, the final paper in this dissertation, *Priorities for Targeted Testing for LTBI among Foreign Born Adults in the United States,* identifies FB subpopulations that should be prioritized for targeted LTBI testing and treatment.

The prevalence of LTBI overall and by risk group is estimated using the results from the interferon-γ release assay (IGRA) examination on the 2011-2012 National Health and Nutrition Examination Survey (NHANES). The annual risk of progression to TB disease overall and by age and medical risk factor group is estimated with meta-analyses and an analysis of the exposure-adjusted relative risk of disease during 2011-2013 from Centers for Disease Control and Prevent (CDC) surveillance reporting. Population prevalence of each FB risk group is estimated with NHANES, the American Community Survey and other surveillance datasets. Discounted cases averted and quality adjusted life years (QALYs) gained by targeting each FB subpopulation are derived from the aggregate risk of TB, life tables and parameter estimates from the published literature.

With base case parameter inputs, testing and treating the average FB person costs $58,000 per QALY gained. Targeted testing is cost-savings for FB persons in the following categories: HIV-infected, end-stage renal disease, transplant recipients, immunosuppressive therapy, hematologic cancer, low bodyweight, and injection drug use. Targeted testing is more cost-effective than the universal approach for FB persons with solid organ cancer, current tobacco use, and alcohol abuse, as well as those from countries with extremely elevated TB prevalence (e.g., Ethiopia, Haiti). Targeted testing is less cost-effective than the universal approach for FB persons with diabetes mellitus and those over 55 years old.

Our results suggest that targeting FB risk groups can dramatically improve the impact of LTBI testing and treatment. Forty-five percent of all QALYs gained from testing the FB can be captured by targeting just 10% of the FB population.

Acknowledgments

Rich people like to say that you're the average of the five people you spend the most time with. That can't be right. Over the past several years I have been blessed with the guidance and support of a group of colleagues and friends within and outside of RAND of whom I can only hope to be at the lower quartile, or, say, the lower 95% confidence limit.

First, my committee: Emmett Keeler (chair), Shanthi Nataraj and Ricardo Basurto-Davila. Emmett: nothing has motivated me more than trying to make you think I was smart. Shanthi: my only professional goal is to be so successful that I can hire you. I'm not kidding. I say that all the time. Ricardo: I would never have found my way out of the abyss of dissertation broken dreams had you not gone so remarkably out of your way to introduce me to the topic and equip me with the tools to study it.

Second: my mentors and colleagues at the Los Angeles County Department of Public Health, particularly Brian Baker, Peter Kerndt, and Jo Kay Ghosh. I am especially grateful to Brian, whose knowledge, passion for the topic and patience with my learning curve was instrumental at every stage of this process.

Third: my RAND family. I would not have made it through the first two years without Shmuel Abramzon or the last two without CAROL Tassot. I am grateful to my brilliant and hilarious classmates for raising the bar and taking everything just seriously enough, especially Abdul Tariq, Beth Katz, Jesse Sussell, Bobby Theologis, Nono Ayivi-Guedehoussou, Eric Warner, Steve Isley and also Chris Lau for doing all of my homework. I owe an enormous debt of gratitude to Susan Gates and Christopher Paul for all that their examples have taught me about effective leadership and the twin pursuits of rigor and impact. I am thankful to the PRGS administration, especially Rachel Swanger for her candor and profound, totally irrational concern for the wellbeing of students.

Fourth, I am deeply grateful for the love and emotional distractions provided by my east-of-the-405 LA crew, especially Beth Rowe, Julia Stein, Danielle Pakdaman, Bruce Francis Cole, Nick Kurzon and Brenda Montez. And a special shout out to Lennon Flowers for reminding me in words and in her spirit that the most important things can't be counted, even in SAS®.

Finally, to my best friend John James Burgeson – thank you for the PowerPoint support, for my sanity, and for never letting me win.

Funding Support

This dissertation was made possible by financial support from the Anne and James Rothenberg Dissertation Award, the Wasserman Prize for Reducing Social and Economic Disparities, and the David I. J. Wang Dissertation Award. I am particularly indebted to these sponsors because my dissertation was unrelated to my day to day research responsibilities at RAND. I came to the Pardee RAND Graduate School from the Pentagon with the intention of transitioning from defense to domestic policy areas, a goal I would not have been able to accomplish without external financial support.

Abbreviations

ARR	Average Risk Reduction
CAGR	Compounded Annual Growth Rate
CDC	Center for Disease Control and Prevention
CHS	Community Health Services
95% CI	95% Confidence Interval
CI	Contact Investigation
CoC	Continuum Of Care
CXR	Chest X-Ray
DEALE	Declining Exponential Approximation Of Life Expectancy
DM	Diabetes Mellitus
DOT	Directly Observed Therapy
DPH	Department Of Public Health
EPI-AID	Epidemiological Assistance
FB	Foreign-Born
FLALE	Fixed Lifetime Approximation of Life Expectancy
ICER	Incremental Cost Effectiveness Ratio
IGRA	Interferon-Y Release Assay
IRR	Incident Rate Ratio
LAC	Los Angeles County
LAHSA	Los Angeles Homeless Services Authority
LE	Life Expectancy
LTBI	Latent Tuberculosis Infection
LOS	Lengths Of Stay
LY	Life Years
MEC	Medical Examination Survey
Mtb	Mycobacterium tuberculosis
NNTest	Number Needed To Test
NNTreat	Number Needed to Treat
NOMCAR	Not Completely Missing At Random
OR	Odds Ratio
PHI	Public Health Investigator
PHN	Public Health Nurse
PIT	Point In Time
PSU	Primary Sampling Unit
PY	Person-Year
QALY	Quality-Adjusted Life Year
RR	Relative Risk
SAT	Self-Administered Therapy
SDF	Shelter-Density-Factor
SMEs	Subject-Matter Experts

SMR	Standardized Mortality Ratio
SOT	Solid Organ Transplantation
TB	Tuberculosis
TBCP	Los Angeles County Department Of Public Health TB Control
TRIMS	TB Registry Information System
TST	Tuberculin Skin Test
YPLL	Years Of Potential Life Lost

The Cost of a Case of Drug-Susceptible Tuberculosis among the Homeless in Los Angeles County

Jessica M. Yeats

Abstract

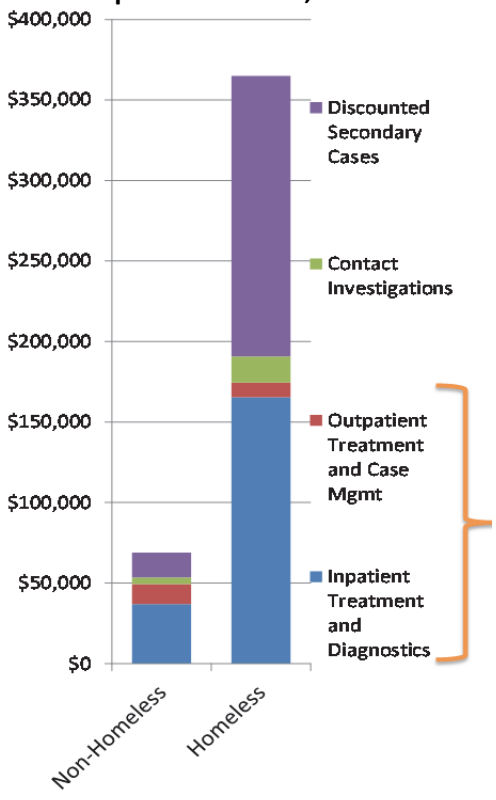
Setting: Homelessness represents one of the largest risk factors for contracting tuberculosis disease in the United States generally and in Los Angeles County (LAC) in particular. Homeless TB patients are perceived to present unique burdens to the health care system due to excessive inpatient stays, aggressive transmission, and challenges with locating and managing active cases and their close contacts. However, most analyses of TB control policies targeting the homeless use cost estimates drawn from the general population, biasing estimates of cost effectiveness.

Objective: Estimate the total direct and indirect costs, lengths of stay (LOS) and patient characteristics associated with cases of TB among the homeless population in LAC in order to inform the design of cost-effective TB control interventions.

Methods: Costs and health outcomes associated with 796 homeless and 12,233 non-homeless cases of TB reported to the LAC Department of Public Health during 1998-2014 were assessed across five categories: inpatient, outpatient treatment and case management, contact investigations, secondary cases and quality-adjusted life years (QALYs) lost. Predictors of hospitalization at diagnosis were analyzed with multivariate logistic regression; LOS among patients with reported hospitalizations were analyzed with a zero-truncated negative binomial regression.

Results: Including the discounted costs of secondary cases, a case of TB in LAC costs the health system an average of $365,000 for a homeless patient and $69,000 for a non-homeless patient. When considering only direct costs of inpatient and outpatient care, each case costs $175,000 and $50,000 for a homeless and non-homeless patient, respectively. The direct cost margin associated with homelessness is driven by longer inpatient LOS, with the average homeless case spending 25 more days in the hospital than their domiciled counterpart (54 versus 19). Indirect costs are driven by higher levels of transmission among the homeless (0.91 discounted secondary cases per case versus 0.29 among the general population), and more resource intensive contact investigations.

Total Costs of a Case of Drug-Susceptible TB in LAC, 1998-2014



Conclusions: Studies examining TB control interventions targeting the homeless may underestimate cost effectiveness if cost inputs are based on the costs of a case among the general population. There are fewer significant predictors of hospitalization among the homeless suggesting that the excess hospitalizations are due to the patient's housing status rather than the burden of disease.

1 Introduction

1.1 Background/Context

Homelessness represents one of the largest risk factors for contracting tuberculosis disease in the United States generally and in Los Angeles County (LAC) in particular [9, 10]. Treating, managing and investigating a case of TB among the homeless presents unique challenges. Anecdotally, homeless patients are harder to locate and treat, are difficult to safely discharge, and have close contacts at higher risk of activation due to comorbidities. Moreover, the unique characteristics of their social networks complicate efforts to identify, locate and screen the contacts that they may have infected. However, the extent to which these challenges shape the per-case costs and health burdens is poorly understood. Most evaluations of TB control policies use estimates drawn from populations that are easier to treat and manage, preventing valid estimates of the effectiveness of interventions targeted at the homeless.

To inform the design of cost-effective TB control interventions, this study examined total direct and indirect costs, lengths of stay and patient characteristics associated with cases of TB among the homeless population in Los Angeles County (LAC). The paper addresses the following research questions:

1. What are the direct costs associated with treating and managing a case of TB among the homeless in LAC, including diagnostic costs, inpatient treatment, outpatient treatment and costs associated with the risks of toxicity and multiple drug resistance?
2. What clinical and demographic factors predict the total hospitalization burden of a case of TB among the homeless, including the likelihood of hospitalization and the length of stay (LOS)?
3. What is the average cost of the contact investigation resulting from a case of TB among the homeless, including the costs associated with generating the list of contacts, locating and screening high risk contacts and treating LTBI test positive contacts?
4. How many secondary cases of TB will arise due to a single case within the Los Angeles homeless population, and what are the discounted costs and health burdens associated with those secondary cases?
5. How many quality-adjusted life years are lost from a case of TB among the homeless?
6. How do the above costs and characteristics compare to costs associated with a case of TB among the domiciled population?

1.2 Data Sources

Broadly, data were gathered on total units per case and total adjusted cost per unit. The primary source of data for units per case (e.g., hospitalization days, total treatments received) was de-identified TB surveillance records from the TB Registry Information System (TRIMS) database owned by the LAC DPH TB Control Program (TBCP). California Code of Regulations Title 17 Section 2500 requires that a health care provider within LAC report a case of suspected TB to TBCP within one working day of identification. California Health and Safety Code Section 121362 additionally mandates DPH to maintain a record of clinical follow up of all TB patients. TRIMS is the repository for all initial and follow up reporting. It comprises several tables documenting patient demographics, disease characteristics, outcomes, inpatient admission and discharge dates, provision of outpatient treatment and case management and evaluated close contacts. Since 2007, TRIMS has also recorded genotyping information for culture-confirmed cases genotyped by CDC. These data were used to estimate the number and timing of secondary cases per active case by fitting a model of TB transmission to local surveillance data [11]. Semi-structured interviews were held with DPH and LAC+USC hospital finance personnel to supplement or explain data generated by TRIMS. The burden of contact investigations, for example, is not sufficiently captured by TRIMS because TRIMS only records contacts found and evaluated.

Costs per unit were obtained from interviews, TB control regulations and manuals, and the published literature. Resources and staff time associated with TB diagnosis, treatment and case management, and contact investigations were estimated from the TBCP TB Control Manual and from semi-structured interviews with subject-matter experts (SMEs) at Community Health Services (CHS) and the public health clinics serving homeless TB patients in downtown Los Angeles [12, 13]. Personnel costs per unit of staff time were drawn from published data on LAC employee compensation by class [12]. Medical costs were estimated from the LAC+USC Affinity Health Information System and the CMS Carrier File for Southern California [14]. Table 1 summarizes the data sources used to estimate costs within each major cost category.

Table 1: Cost of a Case: Data Sources

Cost Category	Data Source And Methods
Inpatient Treatment & Diagnostics	TB Registry Information System [TRIMS] (LAC DPH); Interviews with LAC+USC Hospital Chief Financial Officer [15]
Outpatient Treatment & Case Management	TRIMS, Interviews with TB Control Program (TBCP) Staff, DPH Human Resources (HR) Personnel Cost Estimates
Contact Investigations	TRIMS, Interviews with Community Health Services Staff, DPH HR Personnel Cost Estimates
Secondary Cases	TRIMS Case Records and Genotyping Data (% of Recent Transmission Over Time), Literature Estimates of the Fast and Slow Progression Rates
QALYs	TRIMS, Literature

Costs are expressed in 2013 U.S. dollars, with medical costs adjusted according to consumer price index changes for medical care for urban consumers [16]. Costs were estimated from a societal

perspective. However, no monetary value was assigned to the time-cost of homeless patients because they are nearly universally unemployed. Costs and outcomes associated with secondary cases were discounted at a 3 percent rate [17]. Societal costs were not included due to challenges with assigning a value to lost productivity among the homeless population. Data management and analysis were conducted in SAS 9.3 (SAS Institute, Cary, NC).

1.3 Study Population and Summary Statistics

This study analyzed the costs associated with drug-susceptible, culture or clinically confirmed cases of TB reported to LAC DPH between January 1998 and February 2014 among persons that reported experiencing homelessness within the past year. Cases presenting among incarcerated or institutionalized persons were excluded for two reasons. First, institutionalized patients are categorically different than homeless patients in terms of applicable policy responses and resource requirements. Second, there appeared to be more data processing errors associated with incarcerated patients. For example, there were many instances of overlapping admission and discharge dates, suggesting that dates of incarceration were improperly recorded as dates of admission.

Precise sample inclusion criteria varied according to the data requirements of each study/cost component, as described in each of the following sections. The overall sample included 796 homeless and 12,233 domiciled non-institutionalized, culture-confirmed "closed" cases reported to LAC-DPH during 1998-2014.[1] If a patient was diagnosed with multiple cases of TB during the study timeframe, only the first case was considered.

[1] Cases were excluded if the "closure" variable was missing. Values for the closure variable include "treatment completed," "died," "moved," and so forth.

Table 2: Summary Statistics: TB Cases Reported to LAC DPH Jan 1998 - Feb 2014 Stratified by Housing Status

	All Cases		Homeless Cases		Domiciled Cases	
Characteristic	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Total Cases	13,029		796	6%	12,233	94%
Mean Age (Interquartile Range)	49 (33-65)		47 (40-55)		49 (32-66)	
Completed Treatment	10,586	81%	592	74%	9994	82%
Mean Treatment Duration, If Completed±	271 Days (196-303)		294 Days (215-335)		270 (195 – 301)	
Female	5,220	40%	102	13%	5,118	42%
Foreign Born	10,109	78%	374	47%	9,786	80%
HIV Positive	917	7%	168	21%	745	6%
Smear Negative*	6,517	50%	254	32%	6,261	51%
Extra Pulmonary TB^	969	7%	80	10%	894	7%
Cavitary TB^	2,199	17%	160	20%	2,049	17%
Miliary TB (Disseminated)^	26	0.2%	7	1%	20	0%
Alcohol Abuse in Past Year	1,266	10%	416	52%	849	7%
Injection Drug Abuse in Past Year	210	2%	88	11%	121	1%
Non-Injection Drug Abuse in Past Year	688	5%	248	31%	438	4%
Patient Died During Treatment	1,451	11%	117	15%	1,317	11%
Patient Moved During Treatment	719	6%	45	6%	647	5%
Patient Lost During Treatment	233	2%	38	5%	187	2%

*Cases of active TB disease are classified as "smear positive" or "smear negative" according to whether acid fast bacilli (AFB) were identified in a smear microscopy examination of a sputum specimen. Sputum smear-positive cases are substantially more symptomatic and are 3 to 20 times as infectious as sputum smear-negative cases [18, 19, 20].
^Extra-Pulmonary TB refers to TB outside of the lung. Cavitary TB involves the upper lobes of the lung and is seen in reactivated TB. Miliary TB has disseminated throughout the lungs and is typically more symptomatic and lethal.
±Mean days between treatment initiation and completion with Interquartile range shown in parentheses. Cases were excluded if treatment duration was less than 30 days or greater than 3 years (1095 days).

2 Inpatient Length of Stay and Hospitalization Costs

Most of the direct costs of treating and managing a case of TB are attributable to hospitalizations [21]. Overall inpatient lengths of stay (LOS) vary widely by case. Among the general population, about half of all TB patients are not hospitalized at all [21]. By contrast, difficult-to-treat immunocompromised patients can spend hundreds of days in the hospital spanning more than five episodes. Differences in LOS are theoretically explained by the *burden of disease*, characterized by clinical markers (smear status, whether the disease is disseminated or extra-pulmonary) and patient characteristics (HIV comorbidity, immunosuppression induced by alcohol or drug abuse, the stability of the patient's living situation).[2]

The total LOS associated with a given TB case[3] depends on the value of three variables: first, whether or not the patient was hospitalized at diagnosis; second, whether and how often the patient was subsequently hospitalized post-diagnosis; and third, the LOS associated with each hospitalization episode. These three variables are recorded separately and with varying coverage.

[2] In Taylor (2000), positive sputum smear, HIV status, and homelessness were significant predictors of the likelihood of an initial hospitalization. The homeless and substance abusers had disproportionately greater hospitalization episodes during treatment.
[3] A "case" refers to a patient with TB disease. An "episode" refers to a given hospitalization admission during the duration of disease. One case can have multiple episodes or have no episodes.

While it is typically possible to infer whether or not a patient was diagnosed at a hospital, only a portion of hospitals report admission and discharge dates and/or post-diagnosis episodes. The average hospitalization burden was therefore analyzed in three steps:

1. Determining the average per-case hospitalization burden with two methods.
    a. The *Episode frequency* method multiplied the overall probability of hospitalization by the average number of episodes per hospitalized case by the mean cumulative LOS per recorded episode.
    b. The *Complete Case Analysis* method multiplied the overall probability of hospitalization by the cumulative LOS associated with cases with non-missing hospitalization episodes.
2. Identifying factors associated with hospitalization at diagnosis with multiple logistic regression.
3. Identifying predictors of cumulative length of stay among patients with recorded hospitalizations using a zero-truncated negative binomial model.

2.1 Published Literature on Inpatient Duration for Homeless TB Cases

Published studies assessing the likelihood and expected duration of TB-related hospitalization, as well as the relative risks associated with homelessness, are documented in Table 3. Most cost effectiveness analyses of TB interventions draw hospitalization parameters from the survey-based cohort study conducted by Taylor et al in 2000, which included a subset of homeless persons (N=135) and found a median LOS of 11 days with homeless patients experiencing 1.7 more episodes than domiciled patients [21] (mean figures were not published but are imputed in Table 3). Because it measured self-reported hospitalizations, it may under-estimate total inpatient stays, particularly among the homeless, a notoriously difficult-to-survey population. In addition, the study did not separately analyze ICU or respiratory isolation costs and did not report separate median values for MDR and drug resistant cases, which may explain the significant gap between median LOS (11 days) and imputed mean LOS (21 days).[4] This study fills these and other gaps by excluding MDR cases, accounting for ICU days, and analyzing the distribution of total LOS by case, which is more intuitive and policy relevant than median LOS by episode. Mean rather than median values are reported because policymakers are concerned with the overall resource burden. TB related LOS is over-dispersed with a long-tail; projecting median values would under-estimate total resources required.

Studies evaluating all-cause admissions were also reviewed in Table 3. These studies have demonstrated that homeless persons are about twice as likely to visit the emergency department [22] and have longer lengths of stay by 2-3 days [23]. However, the relative burden of homelessness among TB-related admission is likely to be even greater due to legal requirements surrounding

[4] MDR cases are perceived to be substantially more resource intensive and are often managed separately and with dedicated resources.

respiratory isolation (domiciled individuals can be isolated at home) and the severity of symptoms at diagnosis [24].

Table 3: Literature Estimates of Hospitalization Likelihood and Duration

Study/ Source	Population [Diagnosis, Location, Housing Status]	Methods/Design	Estimate
Taylor et al 2000 [21]	Drug Susceptible and MDR TB, United States Metro Areas (including Los Angeles), General Population with Risk Factor Analysis (including Homeless)	Prospective cohort study of 1493 TB patients followed from diagnosis, in 1995, to completion of therapy (or until November 1997) at 10 public health programs and area hospitals in the US during 1995. Participants were asked to report all hospitalizations occurring prior their TB diagnosis and during treatment.	Hospitalization Episodes per Case: 0.93 for homeless and 0.54 if domiciled %.The only published LOS figure is median LOS overall, which is 11. Imputed mean LOS per episode is 22.8 for homeless (21.1 per case) and 20.2 for domiciled patients (10.8per case).[5] Mean LOS reported in Shepardson 2013 from personal communication with authors is 24 days [25].
Millman et al 2013 [26]	Suspected TB, San Francisco, General Population	Reviewed medical records of inpatients undergoing evaluation for TB during 2009 at San Francisco General Hospital.	5.9 Days per patient (2.7 days in isolation + 3.2 days in a standard room). These estimates are lower than TRIMS because the sample includes suspected TB cases (only 6.4% had culture confirmed TB) whereas our study is concerned only with confirmed cases
Marks et al 2014 [27]	MDR TB, United States, General Population with Risk Factors (including homelessness)	Analyzed inpatient, laboratory, and public health clinic records of sample of135 MDR TB patients reported to the CDC from California, New York City, and Texas during 2005–2007. 6 patients (7%) were homeless	75% of MDR patients were hospitalized with an average duration of 1-month. Direct costs averaged $134,000 per MDR TB. Most costs were covered by the public sector.
Oh and Barry 2012 [28]	Drug-Susceptible, California, General Population	Meta-Analysis + Analysis of CA DPH Costs and TB Surveillance	Average Inpatient Cost: 10,100 – 15,900. Inpatient LOS was derived from Taylor 2000 [21]
Hwang et al 2011 [23]	Hospital all-cause admissions (analyzing duration), Canada, Homeless versus Domiciled	Administrative data on 93,426 admissions at an academic teaching hospital in Toronto, Canada, were collected over a 5-year period. These data included an identifier for patients who were homeless	Mean LOS for homeless discharges was 2.32 days longer in acute care. After adjusting for age, gender, and resource intensity weight, homeless patient admissions cost $2559 more than housed patient admissions ($13,516 versus $12,555).
Ku et al 2010 [22]	All-cause ED visits (analyzing likelihood of visit/admission), United States, Homeless vs Domiciled	Analyzed the ED subset of the National Hospital Ambulatory Medical Care Survey to compare demographic and clinical characteristics of visits by homeless vs. non-homeless people in 2005 and 2006.	Homeless persons are 1.8 times as likely to visit the ED than a person from general population (72 visits per 100 persons vs 40 visits per 100 persons)
California DPH 2006 [24]	Drug-Resistant TB, California, General Population:	LOS Policy Requirements governing the use of California DPH local assistance funding allocated for patients with confirmed or suspected TB	AFB sputum smear positive patients must be singly housed in self-contained housing units that do not share air with other units until: (a) 3 consecutive negative sputum smears from respiratory specimens have been collected, at least 8 hours apart, and; (b) the patient has completed at least 14 daily doses of multi-drug, anti-TB therapy.

[5] There were a total of 125 hospitalization episodes among 135 homeless cases, or 0.93 hospitalization episodes per case (Table5). There were 660 episodes among 1230 domiciled subjects, corresponding to 0.54 episodes per case (Table 5). Cumulatively, there were 0.58 episodes per case among subjects aged 15 and older (785 episodes out of 1365 cases). Mean days per episode was imputed from Table 5 by dividing the total hospitalization cost for patients over 15 (10,427,967 overall) by total episodes (785) and dividing the resulting mean cost per episode ($13,284) by the median cost per day ($644) to arrive at 20.6 days per episode and 11.9 days per case (20.6* 0.58 episodes per case). Mean LOS per case was 21.1 and 10.8 days for homeless and domiciled cases, respectively. Of note, the imputed mean days per episode is much higher than the published median days/episode (11).

2.2 Data Sources and Missing Values

Hospitalization episodes and lengths of stay (LOS) were analyzed by merging several datasets in the TRIMS database: *hospitalization*, *patient*, *reporter* and *bacteriology*. The *hospitalization* table includes an observation for each hospitalization episode reported to DPH TBCP among patients with suspected or confirmed TB. The *patient* dataset provides data on patient characteristics and demographics, the *bacteriology* table records the results of each culture or sputum smear, and the *reporter* dataset describes the source and initial form reporting the case. The percentage of patients having any reported encounter with a hospital (90% of homeless patients) is calculated as the proportion of cases meeting one of the following conditions: a) the case has a recorded entry on the *hospitalization* table (64%); b), the case was reported from a hospital on the *reporter* table (80%).

Figure A.1 in Appendix A illustrates the process through which hospitalization episodes are observed. Missing records arise from two contingencies. First, the hospital reports the episode but there are missing admission and/or discharge dates (incomplete records). Twelve percent of all records have missing dates. Second, the hospital may fail to report the episode to TBCP (unobserved episode). As described in Figure A.1 in Appendix A, one measure of the extent of unobserved episodes is the proportion of cases reported from a hospital that do not have at least one record on the hospitalization table (23% of homeless cases). However, only 6% of cases reported from a county hospital are missing whereas 61% of cases reported from a private hospital do not appear anywhere on the hospitalization tables, suggesting that the likelihood that an episode is unobserved is higher if the patient presented to a private hospital. This coverage discrepancy is likely explained by the closer working relationship between LAC DPH and the three county hospitals facilitated by a public health liaison assigned to each of the three hospitals – LAC/USC, Olive View and Harbor/UCLA.

The challenge of missing hospitalization records complicates the construction of a representative dataset synthesizing cases with and without hospitalization record because it cannot be determined whether a case with zero recorded LOS is missing or was never hospitalized. The *total LOS* value is considered to be "missing" if either (a) there are missing dates or (b) the case does not appear on the hospitalization table but the reporter table suggests it presented to a hospital.

The sample used to characterize inpatient LOS included culture-confirmed, closed cases reported to LAC DPH between 1/1/1998 and 02/27/2014.[6] Cases were excluded from the inpatient sample if the recorded primary diagnosis was significantly different from TB, such as gunshot wounds, cancer, and psychiatric episodes. Further, inpatient stays were excluded if the discharge date preceded the

[6] February 27, 2014 was chosen because it was the last date of diagnosis for a "closed" case as of June, 2014, the time of the TRIMS query.

date of diagnosis by more than 30 days or if other irregularities suggested data processing errors (e.g., overlap between successive stays). Recurrent cases were excluded.

TRIMS data was supplemented with semi-structured interviews with LAC+USC hospital finance personnel and data from the LAC+USC Affinity Health Information System on the workload associated with TB-related ICD-9 codes [29]. These data provided estimates of the percentage of time spent in the ICU by homeless status and the average cost per day by type of care. In addition, they served to validate data recorded in TRIMS.

2.3 Average Per-Case Hospitalization Burden

Mean inpatient costs on a per-case basis were calculated to inform our estimate of the total cost per homeless case. Average inpatient costs were calculated as a function of the mean total length of stay (*Mean_LOS*), the distribution of stays by intensity or room type and the average cost per type of stay (Equation 1). *Mean LOS* is conceptually equal to the probability of hospitalization at any point during the duration of disease (P_HOS) and the average cumulative LOS across all hospitalization episodes. *Mean LOS* was estimated with two approaches to account for partially observed episodes (i.e., cases reported from a hospital without a corresponding hospitalization record or incomplete hospitalization records): the *complete case* method multiplied *P_HOS* by the cumulative LOS associated with cases with non-missing hospitalization episodes. *The episode frequency* method multiplied P_HOS by the mean number of episodes per hospitalized case, including partially observed episodes, by the mean LOS per episode associated with completely observed episodes.

$$\text{Mean_Inpatient_Cost} = \text{Mean_LOS} * (\%\text{_GeneralWard*Cost_General} + \%\text{_ICU*Cost_ICU} + \%_Isolation * \text{Cost_Isolation}), \text{ where} \quad \text{Equation 1}$$

$$\text{Mean_LOS} = \text{P_HOS*} \sum_{n-1}^{8} LOSEpisode_n | Episode_n \quad \text{Equation 2}$$

Total inpatient costs for TB related hospitalization episodes include the costs of a regular hospital stay in addition to the marginal costs incurred by negative-pressure respiratory isolation rooms and stays in the intensive care unit (ICU). California regulations require that if infectious patients cannot be discharged under home isolation, they must remain in a negative pressure respiratory isolation hospital bed until three negative sputum smears have been recorded [24].

Table 4 displays the probability of hospitalization, average episodes per case, LOS per episode and per case, percentage of time in the ICU and estimates of overall LOS and costs per case. 90% of all cases had evidence of at least one hospitalization.[7] Cases that appeared on the hospital table had an average of 1.74 episodes, including partially observed episodes. The mean LOS for completely

[7] While the data suggest that 20% of homeless cases present in an outpatient setting, several local officials insisted that "99.9 percent present to the ED" and questioned the validity of the 86% statistic on the basis that those patients may have been transferred from an out of county or private hospital that did not report them. As a consequence, the adjustment for the likelihood of hospitalization may under-estimate the true hospitalization burden.

recorded episode was 36.1 days. The mean LOS per case with at least one complete episode was 60.1 days with a median LOS per case of 38.5 days. Average cost per inpatient day at LAC+USC for a TB-related ICD-9 code is $2,888 in 2013 dollars. At LAC+USC, 7.6% of the inpatient days for TB patients were spent in the ICU with a marginal cost of $1,546 per day. The average homeless case spends 54 and 57 days in the hospital under the complete case method and episode frequency method, respectively. The average domiciled case spends 12 days in the hospital under either method, approximately equal to the estimate in Marks et al [21, 25].[8] Using the midpoint LOS estimate, inpatient and diagnostic costs average $165,000 for a homeless case and $37,000 for a domiciled case.

Table 4: Average LOS and Inpatient Costs per TB Case Reported To LAC 1998-2014, Stratified By Housing Status

	Homeless		Domiciled		
Variable	**Value**	**Std. Dev**	**Value**	**Std. Dev**	**Source**
Full Sample: All Homeless Cases Meeting Inclusion Criteria	**796**		12,223		[30]
Probability of Hospitalization					
Cases Reported from/Diagnosed at Hospital	80%		53%		[30]
Cases Not Reported from Hospital w/Subsequent Ep.	10%		1%		[30]
Cases With Evidence of >= 1 Hospitalization (P_HOS)	90%		54%		[30]
Episodes: All*					
Cases with >=1 Episode on the Hospital Table	68%		28%		[30]
Mean Episodes/Case Among Cases (EPS_IF_HOS)*	1.74	1.03	1.21	0.69	Derived
Lengths of Stay Per Episode: Complete Records**					
Mean LOS Per Complete Episode (LOS_PER_EP)**	35.8	35.1	18.9	24.31	
Lengths of Stay Per Case: Complete Records**					
Mean LOS Per Case with >=1 Complete Episode **	59.7	61.3	22.3	33.2	
Median LOS Per Case with >= 1 Complete Episode	38.5	N/A	11	N/A	
Distribution of Stay by Intensity					
Intensive Care Unit: Percent of Stays***	7.6%				[29]
Per-Day Costs and Cost Margins	**Cost/Day**				
Hospitalization Costs Per Day (Non-ICU)	$2,888				[29]
Isolation Rooms - Marginal Cost Per Day	$1,100				[26]
ICU Marginal Cost Per Day (*Not Used)*	$1,546				[29]
Diagnostic Costs	$401				Table A.3
Mean Inpatient Days and Costs Per Case					
LOS Per Case Method 1: Episode Frequency Analysis	56.1		12.2		Derived
LOS Per Case Method 2: Complete Case Analysis	53.7		12.1		Derived
Inpatient and Diagnostic Costs Per Case`					
Cost Per Case Using Midpoint of LOS Methods	$165,400		$36,922		

*Total Episode count Incomplete entries (missing admission or discharge dates)

**The denominator for Total LOS by episode and case excludes the 91 episodes with incomplete data

***According to LAC+USC Affinity HIS, 59 out of 776 cumulative inpatient days were spent in the ICU for homeless TB patients in FY12-13 and FY13-14.

These data may under-report the total hospitalization burden because they do not capture unreported hospitalization episodes among patients with multiple episodes. A patient may initially

[8] In Marks et al, 49% of patients were hospitalized for an average of 24 days.

present at a county hospital, and therefore be included in the sample, but subsequently present to a hospital that failed to report the episode.

2.4 Factors Associated with Hospitalization at Diagnosis

Risk factors for hospitalization at diagnosis were analyzed using multiple logistic regression (PROG LOGISTIC in SAS 9.3). Results are presented in Table 5. Eighty percent of homeless patients and 53% of domiciled cases were reported to TBCP from a hospital (OR: 3.5, 95% CI 2.9-4.2). Among homeless patients, only smear status and dying during treatment are significantly associated with whether or not the case was reported from a hospital. Among domiciled patients, there are several more significant predictors: patients that are HIV positive, that abuse alcohol or drugs and patients with disseminated, extra-pulmonary or cavitary TB are all significantly more likely to be hospitalized at diagnosis. *These results suggest that homeless hospitalizations are less related to the clinical features of disease and therefore may be more preventable. Homeless patients may present to the hospital not because they are sicker than their domiciled counterparts but because they lack access to or knowledge of outpatient provider settings.*

Table 5: Logistic Regression Model of Risk Factors for Hospitalization at Diagnosis, Stratified By Homelessness Status

	Homeless Cases (Mean=80%)			Domiciled Cases (Mean = 53%)		
Characteristic	**Coefficient Estimate**	**Coefficient P-Value**	**Odds Ratio (95% CI)**	**Coefficient Estimate**	**Coefficient P-Value**	**Odds Ratio (95% CI)**
Intercept	1.52	0.000		0.22	0.000	
Female	-0.12	0.674	0.89 (0.5-1.5)	0.04	0.273	1.04 (1-1.1)
Foreign Birth	0.21	0.284	1.23 (0.8-1.8)	-0.13	0.009	0.88 (0.8-1)
HIV	0.12	0.625	1.13 (0.7-1.8)	***1.00***	***0.000***	***2.72 (2.2-3.3)***
Smear Negative	***-0.81***	***0.000***	***0.45 (0.3-0.7)***	***-0.51***	***0.000***	***0.6 (0.6-0.6)***
Died	***0.84***	***0.010***	***2.32 (1.2-4.4)***	***0.79***	***0.000***	***2.2 (1.9-2.5)***
Alcohol	0.19	0.323	1.21 (0.8-1.8)	***0.70***	***0.000***	***2.01 (1.7-2.4)***
Drug User	-0.21	0.317	0.81 (0.5-1.2)	***0.44***	***0.000***	***1.55 (1.2-1.9)***
Cavitary	0.20	0.437	1.22 (0.7-2)	0.10	0.058	1.11 (1-1.2)
Extra-Pulmonary TB	0.51	0.164	1.66 (0.8-3.4)	1.09	0.000	2.97 (2.5-3.5)
Miliary	12.82	0.983	N/A	1.26	0.109	3.53 (0.8-16.5)
Age0to24	-0.22	0.651	0.81 (0.3-2.1)	-0.04	0.476	0.96 (0.9-1.1)
Age65plus	-0.57	0.103	0.57 (0.3-1.1)	-0.04	0.419	0.96 (0.9-1.1)

2.5 Determinants of Length of Stay among Patients with at least one Recorded Hospitalization: Zero-Truncated Model

This section examines the determinants of the cumulative length of stay among the 512 homeless TB patients and 2,583 domiciled patients, with at least one complete hospitalization record. The average cumulative LOS was 59.7 days for a homeless inpatient and 22.3 days for a domiciled inpatient. The distributions of cumulative LOS for homeless and domiciled patients are shown in Figure 2, which demonstrates that LOS cannot be analyzed with ordinary least squared regression

because the data are very non-normal, discrete and heteroskedastic (the variance increases with the mean).

Figure 3: Distribution of the Cumulative Length of Stay among TB Patients with At Least One Complete Hospitalization Record

Figure 3A: Homeless TB Patients

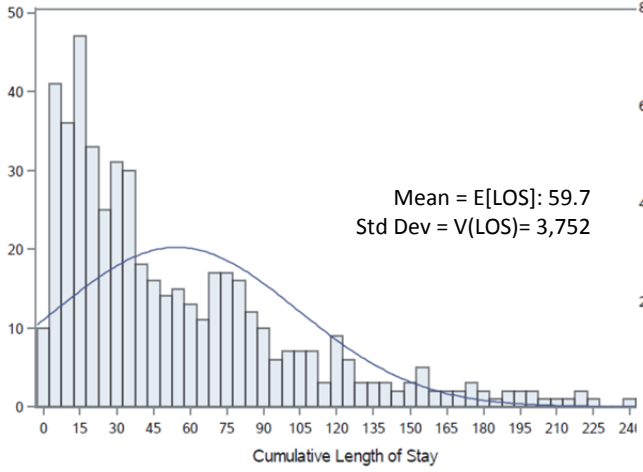
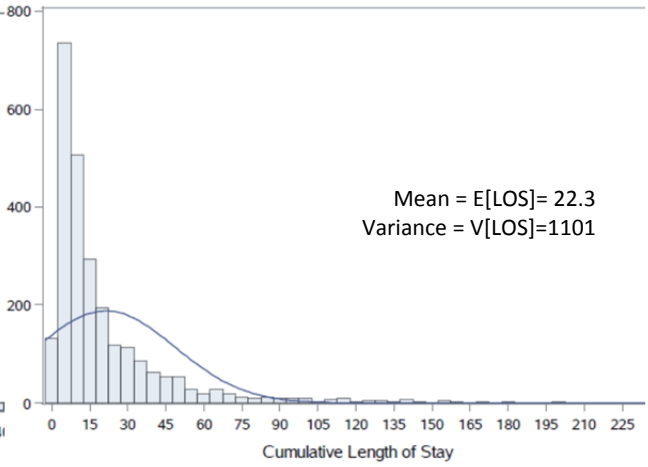


Figure 3B: Domiciled TB Patients



Normal distribution is superimposed; Display truncated at LOS=250

The Poisson regression is typically used for count data, taking the form displayed in Equation 3. Poisson assumes *equi-dispersion* assumption, wherein the variance is roughly equivalent to the mean.

$$Prob[LOS = y] = \frac{e^{-\lambda}\lambda^{y}}{y!}, y = 0,1, \dots, \quad \text{Equation 3}$$

where mean E(LOS) = λ and variance V(LOS) = E(LOS) = λ

The assumption of *equi-dispersion* is too restrictive for the LOS data. As shown in Figure 2, cumulative LOS is *overdispersed, with a variance* more than 60 times larger than the mean.[9] The analysis of LOS therefore calls for a model that explicitly accounts for dispersion. The negative binomial model, which has become the gold standard for analysis of *overdispersed* count data, is a natural choice [31]. The negative binomial model is a generalization of Poisson that replaces the single mean with a continuous mixture of Poisson distributions with the mix distributed as Gamma. The probability that LOS is equal to y days under the negative binomial equation is given in Equation 4. The mean is the same as Poisson (Equation 3) but variance is defined with Equation 5,

[9] Two other tests demonstrate overdispersion. First, the dispersion estimate after fitting the LOS data to a Poisson model, as measured by the deviance divided by the degrees of freedom, is significantly greater than 1 (~46). Second, the dispersion parameter when fitting the data to a negative binomial model is significantly different than zero (CI of 0.67 to 0.94), as shown in Table 6.

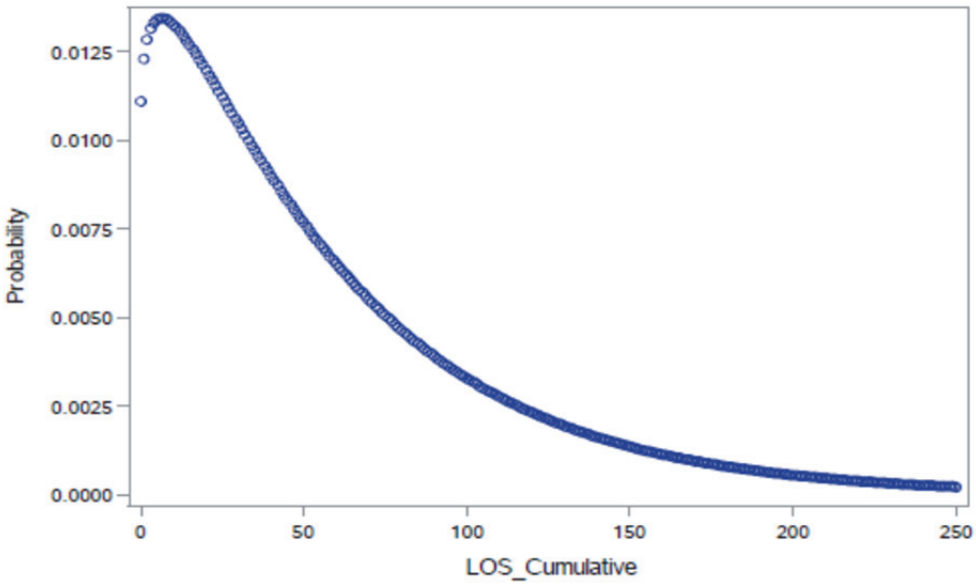
where α represents the *dispersion parameter*, with larger values reflecting greater dispersion. The negative binomial model reduces to Poisson as α approaches zero.

$$Prob[LOS = y] = \binom{y+\frac{1}{\propto}-1}{\frac{1}{\propto}-1}\left(\frac{1}{1+\propto\lambda}\right)^{\frac{1}{\propto}}\left(\frac{\propto\lambda}{1+\propto\lambda}\right)^{y} = \frac{\left(y+\frac{1}{\propto}-1\right)!}{\left(\frac{1}{\propto}-1\right)!y!}\left(\frac{1}{1+\propto\lambda}\right)^{\frac{1}{\propto}}\left(\frac{\propto\lambda}{1+\propto\lambda}\right)^{y}, y = 0,1, \quad \text{Equation 4}$$

$$Variance\ V(LOs): \lambda + \alpha\lambda^2 \quad \text{Equation 5}$$

The probability density function of the negative binomial distribution fit to the mean and dispersion parameter of the LOS data for homeless patients is shown in Figure 4. This provides an adequate fit for the histogram displayed in Figure 2b.

Figure 4: Probability Density Function of the Negative Binomial Distribution of Total LOS among Homeless TB Patients (α =0.885, intercept = 4.09, predicted total LOS of 59.7 days)



Because this regression addresses the population of patients with at least one recorded hospitalization record, the negative binomial model was "zero-truncated." [10] Ordinary negative binomial regression will have difficulty with zero-truncated data. It will try to predict zero counts even though there are no zero values. The zero truncated model calculates the probability that LOS = y conditional on LOS>0, or, LOS ≠ 0, and is therefore defined as $\frac{P(LOS=y)}{1-P(LOS=0)}$. The probability that LOS is equal to zero under the negative binomial distribution is $P(LOS = 0) = \left(\frac{1}{1+\propto\lambda}\right)^{\frac{1}{\propto}}$. The conditional probability associated with the zero truncated negative binomial distribution is therefore given by

[10] In calculated LOS this paper employed the "discharge day" definition in which LOS is calculated by subtracting the day of admission from the day of discharge unless the patient was discharged on the same day as admission, in which case LOS is equal to 1.

Equation 6. Zero truncation was performed in SAS using NLMIXED procedure for fitting non-linear, mixed models.

$$P(LOS = y|LOS > 0) = \frac{\left(y + \frac{1}{\propto} - 1\right)!}{\left(\frac{1}{\propto} - 1\right)!\, y!}\left(\frac{1}{1+\propto \lambda}\right)^{\frac{1}{\propto}}\left(\frac{\propto \lambda}{1+\propto \lambda}\right)^{y}\left(\frac{1}{1-\left(\frac{1}{1+\propto \lambda}\right)^{\frac{1}{\propto}}.}\right) \qquad \text{Equation 6}$$

Results are shown in Table 6, stratified by housing status. For both populations, sputum smear-positive disease and alcohol abuse are significantly associated with longer cumulative LOS. Among domiciled patients, female sex, HIV infection, extra pulmonary disease and dying during disease are significantly associated with longer LOS whereas foreign birth and young age (0-24) are associated with shorter stays. Among homeless patients, drug abuse and disseminated TB are associated with longer stays.

As was found with the analysis of risk factors for hospitalization at diagnosis, the cumulative hospitalization burden posed by a case among the homeless is greater but also less predictable based on patient characteristics and measures of the burden of disease. This finding provides additional evidence in support of the hypothesis that excess hospitalizations among homeless TB patients may be attributed to their housing status rather than the severity of disease. In contrast to domiciled patients, moreover, homeless TB patients that die during treatment spend fewer days in the hospital. This hypothesis is further supported by the finding that dying during treatment (suggesting more lethal disease) is positively associated with LOS for domiciled patients and negatively associated with LOS among the homeless.

Table 6: Determinants of LOS among Patients with a Recorded Hospitalization Using a Zero-Truncated Negative Binomial Regression, stratified by Homelessness Status

	Homeless Patients (N=509)*			**Domiciled Patients (N=2578)***		
Characteristic	**Coefficient Est± (95% CI)**	**Coefficient P-Value**	**IRR**	**Coefficient Est (95% CI)**	**Coefficient P-value**	**IRR**
Intercept	3.9 (3.6-4.2)	0.00	49.6	3.01 (2.9-3.2)	0.00	20.4
Female	-0.03 (-0.3-0.2)	0.80	1.0	***0.16 (0.1-0.3)***	***0.00***	1.2
Foreign Born	0.12 (0-0.3)	0.14	1.1	***-0.12 (-0.2-0)***	***0.04***	***0.9***
HIV Positive	-0.07 (-0.3-0.1)	0.52	0.9	***0.12 (0-0.2)***	***0.06***	***1.1***
Smear Negative	***-0.74 (-0.9--0.5)***	***0.00***	0.5	***-0.57 (-0.7--0.5)***	***0.00***	***0.6***
Died During Treatment	***-0.27 (-0.5-0)***	***0.04***	0.8	***0.55 (0.4-0.7)***	***0.00***	***1.7***
Alcohol Abuse	***0.27 (0.1-0.4)***	***0.00***	1.3	***0.31 (0.2-0.4)***	***0.00***	***1.4***
Drug User	***0.18 (0-0.4)***	***0.04***	1.2	0.12 (0-0.3)	0.12	1.1
Cavitary TB	0.08 (-0.1-0.3)	0.42	1.1	0.05 (0-0.2)	0.31	1.1
Extra Pulmonary TB	-0.02 (-0.3-0.2)	0.90	1.0	**0.19 (0.1-0.3)**	**0.00**	**1.2**
Miliary TB (Disseminated)	***0.76 (0.1-1.4)***	***0.03***	***2.1***	0.04 (-0.4-0.5)	0.85	1.0
Age 0 to 24	-0.01 (-0.5-0.5)	0.96	1.0	***-0.16 (-0.3-0)***	***0.01***	***0.8***
Age 65 Plus	0.06 (-0.3-0.4)	0.78	1.1	-0.04 (-0.2-0.1)	0.58	1.0
Dispersion Parameter (α)	0.78 (0.7-0.9)	0.00	2.2	1 (0.9-1.1)	0.00	2.7

*Patients with more than 365 cumulative inpatient days were excluded from this regression analysis due to potential data

processing errors. For this reason, predicted mean LOS values based on regression coefficients may be slightly smaller than those presented in Table 4 and Figure 2.

±The coefficient estimates can be interpreted as the differences in the logs of expected LOS for a one unit change in the predictor variable given that all other predictors are held constant. Alternatively, the mean LOS response is multiplied by the exponentiated coefficiente^{β_i}, expressed as the Incident Rate Ratio (IRR), per unit increase in the predictor.

3 Outpatient and Case Management Costs

Outpatient treatment and case management costs include all direct costs incurred by the health system associated with the TB diagnosis after hospitalization and before treatment completion. These include the costs of reporting and surveillance, medication costs, the costs of administering treatment by directly observed therapy (DOT), and the provision of "incentives and enablers" to homeless, indigent or otherwise hard-to-treat patient to facilitate treatment completion. The standard treatment regimen for active TB comprises 5 weeks of isoniazid (INH), rifampin (RMP), pyrazinamide and ethambutol followed by 18 weeks of INH and RMP administered by directly observed therapy (DOT). A week of treatment typically consists of a once daily dose, 5 days per week [25]. Patients eligible for incentives and enablers (I&E) can receive vouchers for housing, meals and transportation assistance.

I assume that all patients with culture-confirmed disease initiated treatment.[11] As shown in Table 1, 592 (74%) of homeless patients and 9,994 (82%) of domiciled patients completed treatment for TB disease. The remaining patients either died (15% of homeless, 11% of domiciled) or were lost or moved during treatment (11% of homeless, 7% of domiciled). Less than half of a percent of patients refused treatment and there was only 1 adverse treatment event reported among the cases considered for this study.

Among patients that completed treatment, the average duration of treatment, defined as the number of days between treatment initiation and treatment completion, was 294 days (interquartile range, 216-335) for a homeless patient and 270 days (interquartile range: 195-301) for a domiciled patient.[12] However, a portion of these days may be been spent in the hospital. To avoid double counting treatment costs that may have been incurred in the hospital, I derive average outpatient treatment duration by subtracting the mean inpatient LOS derived in Section 2.3 from total mean treatment duration.

Results are shown in Table 7. Outpatient and case management costs $12,500 per domiciled patient and approximately $9,000 per homeless patient. The higher costs associated with TB housing and incentives for treatment adherence are by shorter outpatient duration due to proportionally greater treatment time spent in the hospital and lower per patient DOT costs. Interviews with TBCP personnel revealed that DOT is typically less resource intensive for homeless patients because they are often residing in a congregate setting close to the public health clinics and can receive DOT in batches. By contrast, public health nurses (PHNs) often have to drive several miles to administer DOT to each domiciled patient.

[11] The actual treatment initiation rate was over 99.5%.

[12] Cases were excluded if the treatment duration was less than 30 days or greater than 3 years.

Table 7: Outpatient and Case Management Costs

Reporting, Surveillance and I&E Liaison Costs Per Case	Homeless	Domiciled	Source
5 Hours of Hospital Public Health Nurse (PHN) Liaison	$308		[32, 12]
4 Hours of TBCP Nurse Manager Time	$420		[32, 12]
3 Hours TBCP Research Assist + 3 Hour Health Education Assistant	$243		[32, 12]
Total Reporting, Surveillance and I&E Liaison Costs/ Case	**$972**	**$972**	
Outpatient Treatment Costs			
Duration/Units of Treatment			
% of Patients Completing Treatment	74%	82%	[30]
Mean Rx Weeks Excluding Hospitalization, If Complete	34	37	[30]
Mean Rx Weeks Excluding Hospitalization, if Not Complete	14	16	[30]
DOT Visits Per Week of Completed Rx	5		[25]
Costs Per Week or Month of Treatment			
Cost of PHN Time per DOT Visitº	$31	$62	[32, 12]
Drug Costs, Months 1-2 (INH, RIF, PZA, ETH)	$11		[25]
Drug Costs, Month 3+ (INH, RIF)	$1.2		[25]
Diagnostics During Rx: 2 CXRs, 2 Cultures, Liver Enzymes	$107		[25]
1 Physician Clinic Visit Per Month of Treatment: Total	$122		[25, 12]
Total Outpatient Treatment Costs	**$5,452**	**$11,336**	
Incentives & Enablers (I&E) Per Case[1]			
Units of Incentives and Enablers Per Case			
Patients Receiving Lodging Vouchers (%)	54%	2%	TRIMS
Patients Receiving Food (Meal/Grocery) Vouchers	62%	12%	TRIMS
Patients Receiving Transportation Vouchers	44%	6%	TRIMS
Unit Costs			
Lodging Costs Per Voucher Recipient (Mean)	$4,476	$3,704	TRIMS
Food (Meal/Grocery) Costs Per Voucher Recipient	$431	$517	TRIMS
Transportation Costs Per Voucher Recipient (Mean)	$77	$77	TRIMS
Total Incentives & Enablers Cost	**2,723**	**$139**	
Total Outpatient Costs	**$11,633**	**$12,447**	

º DOT requires 30 minutes of PHN time for a homeless case and 1 hour of PHN time for a domiciled case. Homeless cases are less resource intensive because they are co-located and require less PHN travel [32].

DOT: Directly Observed Therapy; Rx: Treatment; I&E: Incentives & Enablers; TBCP: Tuberculosis Control Program; PHN: Public Health Nurse

4 Contact Investigations

Due to the high risk of activation in the period immediately following infection, public heath jurisdictions are required to promptly identify, evaluate, and treat test positive household and non-household "close contacts" of each infectious source case. These efforts, known as "contact investigations," (CI) are conducted by Public Health Nurses (PHNs) and Public Health Investigators (PHIs). A study of 2,032 cases reported between 1999 and 2000 in California estimated a cost per contact investigation for drug-sensitive TB among the general population of $4,058 [33].[13]

Costs per CI among the general population may under-estimate CI costs associated with homeless cases. Anecdotally, CIs are "three to five times as expensive" for homeless source cases due to unique challenges associated with eliciting and locating the close contacts of homeless persons. For domiciled patients, close contacts are typically family members, close colleagues, and others that the patient can readily identify and locate. Homeless patients, by contrast, can share living spaces with hundreds of unique contacts during their infectious period, many of who use nicknames and nearly all of whom lack a stable address. A PHN interviewed for this study illustrated the challenge explaining that they have to search for "Papa Joe that stays near the liquor store on San Pedro." Moreover, the source cases are often non-cooperative or even combative with the PHNs tasked with eliciting and evaluating contacts.

Prior studies have documented the challenges associated with CIs of homeless cases [34]. However, the marginal cost attributable to homelessness has not been studied. Moreover, the cost margin is difficult to estimate because TB surveillance data systems (e.g., TRIMs in LAC) only record information on contacts that were successfully evaluated for LTBI and do not record information on the number contacts that were *elicited but not located,* which may consume significant resources.

To estimate the staff time associated with successful and unsuccessful attempts to source contacts per index patient, semi-structured interviews were conducted with three DPH Community Health Services (CHS) employees, including two PHNs responsible for contact investigations among the homeless in downtown Los Angeles and a member of the CHS management staff. Average total CI costs per source case (or "index patient", IP) is characterized by the formula presented in Equation 7, where Total_Contacts_Elicited is equal to the sum of the average contacts evaluated for LTBI (observed) and the average contacts that were elicited but not located (not observed). *Total_Contacts_Elicited* was estimated with data from the semi-structured interviews. *For every one contact successfully evaluated, the PHNs estimate that one contact was elicited but not located.* Thus, *Contacts_Not_Located* is assumed to be equal to *Contacts_Evaluated*.

CI_Cost=C_Contact_Elicitation + Contacts_Evaluated_Per_IP*(C_Locate_Contact + C_Evaluate_Contact) + (Elicited_Contacts_Not_Located*C_Attempt_to_Locate) Equation 7

Where Total_Contacts_Elicited=Contacts_Evaluated + Contacts_Not_Located= 2*Contacts_Evaluated

[13] The study reported a cost per contact investigation of $2,263 in 1998 dollars. I adjust for medical cost inflation of 79.3% between 1998 and 2014.

The average number of contacts evaluated and elicited, and associated costs, are presented in Table 8. These tables show that contact investigations are approximately four times as expensive for homeless patients ($16,250 compared to $4,050). While the costs associated with domiciled cases were not directly evaluated by this study, the cost margin appears to be driven by the costs associated with failed attempt to locate elicited contacts and (~$9,000 per index patient), costs associated with locating homeless contacts on the street (~$1,100 per index patient) and a resource-intensive elicitation process (~$1,300 per index patient). The estimated cost margin derived from the decomposed cost categories presented in Table 8 aligns with 'back-of-the-envelope' estimates provided by those interviewed for this study. Prior to breaking down costs, interviewees estimated that homeless CIs are 3-5 times as expensive.

Table 8: Contacts Investigated, Evaluated and Elicited Per Source Case among Homeless in LAC

Resource Category	Cost/ Contact	Cost/ Index Patient
Contact Elicitation: Total Costs Per Index Patient (IP)		**$1,283**
8hrs of CHS PHA Time to Interview and Report on IP if Homeless		$385
10hrs of CHS PHN Time to Verify IP Location, Contact List and Elicit Contacts		$617
1hr of Area Medical Director's Time to Review List/Recommend Screening		$234
2hrs shelter worker time to facilitate elicitation		$47
Location & Evaluating Contacts: Total Contacts Elicited and Evaluated Per IP	**Percent or Mean**	
Cases with >0 Contacts Successfully Evaluated (%)	50.7%	
Contacts Successfully Evaluated Per Case if >0 Evaluated (Mean)	9	
Contacts Elicited Per Contact Successfully Evaluated (Mean)	2	
Cases in Which No Contacts are Elicited (%)	25%	
Contacts Located in Non-Shelter Locations (%)	25%	
Contacts Located in Shelter Setting if Found (%)	75%	
Contacts Classified as Medium or High-Priority (get CXR) (%)	73%	
Locating & Evaluating Contacts: Total Costs Per IP		**$11,318**
2hrs of PHN time to locate and evaluate contact | found at shelter	$123	$833
8hrs of PHN time to locate & evaluate contact | found outside of shelter	$493	$1,110
8hrs of PHN time to attempt to locate | elicited but not found	$493	$8,881
2hr of shelter worker time to facilitate evaluation		$47
5hrs of PHI time (interviews with difficult-to-locate or combative contacts)		$189
4hrs of community worker + 4hrs of health educator		$257
Management and Support Staff Time to Elicit and Evaluate: Total Costs Per IP		**$1,618**
12hrs of PHN Supervisor (PHNS) time per homeless index patient		$830
6hrs of clerical work (pulling records, courier services)		$135
1hr of laboratory technician per contact evaluated	$45	$402
1hr of radiologist per high-priority contact evaluated	$38	$252
Non-Personnel Costs: Elicitation and Evaluation, Total		**$896**
IGRA Cost	$53	$481
2 Chest Radiographs	$56	$368
Transportation and Parking (~ 4 trips to shelter and back, private vehicle)		$46
LTBI Treatment if Completed		**$1,132**
LTBI Positive Among Patients Evaluated (%)	28%	
Treatment Initiated & Completed if LTBI Positive (%)	40%	
Cost Per LTBI Positive Contact Successfully Treated (3HP), Cite Shelter Screening [11]	$1,128	
	Homeless	**Domiciled***
Average Total Contact Investigation Costs	**$16,246**	**$4,058**

*CI costs per domiciled case were not analyzed in this study. The estimate provided in this table is derived from a study of 2,032 drug-susceptible cases reported within CA during 1999-2000 [33].

Personnel time based on semi-structured interviews [35]. Personnel, unit costs from published salary data [12]. LTBI treatment costs assume 3HP, detailed breakdown of costs is provided in the Shelter Screening CEA [11].

IP: Index Patient; LTBI: Latent TB Infection: PHA; Public Health Analyst, PHN: Public Health Nurse; PHI Public Health Investigator; CHS: Community Health Services

5 Discounted Secondary Cases

5.1 Methods

I estimate the number of secondary cases per homeless index case in LAC using genotyping data on the homeless cases reported to LAC-DPH during 2007-2013, literature estimates of the annual progression rate, and life expectancy estimates. I first derive an estimate of the new infections per case and subsequently estimate the number of new cases that this cohort of newly infected persons will produce in each subsequent year.

Total discounted secondary cases is equal to the sum of discounted near term cases, assumed to present in one year following the primary case, and discounted reactivated cases, which will present at some point during the life expectancy of the newly infected person. As shown in Equation 8, the number of undiscounted near-term secondary cases per active case are equal to the number of secondary infections times the fast progression rate (PR_{Fast}). The number of undiscounted reactivated secondary cases is equal to the remaining infected cases (subtracting those that activate in the near term) times the lifetime risk of reactivation. The lifetime risk of reactivation is shown in Equation 8, where LE is the average life expectancy of an infected person and PR_{Slow} is the annual risk of progression in the years following the fast progressing period.

$$SecondaryNearTerm = InfectedPerCase * PR_{Fast} \quad \text{Equation 8}$$

$$SecondaryReactivated = (InfectedPerCase - SecondaryNearTerm) * (1 - (1 - PR_{Slow})^{LE} \quad \text{Equation 9}$$

The number of new infections per index case is approximately equal to the prevalence of recently acquired infection divided by the incidence of TB disease in the preceding year. I assume that incidence is approximately constant over time (i.e., incidence in the prior year is equal to incidence in the present year). The prevalence of recently acquired LTBI can be estimated by dividing the incidence of recently acquired TB disease ($Inc_{TB-Recent}$) by the "fast" annual progression rate. The incidence of recently acquired TB is equal to the incidence of TB (Inc_{TB*}) times the percent of TB cases attributed to recent transmission. Substituting, the number of new infections per case can be simply estimated by dividing the percent of cases that were recently transmitted by the "fast" annual progression rate (Equation 10). This formula yields a conservative estimate of transmission because it does not account for migration and death. The estimate of transmission in the Shelter Screening CEA is slightly higher because it adjusts for potentially not observing all of the recently transmitted cases due to migration and death.

$$InfectedPerCase = \frac{P_{LTBI-Recent}}{Inc_{TB,Y-1}} = \frac{\frac{Inc_{TB-Recent}}{PR_{Fast}}}{Inc_{TB}} = \frac{Inc_{TB*}\%Recent}{Inc_{TB} * PR_{Fast}} = \frac{\%Recent}{PR_{Fast}} \quad \text{Equation 10}$$

5.2 Trends in TB among the LAC Homeless and the Percent of Recent Transmission Cases, 2007-2013

The percent of recent transmission cases was estimated using genotyping data from homeless TB cases reported to LAC-DPH during 2007-2013 [30]. [14] Summary figures by year are shown in Table 9. Following methods described in Horsburgh et al, the percent of cases due to recent transmission is estimated with the "N-1" method wherein the total number of cases due to recent transmission is equal to the total number of clustered cases minus the total number of *clustered index cases* divided by the total case count with genotyping data available [36]. A case was defined as *clustered* if it shared a genotype with one or more cases reported within LAC during a 3-year time period [37]. The *cluster index case* is the first chronological case in a cluster, which can be assumed to be a case of reactivated disease. GENtype 11610 cases are those that were epidemiologically linked to the large outbreak cluster concentrated in the Skid Row district.[15] During 2007-2013, approximately 79% (95% CI 74%-85%) of all LAC homeless cases and 83% (95% CI 76%-91%) of SPA-4 homeless case were attributed to recent infection.[16] By contrast, only about 20% of cases reported nationally are attributed to recent infection [38].

Table 9: Trends in Tuberculosis Case Counts, Incidence Rates and Percent Due to Recent Transmission among the LAC Homeless, 2007-2013 *

Parameter [30, 39]	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**Total/Avg 2007-2013**
All Homeless TB Cases in LAC*	49	57	35	34	51	39	66	331
GENType 11610 Cases[ɣ]	10	13	9	5	13	15	18	83
Cases in Other Genotype Clusters	22	27	15	21	26	16	28	134[ς]
Index Cases (First in Cluster)	7[ς]	5	3	5	2	1	5	21[ς]
Cases with Genotyping Data	42	42	26	33	41	35	51	228[ς]
% Clustered (Recent Transmission) ±	52%[ς]	76%	73%	67%	83%	89%	75%	79% (74%-85%)

*Non-incarcerated homeless. Excludes cases identified as homeless and in a correctional facility.

[ɣ] Confirmed and Probably GenType 11610 Cases. Includes cases linked to the GENType 11610 outbreak cluster through genotyping data and/or epidemiological linkages (location-based or close-association based linkages

[ς] Genotyping data became available beginning in 2007. The proportion of clustered "recent transmission" cases in 2007 will be underestimated because clustered cases may appear unique or may be incorrectly flagged as an index case due to missing data on earlier cases in the chain of transmission.

± The percent of cases due to recent transmission is estimated with the N-1 method whereby the first case in the cluster ("index") is attributed to reactivated previously acquired infection.

TB: Tuberculosis Disease; SPA: Service Planning Area; GENType: Genotype;

[14] Genotyping data was not available prior to 2007.

[15] Not all of the GENtype 11610 cases were linked through genotyping data. A fraction of the cases were identified through location-based and close association-based linkages during a contact investigation conducted the CDC.

[16] Data from 2007 was excluded from the computation of the average percent clustered because genotyping data was unavailable prior to 2007 which produces upward bias in the estimate of unique cases.

5.3 Annual Rates of Progression to TB Disease among LTBI Infected Homeless in LAC

The lifetime risk of progression to TB disease for a person with LTBI from the general population is typically estimated at 5-10 percent based on data from the placebo arm of controlled trials on LTBI treatments and vaccines [3, 40, 41]. Estimates of the distribution of reactivation risk by time since infection are varied, but the "rule of thumb" is that about half of an individual's lifetime risk of developing TB disease occurs within the first two years after infection [2]. After this "fast progressing" period of 1-2 years the rate of activation, or "reactivation" of previously acquired TB, drops to a low but persistent reactivation rate, with estimates from 30 to 100 cases per 100,000 person years for the general population [41, 42, 43]. The risk of reactivation varies considerably by medical risk factors impacting cell mediated immunity, the host's principal defense against the progression of disease [3].

Annual progression rates in the "fast progressing" and "slow progressing" periods are needed to impute the transmission parameter (secondary infections per source case) and the number of discounted cases associated with the new infections. I estimate both parameters by multiplying literature estimates of the reactivation rate for the general population by the relative risk (RR) of progression associated with homelessness.

Recently infected from the general population individuals are assumed to face a 5% annual risk of progression to TB disease (5,000 per 100,000 PYs) in the first year following exposure [44, 41, 19]. . Following this period, the rate of reactivation drops to 72 per 100,000 person-years (95% CI, 67-77) based on a meta-analysis of five studies conducted within *the Priorities for Testing and Treating FB* paper within this dissertation series [5].[17]

Homelessness is not an independent risk factor for progression. However, it is significantly positively associated with comorbidities such as HIV and substance abuse that compromise the immune system's defense against progression to disease. I estimate the RR of progression associated with homelessness based on the relative prevalence and risk of associated with HIV and alcohol abuse using the weighted RR formula given in **Eq. 8**, where RR_{HIV} and RR_A are the relative risks of HIV and alcohol abuse versus the general population and ΔP_{HIV} and ΔP_A are the differences in the prevalence of HIV and alcohol abuse among the homeless in LAC versus the general population.

$$RR_{Homeless} = RR_{HIV} * (\Delta P_{HIV} - \Delta P_{HIV} * \Delta P_A) + RR_A * (\Delta P_A - \Delta P_{HIV} * \Delta P_A) + RR_A * RR_A * \Delta P_{HIV} * \Delta P_A + 1*(1 - \Delta P_A - \Delta P_{HIV}) \quad \text{Equation 11}$$

The RR of progression versus the general population is 17.8 (95% CI, 10.7-24.5) among persons with HIV infection and 2.7 (95% CI 2-3.8) among persons suffering from alcohol abuse [5]. The rate of HIV infection among the homeless in the Los Angeles County Continuum of Care (CoC0.9% in 2013 [45]. Among the general population aged 15 and older, prevalence of diagnosed HIV was 0.32% in 2012

[17] Among persons aged 15 and older.

[46]. Approximately 37% and 31% of the LAC currently homeless population reports suffering from substance abuse and alcohol abuse, respectively [47, 45].[18] Among the general population, 6.6% report heavy alcohol use [48]. These figures yield a weighted RR of progression associated with homelessness of 1.5. The homeless in LAC therefore face a 7.5% risk of reactivation in the year following exposure and a 0.108% risk in year subsequent year of their life expectancy.

5.4 Secondary Infections And Discounted Secondary Cases Per Active Case

As shown in Equation 10, the number of secondary infections per source case, also known as the "attack rate" or "transmission parameter," is approximately equal to the percent of cases attributed to recent transmission divided by the "fast" progression rate. Incorporating the estimates derived in the following sections yields an estimate 10.5 new infections per source case.[19] Synthesizing the progression rate estimate with the transmission parameter suggests that each active case among the homeless produces 0.79 cases in the first year following exposure and 0.01 cases in each subsequent year [11]. I assume that the average homeless person is 40 years old at infected which yields an undiscounted life expectancy of 22.4 (see the discussion of the standardized mortality ratio associated with homelessness in Section 6). Thus, each active case produces 0.79 new cases in the first year and 0.21 reactivated cases. With discounting, each active case produces 0.91 secondary cases.

In the general population, each case of TB produces approximately 0.23 secondary cases in the near-terms [25, 49, 50]. I assume that infected individuals from the general population face a 5% annual risk of progression to TB disease (5,000 per 100,000 PYs) in the first year following exposure and a 0.072% annual risk thereafter (72 per 100,000 person years) [44, 41, 19, 5, 11]. The average person is assumed to be 40 years with 41.5 remaining life years at infection [51]. The estimate of 0.23 secondary cases therefore implies that each active case produces 4.6 new infections, yielding 0.23 near-term cases and 0.12 reactivated cases over average life expectancy.[20] With discounting, each case of TB among the general population produces 0.29 secondary cases. Homeless patients therefore produce more than 3 times as much transmission as their domiciled counterparts.

[18] Rates of alcohol abuse were reported only for the 2007 homeless count. In 2007, 35% of survey respondents reported suffering problems with alcohol abuse, or about 83% of those reporting any substance abuse problem (LAHSA, 2007). This proportion was applied to reported substance abuse prevalence in 2013 estimate the prevalence of alcohol abuse.

[19] This estimate is conservative and lower than the estimate provided in the Shelter Screening CEA because it does not account for the migration and death potentially decreasing the recently transmitted cases observed in the data. In other words, this estimate characterizes the number of new infections per source case that will be seen within a confined environment.

[20] The estimate of the number of new infections is derived by dividing the total number of near-term secondary cases per case (0.23) by the fast annual progression rate (5%).

Table 10: Secondary Case per Active Case

Category	Homeless*	Domiciled
Secondary Cases Per Active Case		
New LTBI Infections Per Active Case	10.5	4.6
In 1st Year Following Primary Case Diagnosis	0.79	0.23
In each subsequent year of life expectancy	0.010	0.003
Life Expectancy at Infection (Mean Age 40)	22.4	41.5
Total Reactivated Cases*	0.21	0.12
Discounted Secondary Cases	**0.91**	**0.29**
Cost of a Primary Case (Excluding Secondary)	**$193,278**	**$54,170**
Costs of Discounted Secondary Cases	**$176,549**	**$15,615**

*Derived with survival analysis. Total reactivated cases = 1 – ((1-PR) ^LE-U). Where PR is the annual progression risk in the "slow progression" period and LE-U is undiscounted life expectancy.

6 Quality Adjusted Life Years

Quality Adjusted Life Years (QALYs) lost per case were found with life tables, the TB mortality rate from TRIMS (Table 2) and literature estimates of the quality of life decrements associated with active TB disease. Life expectancy for homeless patients is adjusted with a standardized mortality ratio (SMR) of 6, under the simplifying assumptions that the SMR is constant across all future ages and equal to the relative risk of death at each prevalent age of the risk factor. Studies have shown that the standardized mortality ratio (SMR) associated with homelessness can be as high as 9 [52]. Discounted life expectancy (LE_D) was found using the "Mixed DEALE" method proposed by Keeler and Bell [53].The application of the mixed DEALE method is discussed in both of the other papers in this dissertation series [11, 5].

Before accounting for secondary cases, each case of TB among the homeless and non-homeless incurs a QALY loss of 2.5 and 2.7, respectively. Despite higher mortality, QALY losses are lower for the homeless due to reduced life expectancy. Accounting for discounted secondary cases, QALY losses associated with a homeless case exceed non-homeless cases.

Table 11: Quality Adjusted Life Years Lost Per TB Case: Homeless vs. Domiciled

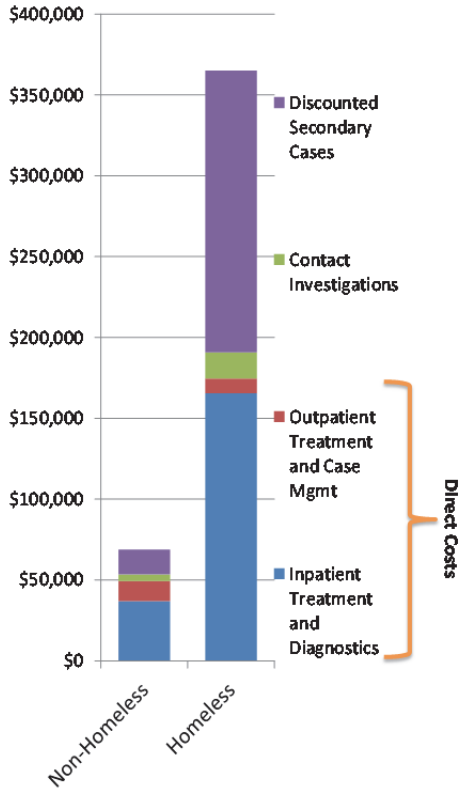
Parameter	Value		Source
QALY Adjustments			
Hospitalization [assume mean LOS]	0.50		[25]
Active Disease (assume 9 months)	0.20		[25]
After Having Disease	0.05		[25]
Remaining Life Years	**Homeless Case**	**Non-Homeless**	
Mean age at Diagnosis	47	47	Table 2
Standardized Mortality Ratio	6	1	[52]
Discounted Life Expectancy	**13.50**	**20.30**	[51]
Probability of Death Per Case (TB or Toxicity)	12%	7%	Table 2
QALYs Lost Per Case			
QALYs Lost Per Case, Excluding Secondary	**2.5**	**2.7**	
QALYs Lost Per Case, Including Discounted Secondary	**4.8**	**3.3**	

*Assume contract TB at same age as primary case. A 46 year old from the general population has 36 expected future life years

7 Discussion

With base case cost and input parameters, this analysis suggests that cases of TB among the homeless in LAC are at least 5 times as expensive as cases among the domiciled population. Including the discounted costs of secondary cases, each case costs the health system an average of $365,000 for a homeless patient and $69,000 for a non-homeless patient. When considering only the direct costs of inpatient and outpatient care, each case costs $175,000 and $50,000 for a homeless and non-homeless patient, respectively. These results are illustrated in Figure 5. The direct cost margin associated with homelessness is driven by long cumulative inpatient lengths of stay (LOS), with homeless patients spending an average of 25 additional days in the hospital. Indirect costs are driven by higher levels of transmission among the homeless (0.91 discounted secondary cases per active cases among the homeless versus 0.29 among the non-homeless), and more resource intensive contact investigations. Total per-case costs by resource category and housing status are shown in Figure 5.

Figure 5: Total Costs of a Case of Drug-Susceptible TB in LAC, 1998-2014, Stratified by Housing Status



Despite the homeless facing TB mortality rates nearly twice as high as the general population, each case of TB in the present time period results in fewer QALY losses (2.5 versus 2.6 for the general population) due to shorter life expectancy. Accounting for discounted secondary cases, 4.8 and 3.2 QALYs are lost from homeless and domiciled cases, respectively.

The likelihood of presenting to the emergency department at diagnosis as well as the cumulative hospitalization burden posed by a case of TB is associated with fewer significant patient characteristics or measures of the severity of disease. A possible interpretation of this result is that the excess hospitalizations associated with homelessness more attributable to the patient's lack of stable housing than the burden of disease and could therefore be reduced by addressing the housing status of the at-risk population. This hypothesis is supported by the fact that smear-positive homeless cases must be placed in respiratory isolation in an inpatient setting because they cannot be safely isolated at home.

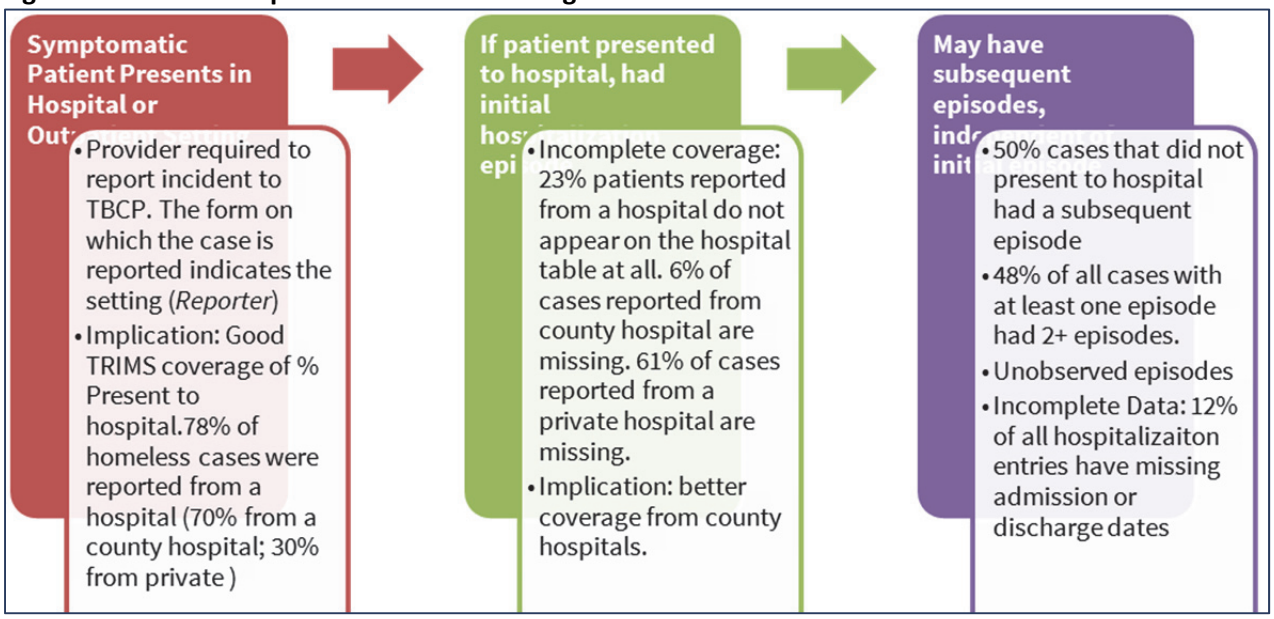
These results suggest that studies examining TB control interventions targeting the homeless may underestimate cost effectiveness of the intervention if cost inputs are based on the costs of a case among the general population. The high cost of averted cases among the homeless suggests that even expensive interventions may generate cost savings, particularly when accounting for transmission.

There are several important limitations to this analysis that should be addressed in subsequent research. With respect to inpatient costs, data should be collected from private LAC-area hospitals to estimate average per-case inpatient days that are not reported to LAC-DPH or captured within the TRIMS database. Further, I was unable to generate an estimate of the percent of time spent in respiratory isolation and the associated per-day cost margin. The outpatient cost estimate is significantly influenced by the per-dose cost of DOT. However, the estimated personnel requirement associated with DOT for homeless and non-homeless cases was imprecise and requires further study. The calculation of secondary cases makes the simplifying assumption that all transmission occurs within the sample population (e.g., homeless cases only cause secondary homeless cases). Further study is needed into the extent to which homeless cases transmit Mtb to domiciled populations and vice versa. Sensitivity analysis is needed to examine the influence of cost input parameters and assumptions. Finally, the study did not account for societal costs. As a consequence, the summary cost estimates may under-estimate the cost associated with a domiciled case.

Appendix A: Cost of a Case Inputs and Supplemental Figures

Illustrating TRIMS Hospitalization Data Coverage

Figure A.1: TRIMS Hospitalization Data Coverage



Per-Day Costs and Cost Margins for Hospitalizations

Inputs for per-day hospitalization costs are listed in Table A.1. The primary data source was an extract from the LAC+USC hospital Affinity Health Information System (HIS) on total and per-day costs for domiciled ad homeless patients accompanied by a semi-structured interview with the Chief Financial Officer at LAC+USC [15].

Table A.1: Hospitalization Per-Day Costs by Type of Stay

Variable	Estimate	Sources/Rationale
Cost per day: General Ward	$2,888	In 2012 the average cost per day for TB patient in LAC+USC acute medical (general ward) was $2831 [15]. In Taylor 2000 the median cost per day is $1,370; in Millman 2013 it is $2,579.
ICU Cost Margin	$1,546	In 2012 the average cost per ICU stay for TB patients at LAC+USC was $4,347 for ICU stays [15]. . In Huynh et al 2013 ICU/day cost $4,364 [54].
Respiratory Isolation	$1,370	Marginal cost (MC) of an isolation room is $1, 1718 in 2013 dollars. However, this assumes a lower per-day general ward cost.
Medical cost inflation	Varies by year	BLS 2013 [16]

Respiratory Isolation Costs and Assumptions

Table A.2: Respiratory Isolation Requirements, Assumptions and Calculations

Variable	Value	Source
Policy Requirements: Conditions for Respiratory Isolation		
Min. Days in Respiratory Isolation if Smear Negative (27)‡	5	CA DPH 2006
Min. Days in Respiratory Isolation if Smear Positive (27)‡	14	CA DPH 2006
Days Until Conditions are Met		
Average Days Until 3 Consecutive Negative Smears ‡	27	TRIMS
Average Days in Respiratory isolation Per Patient	21	Imputed
Cost Margin		
Isolation Rooms - Marginal Cost Per Day	$1,100	Millman 2013

‡ Guidelines set by California DPH. Days until third consecutive smear was set equal to the LOS of the first hospitalization episode if days until the third smear exceeded this LOS.

California DPH guidelines require a minimum of 14 days in respiratory isolation if the patient is smear positive and a minimum or 5 days I respiratory isolation if the patient is smear negative [24], In Millman 2013, the marginal cost of isolation room was $1,527 in 2009 dollars [26]. Accounting for 12.5% medical cost (MC) inflation since 2009, the marginal cost of an isolation room is $1,718. [16]. However, Millman is assuming a lower per day hospitalization cost ($2,338 versus $2,888 in 2013 dollars), so the MC of the isolation room is reduced by the margin with which the estimate of per day costs is higher (2888- 2338). This results in a total MC of isolation rooms of $1,100.

Diagnostic Costs

Table A.3: Diagnostic Costs Associated with a Case of TB

Diagnostic Costs (Smears, Cultures, CXRs)	Estimate	Sources
3 Sputum Smears + 3 Cultures + 2 Chest Radiographs	$63	[14, 13, 16]
3 Bacterial Cultures	$16	[14, 13, 16]
2 CXRs	$56	[14, 13, 16]
1 Hour of Physician Time	$137	[12, 25]
2 Hours of Nurse Time	$129	[12, 25]
Total Diagnostic Costs	$401	

The Cost Effectiveness of Mandatory Annual Screening for Latent Tuberculosis Infection in Los Angeles Homeless Shelters

Jessica M. Yeats

Abstract

Setting: The Los Angeles County (LAC) Department of Public Health (DPH) is currently combatting the largest outbreak of Tuberculosis (TB) among the homeless to have been reported in the United States. In response to the TB outbreak concentrated in Downtown LA's Skid Row District, in 2013 LAC-DPH issued the recommendation that LAC shelter operators screen all clients at least once annually for latent TB infection and refer positive cases to treatment. However, compliance with the screening requirement is not yet mandatory.

Objectives: To characterize the transmission of TB in downtown Los Angeles and to estimate the cost effectiveness of annual LTBI screening in homeless shelters in order to inform the decision on whether to reissue the shelter screening recommendations as a mandatory Health Officer order.

Methods: A discrete time-driven stochastic microsimulation that compares simulated costs and outcomes associated with mandatory, annual LTBI screening to those associated with no LTBI screening in a hypothetical cohort of 20,000 persons experiencing homelessness in downtown Los Angeles. The model was calibrated to reflect trends in TB in downtown Los Angeles during 2007-2013.

Results: This study estimates the prevalence of LTBI to be 16% among the downtown LA homeless population and 11.5% among the broader LAC homeless population. Incorporating estimates of migration, these data suggest that each case of active TB produces approximately 13.2 new Mtb infections in SPA-4 and ~12.6 new Mtb infections in LAC. Due to fixed up-front and annual costs per participating shelter, the efficacy of a mandatory annual shelter screening intervention depends on treatment capacity. Public health clinics serving the population may only have the capacity to initiate treatment for about 7% of the LTBI infected population per year. Under this constraint, the mandatory screening initiative is equivalent to randomly testing 7% of the population per year, which may be a less effective use of limited treatment resources than targeting groups facing an elevated risk of progression (in particular, close contacts of infectious cases). If LAC-DPH could increase capacity to approximately 600 treatment starts per year within SPA-4 the intervention would be cost saving between the fifth and ninth year and would be cost-saving under a wide range of compliance and initiation parameters. The study finds that there are diminishing returns to increasing annual treatment capacity beyond 600 starts per year.

1 Quick Start User Guide

1.1 Overview and Running the Model

This enclosed model simulates the transmission of TB and associated health and economic outcomes in a homeless population without LTBI screening (status quo) and with mandatory annual LTBI screening at homeless shelters (intervention). The model compares total discounted societal costs and life years lost under the intervention and status quo scenarios over a user-defined time-horizon ("simulation-years") to evaluate the cost effectiveness of mandatory annual shelter screening. The simulation proceeds in one-week time increments.

The program is implemented in NetLogo, a freely available simulation environment developed by the Center for Connected Learning and Computer-Based Modeling. The program can be downloaded at https://ccl.northwestern.edu/netlogo/download.shtml. The specific model described in this paper is available by request to the author at Jessica.yeats@gmail.com.

To run the model, open the attached TBShelterScreeningCEA.nlogo file using the NetLogo program. On the "Interface" tab, press the "Setup" button followed by the "Go" button. The model runs in one-week increments and will run for the number of weeks implied by the user-defined "Simulation-Yrs" parameter. Once it has run for the specified number of years model results will be saved in the *TBShelterCEA_Results.csv* file.

Default intervention model parameters for the initial status quo and intervention cohorts were calibrated to replicate the epidemiology of tuberculosis among the homeless population in Downtown Metropolitan Los Angeles (Service Planning Area-4) during 2007-2013, as displayed in Table 7. It can be adapted to fit the population and epidemiological dynamics of different jurisdictions by adjusting the default user-input parameters. If you wish to make changes to the default user-input values, do so before pressing the "Setup" button. If you wish to discard the changes, press the "Reset Defaults" button.

Transmission of LTBI, disease activation, transitions between shelters, and LTBI treatment initiation and continuation occur stochastically based on pseudo-random numbers generated by NetLogo. The numbers are generated by a deterministic process initiated by a random "seed" that can be pre-determined to enable reproducible results.[21] The model is initialized with seed -832181 at setup and during transmission and activation transitions, which correspond to the average results of 75 runs in which the seed was varied but all other parameters were held constant.

The simulation environment is represented in the NetLogo world of "turtles" (homeless clients or "agents") and "patches" (land). The status quo scenario is represented in the top half of the world; the intervention in the lower half. Users wishing to increase the speed of the model may uncheck the "view updates" checkbox in the toolbar. Model results are saved in the CSV file *TBShelterCEA_Results.csv*. Each row represents a single model run.

[21] Seeds can be selected within the range of -2147483648 to 2147483647.

1.2 Model Assumptions

An overview of key modeling assumptions is provided in this section. See the accompanying paper and model documentation for the full set of assumptions.

- The population is constant over time. New entrants replace individuals that die or migrate out of the simulation environment. Death and migration reduce transmission because agents within the replenishing cohort are less likely to be infected with LTBI.
- Agents transition through the shelter and the street probabilistically. Agents stay in a shelter for six weeks, or the duration defined by the user. At the end of the shelter duration period, all agents within the shelter return to the street and a new cohort of shelter participants is randomly selected from the population. As a consequence, each agent is equally likely to seek admission to each of the shelter at each transition point.
- Agents with LTBI face the greatest risk of TB disease activation during the first year following exposure. At the beginning of the second year, the risk drops to a low but persistent reactivation rate. Annual progression risk is the product of hard-coded reactivation risks of the general population (defined in Table 4) and the user-input parameters for the relative risk of progression associated with homelessness.
- TB disease progresses through three stages following disease activation: an infectious period wherein the patient is undiagnosed, infectious and progressively symptomatic; an inpatient treatment period following diagnosis; and an outpatient period wherein the patient may reside in dedicated "TB housing." At the end of the treatment regimen the agent either dies or recovers completely.
- Transmission of latent TB infection can occur when an agent with undiagnosed, active TB disease comes into contact with an uninfected agent. Diagnosis is always immediately followed by treatment, which renders the agent non-infectious. There is no exogenous re-infection. Infection with LTBI confers immunity to subsequent infections.
- The percent of TB disease cases that were due to recent transmission (as opposed to reactivation or previously acquired LTBI) is constant over time. The percent of cases recently transmitted is equal to the percent of cases occurring in a genotype "cluster" with the exception of the first or "index" case ("N-1 method").
- There are constraints on the total number of homeless clients that can be tested and treated for LTBI in downtown LA. LTBI treatment resources are the bottleneck constraining capacity given high LTBI test positive prevalence and the relative costs and personnel requirements associated with treatment.
- Mandatory annual shelter screening (the intervention) is implemented as follows. Complying shelters ask shelter participants to provide proof of LTBI "clearance" within 7 days of entry. This "shelter screen" incurs a small cost for each agent seeking admission to a shelter regardless of the agent's clearance status and whether or not the clinics have met their treatment capacity limits. Agents are "cleared" for shelter entry if they were LTBI test negative or LTBI test positive and treated within the past year. If the client is not cleared, they are referred to LTBI testing if there is residual treatment capacity at the public health clinics serving the downtown LA population. Clients that refuse testing or are test positive

and do not initiate treatment are required to leave the shelter. If the clinics have met their capacity limits for initiating treatment, the agent is not tested and is permitted to stay within the shelter.

- Users can choose whether adhering agents are tested for LTBI with the IGRA blood assay (QuantiFERON®-TB Gold In-Tube) or the Tuberculin Skin Test (TST). LTBI test positive individuals are evaluated for TB disease with a chest X-ray (CXR) and medication evaluation. Test positive agents are offered treatment with a 12-dose regimen of weekly Rifapentine plus isoniazid ("3HP") administered by directly observed therapy (DOT). Treatment reduces but does not eliminate the probability of progression to TB disease.
- There are fixed costs overall and per participating shelter. There is a one-time cost associated with system upgrades that is imposed regardless of the number of shelters participating. Each participating shelter also incurs up-front and annual costs associated with training and system upgrades. These costs do not vary with the number of agents tested or treated.
- The intervention reduces transmission through two mechanisms: first, a portion of LTBI test positive agents are treated which reduces the probability of progression to disease and therefore of transmission; second; some active TB cases are actively diagnosed through LTBI screening.
- All costs and health outcomes, including future life years, are discounted at a 3% rate.

1.3 Parameters

The model has been populated with default values calibrated to approximately represent trends in TB in LAC's SPA-4 during 2007-2013 (see Section 4.1). Table 1 - Table 3 document the user-input parameters, those that can be modified on the NetLogo interface to adapt the model to different jurisdictions or epidemiological trends. Table 4 describes the hard-coded parameters. Table 4 describes the parameters that are implied by the user-input variables.

1.3.1 User-Input Parameters

Table 1: Population, Environment and TB Morbidity and Transmission

Parameter	Description	Default Value	Ref./Section
Population & Environment			
Simulation-Yrs	Years to be simulated by the model. The model proceeds in one-week increments. The total number of transitions is equal to 52 * Simulation-yrs.	10	
Population	Approximate initial population. The exact initial population is adjusted to ensure consistency with given population density parameters.	20,000	4.2.1
Pct-Sheltered	Percent of the population residing in a homeless shelter on a given night.	36%	4.2.4
Shelter-Density-Factor	The multiple by which population density within shelters exceeds density on the street. Higher values will correlate with greater shelter screening efficacy.	2.5	
Homeless-SMR	The standardized mortality ratio (SMR) associated with homelessness, operationalized as the relative risk of death vs the general population by age. A higher SMR leads to a higher annual death rate which reduces transmission.	5	4.2.3
TB Morbidity & Mortality			
TB-Incidence-Start	Approximate initial incidence of TB disease per 100,000 persons. The actual incidence is adjusted due to rounding in assigning of initial prevalent cases.	95	4.3.1
Mortality-Rate	Probability that a homeless person with TB will die from TB related causes.	15%	4
Transmission			
TB-Pct-Recent	The percent of incidence TB disease cases that were recently transmitted. Equivalent to the percent of cases that were non-index “cluster” cases.	83%	4.2.1
Prog-Rate-RR-Homeless	The relative risk of progression to TB disease (in both the fast progressing and slow progressing states) associated with homelessness due to relative prevalence of comorbidities/ immunosuppression	1.5	4.3.3
Migration-Rate	Annual migration rate. Migration reduces transmission. The true rate may be higher but	20%	4.2.6
LTBI-Prev-RR-New-Entrants	The relative risk of LTBI infection among new entrants versus individuals within the simulation. Lower values reduce transmission.	0.75	4.3.9

Table 2: LTBI Testing and Treatment Efficacy

Parameter	Description	Default Value	Ref./Section
LTBI Testing and Treatment Efficacy			
Treat-Capacity-Starts-Add-Annual	Total number of homeless clients that LAC-DPH can treat (initiate) per year, in addition to those already treated.	200	4.6.7
Shelters-Complying	Total number of shelters (out of 8) that are implementing the intervention.	50%	4.6.3
Pct-Shelter-Refusers	The percent of the simulated population that does not seek shelter. Higher values will correlate with lower shelter screening efficacy.	10%	4.2.4
Pct-Client-NonCompliers	Percent of homeless clients that refused to test if referred. This propensity is indexed when the agent enters the simulation.	17%	4.5.3
Clearance-Period-Wks	The number of weeks that a client is granted permission to a shelter following a negative LTBI test or LTBI treatment initiation	65 Weeks	4.6.6
Initiation-Rate-3HP	Percent of test positive homeless clients that initiate treatment. Data from Horsburgh 2011 study.	65%	4.5.8
Completion-Rate-3HP	Percent of clients initiation treatment that complete it.	61%	4.5.9
Risk-Reduction-3HP	The reduction in the risk of progression to TB disease conferred by completing 3HP LTBI treatment. Partial completers have partial risk reduction.	0.85	4.5.10

Table 3: Cost Inputs

Parameter	Description	Default Value	Ref./Section
Costs: LTBI Screening, Testing and Treatment			
Discount-Rate	Rate at which all future costs and QALYs are discounted.	3%	4.6
C-Shelter-Screen	The cost to the shelter to screen for LTBI clearance at entry. Assuming 10 minutes at $24/hour. Cost incurred regardless of clearance status.	$3	Table 11
C-IGRA	The cost to administer and interpret the IGRA LTBI test.	$56	Table 11
C-TST-Placement	The cost of TST placement	$24	Table 11
C-TST-Read	The cost to read the TST result	$21	Table 11
C-Eval-LTBI-Pos	Cost to evaluate the agent if they are LTBI test positive. MD Visit + CXR	$119	Table 11
C-3HP-Weekly	Weekly costs of 3HP dose, DOT visit and incentive vouchers. Amortized monthly clinic visit and labs.	$94	Table 13
C-Shelters-Adopt	The cost incurred by each complying to adopt the screening intervention, including training and data system changes.	$400	Table 13
C-Annual-Training	The annual cost incurred by each complying shelters associated with training new staff on the intervention	$500	Table 11
Costs of a Case			
Hosp-Weeks-Mean	Average inpatient length of stay attributed to TB disease. Actual LOS is assigned stochastically and exponentially distributed.	7 Weeks	Yeats 2015
C-Inpatient-Daily	Average cost of a general ward hospital stay – from LAC+USC hospital	$2,888	
Outpatient-Mgmt-Weekly	Average weekly costs of mediation, DOT, clinic visit, TB housing, and other incentives and enablers		Table 11
CI-Cost	Cost of a Contact Investigation. Methodology in 'Cost of a Case' Paper	$15,000	

1.3.2 Assumed or Hard Coded Parameters

Assumed and hard-coded parameters are described in Table 4. Because the model has been calibrated against these assumptions, changing these parameters is not recommended.

Table 4: Assumed or Hard-Coded Parameters

Parameter	Description	Default Value	Ref./Section
Environment			
Shelters	Number of Shelters	8	
Contacts-Per-Day	Number of contacts that an agent comes into contact with per day. Derived from exposed contacts identified during 2013 EPI-AID investigation. Transmission parameters calibrated based on this.	2.8	4.2.5
Shelter Stay Duration	Duration of each agent's stay at a shelter.	6 Weeks	
B Epidemiology / Morbidity			
Prog-Rate-Slow-General	Cases of TB that activate per year per 100,000 persons in the general population with previously acquired (slow progressing) LTBI. The rate for the homeless is multiplied by the Prog-Rate-Homeless-RR	72	Yeats et al 2015
Prog-Rate-Fast-General	Cases of TB that activate per year per 100,000 persons in the general population with recently acquired (fast progressing) LTBI. The rate for the homeless is multiplied by the Prog-Rate-Homeless-RR.	4000	Yeats et al 2015
Fast Progressing Period	The weeks following exposure during which the activation rate is elevated.	52 Weeks	
Infectious-Period-Mean	Mean duration of the infectious period per the 2013 EPI-Aid. The actual duration of the infectious period is assigned stochastically according to the exponential distribution.	18 Weeks	4.3.4
TB Treatment Duration	Total duration of active TB treatment, including inpatient and outpatient treatment.	26 Weeks	
Smear-Pos-Risk	The proportion of active TB cases that are smear positive	68%	4.3.10
LTBI Testing and Treatment Efficacy			
IGRA Sensitivity	The percentage of true positives diagnosed by the IGRA	83%	4.5.5
IGRA Specificity	The percent of true negatives accurately classified by the IGRA.	99%	4.5.5
TST Sensitivity	The percentage of true positives diagnosed by the TST.	92%	4.5.5
TST Specificity	The percent of true negatives accurately classified by the TST – assumes that 30% of the homeless population is foreign born.	96%	4.5.5
3HP Toxicity Severe	The probability that a patient on LTBI treatment is hospitalized due to treatment-related toxicity	0.3%	4.5.11
Severe Toxicity Hosp LOS	The length of stay (LOS) of the typical LTBI treatment-related hospitalization episode.	2 Weeks	4.5.11
Risk of Death from Toxicity	The risk, over the course of the LTBI treatment regimen, that a patient undergoing treatment for LTBI will die from toxicity.	0.014%	4.5.11
TST-Pct-Return-Read	The fraction of patients that had a TST placed that will return to have it read	65%	4.5.4

1.3.3 Implied or Derived Transmission and Epidemiological Parameters

LTBI prevalence is not directly observed. However, given that the fast and slow progression rates are the ratio of incident TB cases to prevalent LTBI cases, this paper proposes that the prevalence of recent and previously acquired LTBI can be imputed based on the observed percent of cases due to recent transmission, literature estimates of the fast and slow progression rates, and the average incidence of TB disease. Overall prevalence is the sum of the prevalence of recent infections ($P_{LTBI-Recent}$, which is equivalent to the incidence of LTBI given our 1-year definition of the fast progressing period) and the prevalence of previously acquired infections ($P_{LTBI-Old}$). The prevalence of recently acquired LTBI is equal to the number of cases recently transmitted divided by the fast progression rate. Likewise, the prevalence of previously acquired LTBI is the percent of reactivated cases divided by the slow progression rate:

$$P_{LTBI} = P_{LTBI-Recent} + P_{LTBI-Old} = \frac{Inc_{TB} * \%CasesRecent}{PR_{Fast}} + \frac{Inc_{TB} * (1 - \%CasesRecent)}{PR_{Slow}}$$

The transmission parameter can be approximated based on the equation above. Before adjusting for migration inflow and outflow, new infections per case is approximately equal to the incidence of new infections ($P_{LTBI-Recent}$) divided by the incidence of TB disease in the preceding year, which reduces to %CasesRecent/Prog-Rate-Fast. The probability of infection if exposed can be derived by dividing the new infections per case by the average number of uninfected contacts per infectious case. For a complete treatment of this topic incorporating migration and background mortality parameters see Section 4.4.3.

Although incident TB cases are observed with the Department of Public Health (DPH) TB surveillance system, it is difficult to assess trends in TB incidence by evaluating data from LAC during 2007-2013 for two reasons: first, the signal-to-noise ratio is small with large year to year variation and a relatively small number of cases per year; second, the true denominator is poorly estimated by surveillance data (see Section 4.1). However, as demonstrated in Section 4.4.2, growth in TB incidence on average should equal the growth in LTBI prevalence if the percent of cases due to recent transmission is approximately stable over time. Thus, we can use average TB incidence to impute LTBI prevalence, and can use our estimates of LTBI prevalence to derive changes in TB incidence.

Table 5 describes the transmission and epidemiological parameters that are implied by these methods. Several of these implicit parameters are displayed on the user interface to the right of the four plots under the header “Transmission Parameters Implied by User-Input Parameters.”

Table 5: Implied or Derived Transmission and Epidemiological Parameters

Parameter	Description	Default Value	Ref. /Section
TB Transmission and Trends			
LTBI-Prevalence	Prevalence of LTBI – derived from the percent of cases due to recent transmission and the fast and slow progression rates.	16%	0
Incidence of LTBI	The rate of new LTBI infections within the population, or, the prevalence of infections acquired within the past year.	1.1%	0
Incidence of LTBI, Endogenous	New LTBI infections per year from endogenous active TB cases (e.g., excluding the new infections from migration). Derived from the fast progress rate and the percent of clustered cases.	1.3%	4.4.1
Infected-per-case-avg	Average number of new LTBI infections per active case of TB. Imputed (approximately) by dividing the new infections per year (endogenous) by the number of active TB cases in the preceding year. Approximately equal to the Pct-TB-Recent / Prog-Rate-Fats.	13.4	4.4.3
Probability of Infection if Exposed: Smear-Positive	The number of new infections per smear-positive case divided by the number of uninfected contacts of each infectious case during their infectious period.	6.0%	4.4.3
Probability of Infection if Exposed: Smear-Negative	The number of new infections per smear-negative case divided by the number of uninfected contacts of each infectious case during their infectious period	1.3%	4.4.3
Annual Growth of LTBI	Annual growth in LTBI prevalence, which on average should equal the annual growth in TB incidence	1.72%	4.4.1
TB Epidemiology and Morbidity			
Prog-Rate-Homeless-Fast	Fast progression rate for the target population per 100,000 PYs. Rate for general population times the RR.	108	4.3.3
Prog-Rate-Homeless-Slow	Slow progression rate for the target population per 100,000 PYs. Rate for the general population times the RR.	7500	4.3.3

1.4 Outcome and Output Monitors

The NetLogo model interface displays several key outcome, output and calibration monitors. The four plots display prevalent TB cases, LTBI prevalence, total discounted life years lost and total discounted costs for the status scenario (blue line) and the intervention scenario (red line).

1.4.1 Outcomes: Effectiveness of Annual Screening

The outcomes monitors, displayed to the right of the four plots, are described in Table 6.

Table 6: Outcome Monitors Characterizing the Effectiveness of the Annual Screening Intervention

Parameter	Description
Cost Per LY Gained	Net cumulative discounted net cost of the screening intervention (costs of the intervention less costs incurred in the status quo scenario) divided by the discounted life years (LY) gained by the intervention. LY discounting is described in Section 4.2.3. A negative number implies cost savings. If no LYs have been gained this monitor will display "No LY Change" or "LYs lost."
Cases Averted, Discounted	Cumulative discounted cases in the status quo scenario less cumulative discounted cases in the intervention scenario.
Net Cost to Prevent 1 Case	The cumulative discounted net cost of the screening intervention divided by the total discounted cases averted .
NNS to Prevent 1 Case	Number needed to screen (NNS) to prevent a case. The total number of agents screened divided by the total discounted cases averted.
Program $ / Year	The costs incurred per year associated with the intervention – e.g., excluding the costs incurred by active cases of TB.
Cost Savings	The cumulative discounted cost savings, if the total discounted costs of the status quo scenario exceed those of the intervention.
Active Cases Yield	The total number of active cases that were diagnosed through LTBI screening.
Reduction in Infectious Period	The reduction in the duration, measured in days, of the mean infectious period of an active TB case due to active case findings from the LTBI screening intervention.
False Positives Treated	The number of true negatives that were diagnosed with LTBI from LTBI screening that completed LTBI treatment.
% LTBI Clearance	The percent of agents in the intervention scenario that are currently "cleared" for shelter admission (LTBI test-negative of have initiated LTBI treatment within the shelter clearance period).
Severe Toxicity Events	The cumulative number of agents that were hospitalized due to LTBI treatment-related toxicity.

1.4.2 Status Quo Scenario Outputs and Calibration Monitors

The user interface monitors changes in several status quo parameters. These monitors, defined in Table 7, enable the user to assess the extent to which status quo model behavior conforms to anticipated trends in TB and LTBI prevalence over time.

Table 7: Outcome Monitors Characterizing the Effectiveness of the Annual Screening Intervention

Parameter	Description
TB % Recent	The percent of prevalent TB cases that were recently transmitted, operationally defined as the fraction of cases that activated from an agent infected with LTBI for less than 1 year. This fraction should be stable over time.
Incidence New LTBI	The rate of new LTBI infections in the population. This should change at the same rate as the expected annual change in LTBI prevalence.
Infectious Cases	The number of prevalent undiagnosed, infectious cases.
Implied Annual Growth in LTBI Prevalence	Defined in Table 5. The expected annual change in LTBI prevalence implied by user-input parameters. Equal to the expected annual change in TB disease incidence.
Actual Annual Growth in LTBI Prevalence.	The actual change in LTBI prevalence within the simulation environment measured at the end of each year. The average LTBI growth rate over several model iterations should equal the implied rate of change.

2 Background

2.1 The Tuberculosis Outbreak in Skid Row and Policy Responses

Homelessness is a risk factor for both *TB infection* (congregate living spaces, high rates of foreign birth, poverty, etc.) and *progression to TB disease* (high prevalence of immune-suppressing comorbidities).[22] As a consequence, environments with high rates of homelessness, like downtown Los Angeles' Skid Row, are particularly prone to TB outbreaks.

The Los Angeles County (LAC) Department of Public Health (DPH) is currently combatting the largest outbreak of TB among the homeless to have been reported in the United States. Since 2007, over 330 cases of active TB have been identified among homeless persons. Among them, over a quarter have been epidemiologically linked by genetic markers to a single chain of transmission, Genotype 11610-PCR8263 ("GENType 11610"). The persistent transmission of TB within this high at-risk population coupled with the high mortality rate of about 20% underscore the need for cost-effective interventions to reduce the ongoing spread of disease.

In response to the TB outbreak in Downtown LA's Skid Row District, LAC-DPH issued guidelines for LAC shelter operators aimed at preventing the transmission of TB among their client population. Among the guidelines, issued in 2013, is the recommendation that shelters screen all clients at least once annually for LTBI and refer positive cases to treatment [55]. Compliance with the screening requirement is not mandatory, however, because it was issued as a guideline rather than a legal mandate in the form of a *Health Officer Order.*

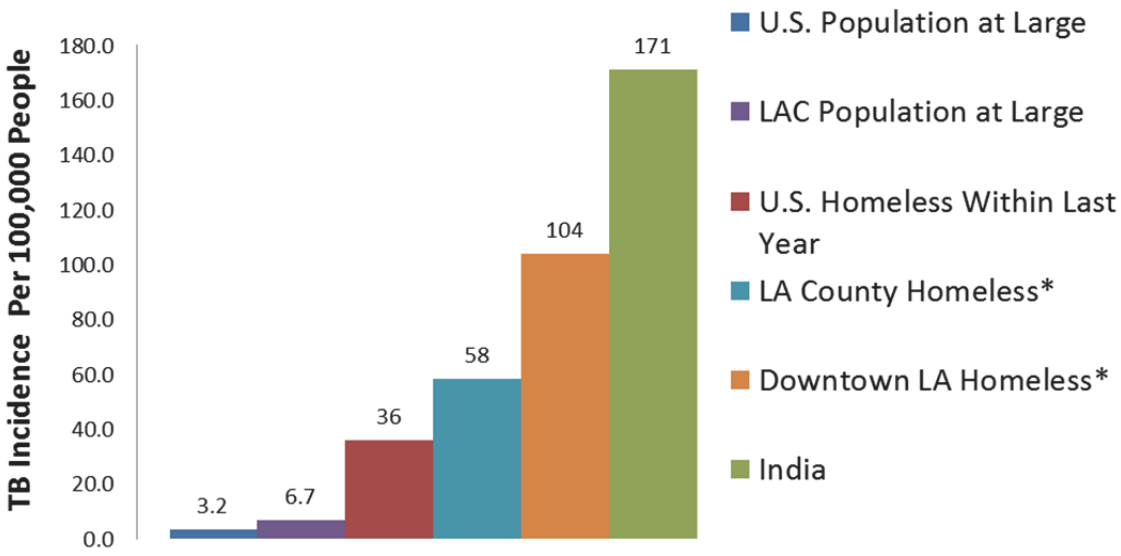
In the general population, annual screening is difficult to rationalize; the low proportion of recent transmission cases (~20%) suggests that less than one half of one percent of all LTBI positive persons were recently infected, or an annual incidence about 18 per 100,000 persons.[23] In an outbreak, however, annual screening will have much higher yield. Higher rates of LTBI and a higher proportion of cases due to recent transmission imply that close to 1-1.5% of the homeless population in downtown Los Angeles is infected with LTBI annually (see Sections 4.3.7 and 4.4.1).

This study proposes a simulation model to evaluate the costs, benefits and cost effectiveness of mandatory annual shelter screening in downtown LA in order to inform policy decisions concerning the extent to which LAC should require homeless shelters to conduct annual LTBI screening.

[22] Thee distinction between TB infection and TB disease is discussed in the introduction to this manuscript.

[23] Using the formula defined in Eq. 26 in the Shelter Screening Evaluation (Paper #2) and assuming reactivation rates documented in the following sections. If the annual risk of progression is 5% in the first year and 0.072% thereafter, and if only 20% of all cases are due to recent transmission, approximately 0.36% of LTBI infections were recently acquired. With an overall LTBI prevalence of 5.1%, this suggest that 0.018% of the general population was recently infected with LTBI.

Figure 1: Incident TB Cases by Population, 2013



*Using the adjusted annualized homeless population derived in Section 4.1.

2.2 Research Objectives

This paper will help to inform the decision on whether to reissue this recommendation in the form of a legal mandate by simulating the outcomes and costs over 10 year period associated with mandatory annual shelter screening in downtown Los Angeles homeless shelters.

This essay will address the following research questions:

1. How quickly was TB transmitted among the homeless population in downtown Los Angeles during 2007-2013?
2. What is the Number Needed to Screen (NNS), among homeless clients in order to prevent one case of active pulmonary TB disease?
3. How much does it cost to screen and treat enough cases of LTBI among the homeless to prevent one active case of TB?
4. What is the net, discounted cost of annual screening per life year saved over a 10-year period and a 20-year period? At what cost effectiveness threshold (per live-year saved) is this policy cost effective?
5. What percentage of homeless clients would need to be screened in order to end or nearly end transmission of the TB outbreak genotype within homeless shelters? What percentage would need to be screened to end or nearly end transmission of all TB genotypes?

2.3 Literature Review

The cost effectiveness of mandatory LTBI shelter screening has yet to be examined in a published study. In assessing the effectiveness of the IGRA LTBI tests versus the tradition TST, Linas et al found that the ICER of TST screening versus no screening was less than $100,000 but that screening with

the IGRA was less economically attractive. However, the study did not explicitly address the homeless and therefore used cost and TB progression risk parameters from the general population, which this paper demonstrates to be inappropriate. It also did not consider dynamics unique to an outbreak environment including elevated rates of transmission [56].

At the 2013 California TB Controllers Association, Grinsdale presented preliminary results from the mandatory annual LTBI screening program implemented in 2005 in San Francisco. The annual cost of the program, excluding treatment, was approximately $69,000 for the 1,729 homeless persons requiring screening. The incidence of TB cases had fallen somewhat during 2005-2013 within city-operated shelters (5 in 2010-2012 versus 8 in 2005-2007) and on the street (30 in 2005-207 vs 15 in 2010-2012) though the change over time was not quantified. Ancillary benefits of the program included improved relationships with shelter operators, increasing TB awareness among shelter staff, easier contact investigations of infectious cases, and better surveillance data. A formal cost effectiveness analysis was not conducted.

Kong and colleagues evaluated a TST LTBI screening program in 4 shelters and 6 residential drug and alcohol treatment programs in Denver during 1995-1998. Screening compliance among the Denver homeless population was 27%, 43%, 69% and 67% in 1995,1996, 1997 and 1998, respectively. TB incidence among the homeless declined from 510 to 121 per 100,000 during 1995-1998. The percent of cases attributed to recent transmission declined from 49% in 1998-1994 to 14% in 1995-1998. Program costs were not assessed or reported [57].

Several other studies have assessed the effectiveness of active case finding programs among the homeless. These programs typically use mobile chest x-rays (CXRs) to identify active cases but do not screen for LTBI. Bernard et al designed and studied a TB screening program among the homeless in 28 shelters across Paris during 1994-2007. They found a decline in total cases and the percent attributed to recent infection from 14.3 per year with 75% recently transmitted in 1997-1999 to 2.7 a year with 30% recently transmitted in 2005-2007. [58] In De Vries et al (2007), a mobile CXR targeting methadone clinics and homeless shelters in Rotterdam screened 3,248 homeless persons during 2002-2005. Prevalence of TB was 3,270 per 100,000 overall. Annual incidence of TB and the percent of cases attributed to recent infection (clustered) fell from 24 and 16% in 2002 to 11 and 8.5% in 2005 [59]. Program costs were not evaluated or reported in either study.

The design of the simulation model proposed in this paper was informed by two studies assessing different TB-related policy initiatives. Porco et al (2006) assessed the cost effectiveness of TB testing and treatment of newly-arrived immigrants using a continuous-time, discrete-event simulation based on a natural history model of tuberculosis [19]. The present study draws heavily from the methods and parameter presented in Porco et al. Shepardson and colleagues used the NetLogo modeling platform to build an open-source simulation model that allows jurisdictions to compare the costs and health outcomes of treating LTBI test positive persons with a 12-dose

regiment of weekly Rifapentine (3HP) compared to a 9 months of daily isoniazid (9H) by self-administered therapy (SAT). [25].

3 Model

3.1 Conceptual Overview

This study uses a discrete time-driven stochastic microsimulation to compare simulated costs and outcomes associated with mandatory, annual LTBI screening (the intervention) to those associated with no LTBI screening (the status quo) in a hypothetical cohort of 20,000 persons experiencing homelessness in downtown Los Angeles. The simulation employs a multistage transition model for TB transmission and progression, proceeding in one-week intervals. Potential transitions are depicted in Figure A.1 and annotated in Table A.1 and Table A.2 in Appendix A.

The model was implemented in NetLogo, [60], a free-available individual-based simulation environment used widely throughout the agent based modeling community [61] [62]. The program can be downloaded at **https://ccl.northwestern.edu/netlogo/download.shtml**. The specific model described in this paper is available by request to the author at **Jessica.yeats@gmail.com**.

The model is initialized with two identical populations representing the status quo (top half) and intervention (bottom half) cohorts. Agents are initially assigned to the street (white patch) or one of eight shelters (orange patch) and transition through shelters probabilistically. At baseline, agents in either cohort may be latently infected (yellow), may be uninfected (blue), or may have active smear-positive or smear-negative disease. Active TB patients are either infectious (red) or on treatment (green). Infectious agents are undiagnosed and therefore transition between shelters and the street at the same rate as their uninfected counterparts. Patients undergoing treatment for TB disease are located in a single, grey patch representing the hospital and TB housing facilities.

Agents with latent infection are assigned an annual risk of progression to TB disease. Agents infected within the past year are assigned a much higher annual risk ("fast progressing") than agents infected at some point in the past ("slow progressing"). No LTBI positive patients have been screened or treated at baseline. Patients with active TB may infect new individuals that they expose during their "infectious period," which begins at disease activation and ends at diagnosis.[24] Exposure is defined as being on the same "patch" as a turtle with active TB. Unless they are treated, agents with LTBI remain infected for their lifetime.

Agents in the intervention cohort are asked by compliant shelters to provide proof of LTBI test "clearance" to gain admission. Agents that have not been tested within the clearance period are referred to testing. Test positive patients are offered treatment, which, if completed, reduces but does not eliminate the probability of progression to disease. The intervention may avert future TB cases in two ways (1) treated agents with LTBI are less likely to progress to active disease and therefore less likely to infect new agents; (2) LTBI screening may detect active TB disease before it

presents passively to the emergency department. The benefits of the intervention, in terms of averted life years lost and resources saved, are derived entirely from the number and timing of cases averted. For this reason, benefits will not begin to accrue until infected agents in the intervention complete treatment and infected agents in the status quo scenario progress to TB disease, which could take several years.

There is no LTBI testing or treatment in the status quo scenario. The impact of status quo LTBI testing and treatment and active case findings initiatives has been accounted for in our calibration of status quo epidemiological and transmission parameters.

Transmission of LTBI, disease activation, transitions between shelters, and LTBI treatment initiation and continuation occur stochastically based on pseudo-random numbers generated by NetLogo. The numbers are generated by a deterministic process initiated by a random "seed" that can be pre-determined to enable reproducible results.[25] The model is initialized with seed -832181 at setup and during transmission and activation transitions, which correspond to the average results of 75 runs in which the seeds were varied but all other parameters were held constant.

The default parameter values for the model presented in this paper were calibrated to reflect trends in TB in downtown Los Angeles during 2007-2013. However, the model can be easily adapted to fit the population and epidemiological dynamics of different jurisdictions.

The state and attributes of each simulated individual on day *t* are represented by the variables identified in Table A.1 in Appendix A. Possible transitions between each state are identified and described in A.2. Individuals are indexed by *j.*

3.2 Outcomes

Model outcomes includes number needed to screen (NNS) among homeless shelter clients to prevent one active case of TB and the incremental cost effectiveness (ICER) of annual screening per life-year gained. Quality adjustments were not considered for two reasons: first, it is difficult to apply traditional assessments of quality adjustments to the homeless population because their quality of life without TB is not comparable to the general population; second, quality adjustments have an insignificant impact on model outcomes because TB patients either fully recover or die within a year and because LTBI treatment has a minimal impact on quality of life. Pursuant to guidance from *the Panel on Cost-Effectiveness in Health and Medicine*, all future costs and quality adjusted life years were discounted at a 3% rate [17]. Simulation outcomes were analyzed in R using the RNetLogo package [63] [64]. Reported results represent the average of 100 replications of the model.

3.3 Data Sources

[24] The model logic and structure is similar to that described in Porco, et al. 2006.
[25] Seeds can be selected within the range of -2147483648 to 2147483647.

Model parameters were populated from four primary sources: LAC DPH TB surveillance data (TRIMS), the CDC report from the epidemiological assistance (EPI-AID) investigation of the GENType 11610 homeless outbreak in March 2013, interviews with public health and shelter staff, and peer-reviewed literature. Data sources for each parameter are described in Section 4.

4 The Simulation Environment: Parameters, Mode Calibration and Output Monitors

4.1 Overview: Characterizing Trends in TB and in the Homeless Population in LAC during 2007-2013

Initial model parameters for the status quo and intervention scenario cohorts were calibrated to replicate the epidemiology of tuberculosis among the homeless population in Downtown Metropolitan Los Angeles during 2007-2013. Administratively, downtown LA is represented by Service Planning Area 4 (SPA-4). SPA-4 serves 11% of the LAC population but about 27% of its homeless population (see Table 8) [65, 45]. The service area includes the Skid Row district of downtown LA and most of the shelters implicated in the large TB outbreak cluster. Population and epidemiological trends related to the transmission of tuberculosis in LAC at-large and in SPA-4 during 2007-2013 are shown in Table 8 and Table 9, respectively.

4.1.1 The Incidence of TB among the Homeless in Downtown LA

Characterizing incidence among the homeless population requires that the definition of homelessness used for the numerator (homeless cases) corresponds exactly to the definition used in the denominator (homeless population at risk). Whether homelessness is defined as “currently homeless” or “homeless within the past year” has a tremendous impact on estimated incidence. For example, the Los Angeles Homeless Services Authority (LAHSA) estimates that 39,463 persons were homeless in shelters or on the street on a given night in 2013 (“point-in-time count”) but that 153,595 persons experienced homeless at some point during 2013 (“annualized projections”). The annualized projection is derived by applying an “annualization factor” to the point-in-time (PIT) count. Table 8 displays the imputed annualization factor by year. Annualized projections for SPA-4 were available only in 2007.

Patients with active TB (the numerator) are classified as homeless on TB Control Program reporting forms if the patient reported experiencing homelessness in the past 12 months. This definition would argue in favor of using the annualized homeless count to impute incidence. However, the unadjusted annualized count may under-estimate incidence in the population of interest for several reasons:

1. Patients that had a transient episode of homelessness in the past year may avoid self-identifying as homeless.
2. According to TBCP analysis, the overwhelming majority of homeless cases are among those currently experiencing homelessness – particularly in SPA-4. Local policymakers felt that the

true denominator for the incidence statistic was "somewhere in-between" the PIT and annualized counts [66].

3. The annualization factor for SPA-4 is unknown. However, local experts feel that the annualization factor for SPA-4 is likely much lower than that projected for LAC.
4. The study is concerned with the population that will encounter the intervention. Because only a fraction of shelters adopt the implementation and because not all homeless clients seek shelter, persons experiencing short-duration transient episodes of homelessness are less likely to encounter the intervention and are therefore less relevant to the calculation of incidence.
5. The TB incidence implied by the reported annualized count (~36 per 100,000 in LAC) would imply an LTBI prevalence of about 6%, much lower than the figures suggested by LAC-DPH screening programs the published literature (see Section 4.3.7).

The denominator used for calculating incidence was therefore set equal to PIT count multiplied by an adjusted annualization factor, equal to the midpoint between 1 and the reported factor. The adjusted annualization factor for SPA-4 during 2008-2013 was derived by multiplying the annual adjusted annualization factor for LAC by the ratio of the reported adjusted factor in 2007 for SPA-4 to LAC. The adjusted annualized population estimates yield an estimated incidence of 52 in LAC and 95 in SPA-4 per 100,000 persons. Model calibration techniques, described in subsequent sections, validated this approach. The TB incidence implied by the adjusted annual population (~56 per 100,000 in LAC) imply an LTBI prevalence of about 11%, which is consistent with LAC-DPH screening programs and the published literature (see 4.3.7). TB incidence estimates over time using adjusted and unadjusted homeless population denominators are shown in Figure 2 and Figure 3, respectively.

4.1.2 Recently Transmitted and Reactivated Cases among the Homeless in Downtown LA

Table 9 presents data on the number and type of TB cases reported in LAC and SPA-4 during 2007-2013. I report the percent of cases occurring within a genotype cluster in order to estimate the proportion of cases recently transmitted. A case was defined as *clustered* if it shared a genotype with one or more cases reported within LAC during a 3-year time period [37]. GENtype 11610 cases are those that were epidemiologically linked to the large outbreak cluster concentrated in the Skid Row district.[26] Distinguishing clustered cases from non-clustered or "unique" cases is important because it enables estimation of the percent of cases attributed to recent transmission, which is needed for model calibration and for estimating LTBI prevalence and rates of new infection [67].

Following methods described in Horsburgh et al, the percent of cases due to recent transmission is estimated with the "N-1" method wherein the total number of cases due to recent transmission is

[26] Not all of the GENtype 11610 cases were linked through genotyping data. A fraction of the cases were identified through location-based and close association-based linkages during a contact investigation conducted the CDC.

equal to the total number of clustered cases minus the total number of *clustered index cases* divided by the total case count with genotyping data available [36]. The *cluster index case* is the first chronological case in a cluster, which can be assumed to be a case of reactivated disease. Data from 2007 was excluded from the computation of the average percent clustered because genotyping data was unavailable prior to 2007, which produces upward bias in the estimate of unique cases. During 2007-2013, approximately 79% (95% CI 74%-85%) of all LAC homeless cases and 83% (95% CI 76%-91%) of SPA-4 homeless cases were attributed to recent infection. By contrast, only about 20% of cases reported nationally are attributed to recent infection [38].

Annual growth was found using the 4-year compounded annual growth rate (CAGR) between the 3-year averages during 2007-2009 and 2011-2013. It is difficult, however, to reliably assess trends in incidence given the significant year-to-year variation and the aforementioned challenges associated with defining the denominator. Moreover, it is possible that the persons transitioning out of the PIT homeless count from 2007-2013 were less susceptible to TB than the chronically homeless. Transmission and associated growth in incidence parameters were therefore derived implicitly from the percent of cases recently transmitted and TB progression rate parameters (see Section 4.4.1).

Table 8: Trends in the Homeless Population and the Derived Denominator for the Incidence Rate, 2007-2013

	2007	2008	2009	2010	2011	2012	2013	Avg 2007-2013	Smoothed CAGR[ɲ]	Sources
All Los Angeles County (LAC) Homeless										
Homeless Pop: Sheltered & Unsheltered PIT*	73,702	60,878	48,053	43,734	39,414	39,439	39,463	49,240	-10%	[47, 45, 68]
Homeless Population: Annualized Estimate[x]	141,737	118,953	96,169	108,120	120,070	153,595	187,119	132,252	7%	
Annualization Factor Reported	1.92	1.95	2.00	2.47	3.05	3.89	4.74			
Adjusted Annualization Factor for Incidence [ϕ]	1.46	1.48	1.50	1.74	2.02	2.45	2.87			
Weighted Avg Homeless Pop Used for Incidence[ϕ]	107,720	89,915	72,111	75,927	79,742	96,517	113,291		2%	
Percent Sheltered, Among PIT Count*	83%	64%	33%	40%	47%	42%	36%	49%	-9%	[47, 45, 68]
LAC Service Planning Area (SPA)-4 Homeless										
Homeless Pop: Sheltered & Unsheltered PIT*	22,030	16,562	11,093	10,590	10,086	10,278	10,470	13,015	-11%	[47, 45, 68]
Homeless Pop: Annualized Estimate[x]	36,429	N/A	N/A	N/A	N/A	N/A	N/A		N/A	
Annualization Factor Reported	1.74	N/A	N/A	N/A	N/A	N/A	N/A			
Adjusted Annualization Factor for Incidence[ϕ]	1.26	1.27	1.29	1.49	1.74	2.10	2.47			
Weighted Avg Homeless Pop Used for Incidence[ϕ]	27,686	21,033	14,314	15,808	17,546	21,628	25,845	20,552	1%	
Percent Sheltered, Among PIT Count*	83%	73%	54%	51%	47%	53%	59%	60%	-7%	[47, 45, 68]

* The Point in Time (PIT) count is the number of homeless on a given night. Homeless counts were conducted in 2007, 2009, 2010 and 2013. Data for years without a homeless count are imputed as a running average. The population of "hidden homeless" is excluded from our population totals. The distribution of sheltered and unsheltered for year 2007 for all of LAC and for SPA-4 is estimated based on the LAC Continuum of Care (CoC) distribution.

[ϕ] The adjusted annualization factor for LAC is equal to the midpoint between 1 and the reported factor. For SPA-4 this adjusted factor is multiplied by 0.86, the ratio of the reported adjusted factor in 2007 for SPA-4 to LAC.

[x] The annualized population is the number of persons who experienced homelessness during a twelve month period. The annualized estimate was unavailable by SPA only during 2007. Annualized estimates for subsequent years were derived by applying the 2007 annualization factor for SPA-4.

[ɲ] The smoothed compounded annual growth rate (CAGR) is equal to the4-year CAGR between the average incidence for 2007-2009 and 2011-2013.

TB: Tuberculosis Disease; SPA: Service Planning Area; GENType: Genotype; LAHSA: Los Angeles Homeless Services Authority; PI: Point in Time

Table 9: Trends in Tuberculosis Case Counts, Incidence Rates and Percent Due to Recent Transmission among the LAC Homeless, 2007-2013

	2007	2008	2009	2010	2011	2012	2013	Total/Avg 2007-2013	Smoothed CAGR[ɲ]	Sources
All Los Angeles County (LAC) Homeless										
All Homeless TB Cases in LAC*	49	57	35	34	51	39	66	331	3%	[30, 39]
GENType 11610 Cases, Confirmed and Probable[ɣ]	10	13	9	5	13	15	18	83	9%	[30, 39]
Cases in Other Genotype Clusters	22	27	15	21	26	16	28	134[ς]	2%	[30]
Index Cases (First in Cluster)	7[ς]	5	3	5	2	1	5	21[ς]		
Cases with Genotyping Data	42	42	26	33	41	35	51	228[ς]	4%	[30]
% Clustered (Recent Transmission) ±	52%[ς]	76%	73%	67%	83%	89%	75%	79% (74-85)	2%	
TB Incidence Per 100,000 by Population Est.:										
Reported Sheltered & Unsheltered PIT	66	94	73	78	129	99	167	96 (86-106)	14%	
Reported Annualized Homeless Population	35	48	36	31	42	25	35	36 (29-42)	-3%	
Adjusted Annualization Factor[ϕ]	45	63	49	45	64	40	58	52 (44-60)	0.8%	
LAC Service Planning Area (SPA)-4 Homeless										
All Homeless TB Cases in SPA-4*	26	24	10	11	21	18	26	136	2%	[30, 39]
GENType 11610 Cases, Confirmed and Probable[ɣ]	7	8	6	5	8	10	10	54	7%	[30, 39]
Cases in Other Genotype Clusters	11	12	2	6	7	5	9	42[ς]	-5%	[30]
Index Cases (First in Cluster)	2[ς]	1	0	3	1	0	3	8[ς]		
Cases with Genotyping Data	21	19	7	10	17	15	22	90[ς]	4%	[30]
% Clustered (Recent Transmission) ±	62%[ς]	84%	86%	70%	82%	87%	77%	82% (76-91)	-2%	
TB Incidence Per 100,000										
Reported Sheltered & Unsheltered PIT	118	145	90	104	208	175	248	149 (124-174)	16%	
Reported Annualized Homeless Population	71	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Adjusted Annualization Factor[ϕ]	121	112	46	51	98	84	121	95 (75-114)	2.2%	
LAC Homeless Excluding SPA-4 (New Entrants)										
TB Incidence Per 100,000: Adjusted Pop.	29	48	43	38	48	28	46	40 (34-45)		
% Clustered (Recent Transmission)	77%	70%	68%	65%	83%	90%	72%	77% (70-84)	3%	

*Non-incarcerated homeless. Excludes cases identified as homeless and in a correctional facility.

[ɣ] Includes cases linked to the GENType 11610 outbreak cluster through genotyping data and/or epidemiological linkages (location-based or close-association based linkages

[ς] Genotyping data became available beginning in 2007. The proportion of clustered "recent transmission" cases in 2007 will be underestimated because clustered cases may appear unique or may be incorrectly flagged as an index case due to missing data on earlier cases in the chain of transmission.

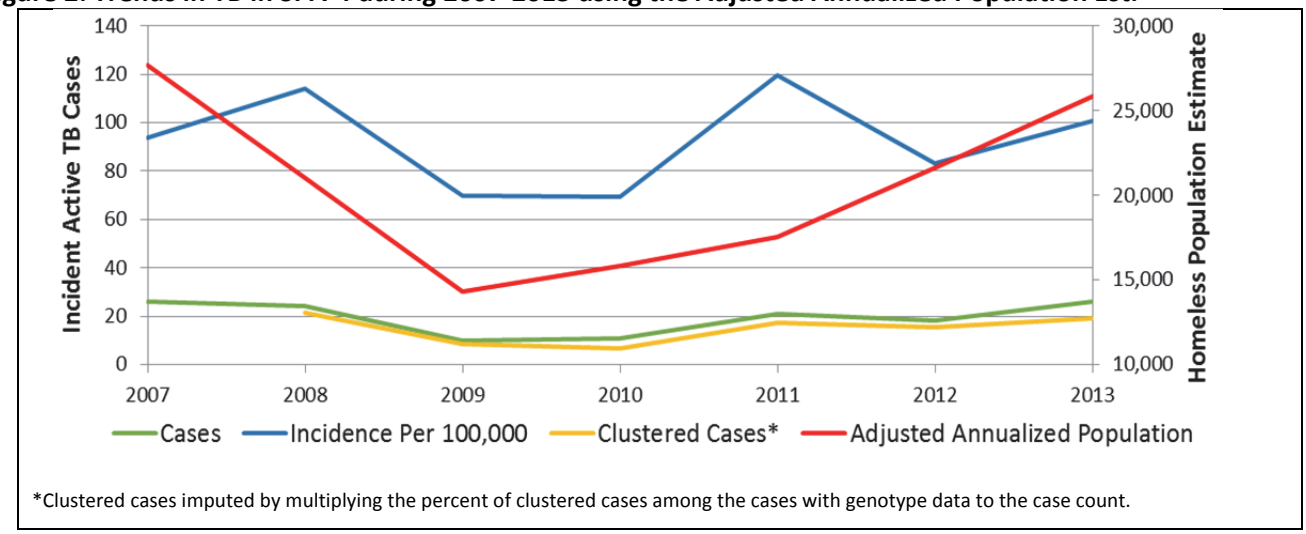
[ɲ] The smoothed compounded annual growth rate (CAGR) is equal to the4-year CAGR between the average incidence for 2007-2009 and 2011-2013.

± The percent of cases due to recent transmission is estimated with the N-1 method whereby the first case in the cluster ("index") is attributed to reactivated, previously acquired infection.

[ϕ] Using the adjusted population as the denominator for the incidence rate, as described in Table 8.

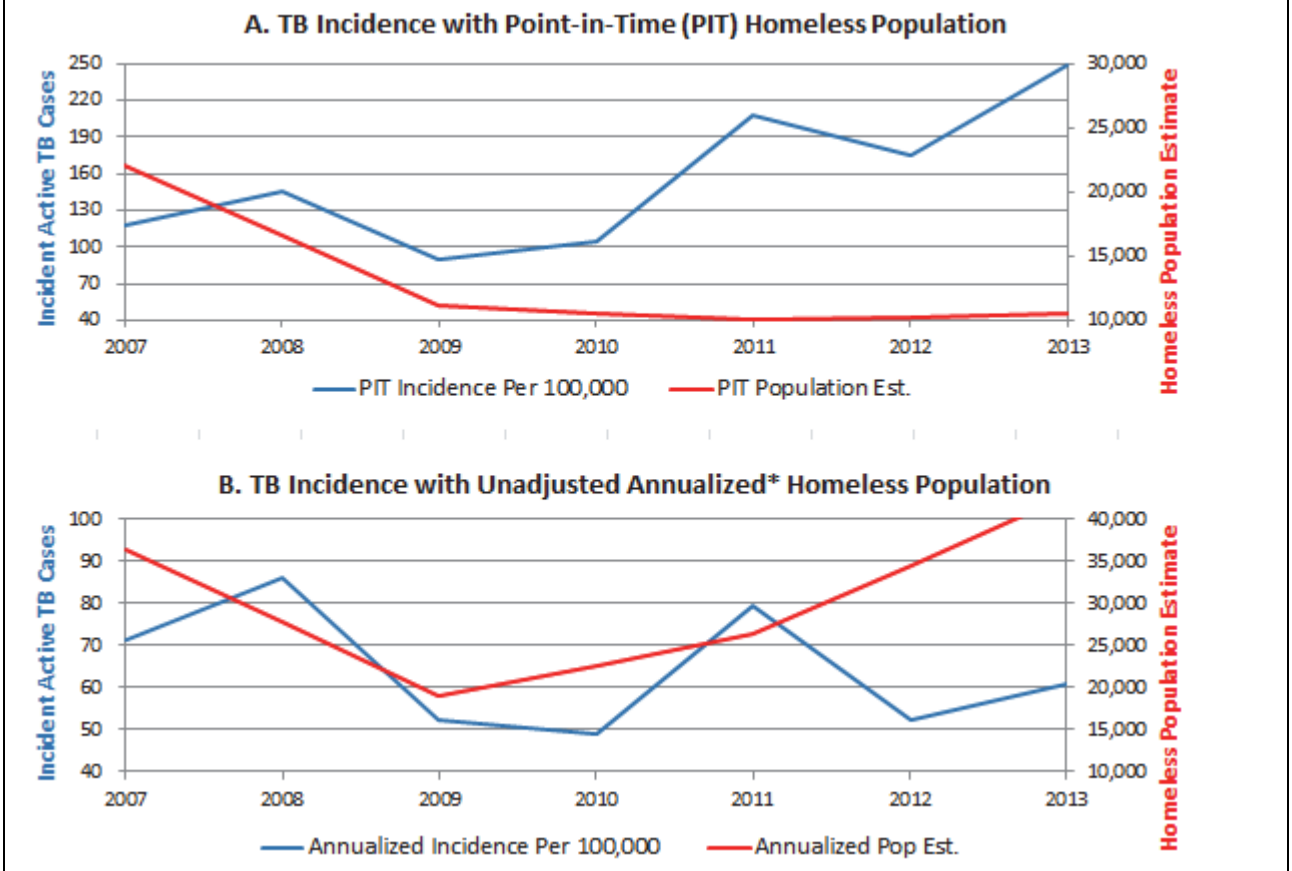
TB: Tuberculosis Disease; SPA: Service Planning Area; GENType: Genotype; LAHSA: Los Angeles Homeless Services Authority; PI: Point in Time

Figure 2: Trends in TB in SPA-4 during 2007-2013 using the Adjusted Annualized Population Est.



*Clustered cases imputed by multiplying the percent of clustered cases among the cases with genotype data to the case count.

Figure 3: TB Incidence in SPA-4 with the Point in Time and Unadjusted Annualized Population Est.



*Annualized homeless population projections were only available for SPA-4 in 2007. Subsequent years were derived by multiplying the annualization factor for LAC by the ratio of the 2007 annualization factor for SPA-4 to LAC.

4.2 Environment, Population Size and Population Flows

4.2.1 Population Size and Growth over Time

Users can choose the size of the simulated population at model initialization (*population-start*). We initialize the model with a population of 10,000 homeless persons based, approximately half of the average adjusted annualized homeless population in SPA-4 (see Table 8). A smaller population is used to increase the speed of the model and because outcomes are expressed per capita or per case averted/LY gained, which should not change with absolute population size. The methodology used to impute population size and incidence is described in Section 4.1. The simulation assumes the entire initial population is currently homeless. In reality, many of these individual are not currently homeless. This will not impact model predictiveness, however, because incidence, prevalence, transmission and associated population density parameters were calibrated against this assumption to match trends observed in LAC.

Population size is assumed to be constant over time. To implement this assumption, all individuals that die or that migrate out of the simulated environment are "replaced" by new entrants into the SPA-4 homeless population.

4.2.2 Age Distribution

The precise distribution of ages of the Skid Row homeless population is not available. Age was assigned stochastically based on a uniform distribution of ages within the individual's assigned age band. Age bands were assigned with probabilities equal to the proportion of the homeless population falling within each age band in 2013, as reported by LAHSA: 8.7% of the unsheltered homeless population were under 18, 10.7% were between the ages of 18-24, 57.6% were between the ages of 25-54, 14.5% were between the ages of 55-61 and 8.5% were aged 62 or older [45]. We assume all individuals are between the ages of 10 and 75.

4.2.3 Background Mortality and Remaining Life Years

Background mortality is determined by the life tables for the general population and the user-defined standardized mortality ratio associated with homelessness (*homeless-SMR*). Annual probabilities of death by age for the general population were derived from 2010 life tables and can found in the file "deathprob_table_2010.txt" [69]. Baseline, undiscounted life expectancy (LE) by age (assuming no excess mortality) can be found in the file "LE_2010_SMR1.txt." Individuals die annually with probability p = *death-rate-homeless*, the product of the annual death rate from the general population and the *homeless-SMR*.

Users can choose a value for the standardized mortality ratio (SMR) for all-cause mortality among homeless compared to the general population. An SMR of 1 implies that the homeless face an equal annual probability of death. Users can choose an SMR between 1 and 10 with a default value of 5. Studies have shown that the SMR associated with homelessness can be as high as 9 [52]. The SMR is applied to the annual risk of death at each age between the ages of 18 and 100 from the 2010 life tables to produce estimates of background mortality within the Skid Row population [69]. This

method assumes that the average person in Skid Row became homeless at the age of 18 and that the relative risk of death compared to the general population is equal to the SMR at each prevalent age. The user-determined homeless-SMR parameter also determines undiscounted life expectancy for each agent in the model. LE by SMR and age can be found in the files "LE_2010_SMR1.txt", "LE_2010_SMR2.txt" and so forth for SMRs of 1 through 10.

When a simulated agent dies of TB, the agents discounted LE at their age of death is added to the aggregate count of years of potential life lost (YPLL). Discounted life expectancy (LE_D) was found using the "Mixed DEALE" method proposed by Keeler and Bell [53]. The mixed DEALE method sets discounted LE equal to the weighed sum of LE under the declining exponential approximation of life expectancy (DEALE) method and the fixed lifetime approximation of life expectancy (FLALE) method. The DEALE method, proposed by Beck et al, adjusts LE for a constant hazard r [70], as shown in shown in Equation 12, where r is the discount rate and LE_U is the undiscounted life expectancy.[27] The DEALE constant hazard assumption under-estimates life expectancy because, except for the severely ill, mortality increases exponentially with age. The FLALE method, by contrast, over-estimates discounted LE by assuming that everyone lives out their full LE (Equation 11). The combined, weighted discounted LE is shown in Eq. 3, where p is the weight assigned to the DEALE computed LE, which is set equal to 0.3 based on life table analysis conducted in a study of breast cancer effectiveness [71]. LE is discounted at a 3% rate [17].

$$LE_{DEALE} = \frac{LE_U}{(1 + r * LE)} \quad \text{Eq. 1}$$

$$LE_{FLALE} = \frac{(1 - \exp(-r * LE_U)}{r} \quad \text{Eq. 2}$$

$$LE_D = \frac{p * LE_U}{(1 + r * LE)} + \frac{(1 - p) * (1 - \exp(-r * LE_U)}{r} \quad \text{Eq. 3}$$

Because age is assigned stochastically, the average annual death rate from non-TB causes varies across model runs. The annual death rate is approximately 1.91% (range: 1.88% - 1.94%). The undiscounted and discounted life expectancy of the average homeless client is 26 and 16.2 years, respectively.

4.2.4 Homeless Shelters, the Distribution of the Sheltered Population, Duration of Stay, and Churn Rates Between Shelters and the Street

The user interface allows users to determine the total number of shelters and the size of the sheltered population. The *Percent-Sheltered* parameter defines the percent of the population that is sleeping in a homeless shelter on the first night of the simulation. The size of the sheltered population is the product of *percent-sheltered* and the starting population. The model is initialized with 36% of the population sheltered, based on LAHSA's 2013 homeless count in SPA-4 [45].[28]

[27] Accounting for disease-related mortality with a constant hazard r is equivalent to discounting at rate r [53].

[28] In 2013, 59% of the sheltered and unsheltered PIT count was sheltered. The annualized population is 1.65 times as large as the PIT count, and we assume that those currently not experiencing homelessness are not sheltered. The percent sheltered among the annualized population is therefore 0.59/1.65 = 36%.

The NetLogo environment is defined by *turtles*, each representing a single homeless individual, and *patches*, which represent a square unit of ground on which a turtle may be located. In the present model, orange patches represent homeless shelters, white patches represent unsheltered areas and black patches are excluded from the simulation environment. The model is initialized with 8 shelters, approximately representing downtown Los Angeles' SPA-4 (see Figure A.2 in Appendix A) [72].[29] Changing the number of shelters without changing the underlying population density will not impact model outcomes. Sheltered homeless clients are assumed to be equally distributed across the simulated shelters. The population of each shelter is therefore equal to (*percent-sheltered * population-start / 8*). Turtles are assigned to a shelter stochastically with probability proportionate to the relative size of the sheltered or unsheltered space in terms of population. All new entrants into the simulation environment are initially unsheltered.

Users can set the duration of each shelter stay (Shelter-Duration-Wks). This value is assumed to be constant across shelters. Shorter stays are associated with more "churn" which improves the efficacy of the intervention. This value is assumed to be constant across shelters. The default value is a 6-week stay.

Agents transition between shelters together at the end of each shelter transition period, which is defined by the shelter-duration parameter. Sheltered agents move to the street and each shelter randomly selects a group from the unsheltered population, equal to the size of its bed capacity, to seek admission to the shelter.

The assumption that turtles are equally likely to seek admission at each of the shelters at each transition significantly influences the design of the model because it characterizes "churn" and the associated probability that an agent will encounter the intervention given the number of shelters adopting the policy. With 36% of the population sheltered at a given point in time and a 6-week shelter duration, each agent will transition through approximately 3 shelters per year.

We assume that shelters are always at capacity, or that demand for shelter always exceeds supply of shelter beds [73]. This assumption has a significant impact on the design of the intervention because agents that are denied shelter are always "replaced" by new agents seeking shelter admission.

4.2.5 Population Density Overall and Within Shelters

Broadly, the extent and severity of Mtb transmission is determined by three factors: the duration of the infectious-period (see Section 4.3.4); the average number of contacts each infectious case exposes per day, determined in the present model by "population density"; and the average risk of becoming infected if exposed (*p-infected-if-exposed*, see Section 4.4.1). This model treats the first two parameters as fixed and calibrates *p-infected-if-exposed* to match observed trends in tuberculosis transmission in LAC's SPA-4 homeless population during 2007-2013 given model assumptions about the duration of the infectious-period and population density.

[29] Major shelters in SPA-4 include the Urban Rescue Mission with 700 beds, the Midnight Mission with 500 beds, the Los Angeles Mission with 320 beds; Pathways to Home with approximately 500 beds; the Weingart Center Association with 300 beds; and the Single Room Housing Corporation with 400 beds.

The total number of patches in the simulated environment is equal to the total number of turtles *(population-start*) divided by average population density ($\overline{Density}$) . Population density within the shelters ($Density_S$) is presumably greater than density on the street ($Density_U$), explaining the heightened risk of transmission. The user-defined *Shelter-Density-Factor (SDF)* is the multiple by which density within the shelters exceeds density on the street. This parameter allows the user to specify the extent to which shelters are risker, in terms of transmission. A higher SDF will correlate with greater shelter screening efficacy. An SDF of 1 implies an equal risk of transmission within and outside of shelters. The model is initialized with an *SDF* of 2.5.

$$Density_S = SDF * Density_U \quad \text{Eq. 4}$$

The section proposes a method for deriving the average population density of the environment from available estimates of the average number of exposed contacts per case per week. The 2013 CDC EPI-AID into the large homeless outbreak in LAC identified 18,708 exposed contacts of 45 active cases linked to the GenType 11610 outbreak. The mean infectious period of the 45 infectious cases was 150 days, suggesting that each case exposed on average 2.8 new contacts per day or 19.6 contacts per week [74].

This estimate of the average number of contacts per day ($\overline{ContactsPerWeek}$) can be used to approximate the average population density (agents per "patch"). Eq. 5- Eq. 6 demonstrate $\overline{ContactsPerDay}$ is approximately equal to the average density parameter, where P is the total number of patches, Pop is the initial population, and T_p is the number of turtles on a given patch p. Because the assignment of a given turtle to a patch is a discreet probability, the number of turtles per patch, T_p is distributed according to the Poisson distribution with mean $= \sigma^2 = \overline{Density} = \frac{Population}{Patches}$.

$$\overline{ContactsPerWeek} = \frac{1}{Pop} * \left(\sum_{p=1}^{P} (T_p - 1) * T_p \right) = \frac{1}{Pop} \left(\sum_{p=1}^{P} {T_p}^2 - \sum_{p=1}^{P} T_p \right) = \frac{1}{Pop} \left(\sum_{p=1}^{P} {T_p}^2 \right) - 1$$
$$= \frac{\overline{Density}}{Pop} \left(\sum_{p=1}^{P} \frac{{T_p}^2}{\sigma^2} \right) - 1 \quad \text{Eq. 5}$$

Where $\sum_{p=1}^{P} \frac{{T_p}^2}{\sigma^2}$ is approximately distributed according to the non-central chi-squared distribution with *P* degrees of freedom and non-centrality parameter $\lambda = \sum_{p=1}^{P} Density = Pop$ and mean $\mu = (\lambda + P) = Pop * +P$. Contacts per week therefore reduces to weighted average density:

$$\overline{ContactsPerWeek} = \frac{Density * (Pop + P)}{Pop} - 1 \approx \frac{Density * Pop}{Pop} + \frac{Density * P}{Pop} - 1 \approx Density \quad \text{Eq. 6}$$

Density within the shelters ($Density_S$) and in the unsheltered patches ($Density_U$) can be derived form the weighted average density parameter (equal to the average contacts per week) by accounting for the Shelter Density Factor (SDF) and the percent of the population residing within a shelter $\%Sheltered$. The formulas are shown in Eq. 7.

$$Density_U \approx \frac{ContactsPerDay}{(\%Sheltered * (SDF - 1) + 1)} \approx \frac{19.6}{0.36 * (2.5 - 1) + 1} \approx 12.7$$
$$Density_S \approx Density_U * SDF \approx 31.8$$

Eq. 7

4.2.6 Migration

Individuals in the model migrate out of the simulation environment at an annual rate equal to the user-defined *Migration-Rate-Annual* parameter. Migration and death reduce TB transmission because new entrants are less likely to have LTBI infection than those leaving the simulation (see Section 4.3.9). The migration rate parameter has a large influence on the incidence and trends in incidence over time, as formally demonstrated in Section 4.4.1. The default value for the migration parameter was therefore determined by surveying the literature and by testing model outcomes under various migration rate assumptions.

A survey of male Skid Row inhabitants in 1985 showed an annual migration rate of approximately 33%. [75]. However, we would expect to see lower levels of migration today given declining rates of homelessness and greater levels of service provision in the Skid Row area. Moreover, it is possible that migration risk is negative correlated with the likelihood of LTBI infection (e.g., those most likely to be exposed are those most dependent on Skid Row services), which would argue in favor of using a lower overall migration rate. It is additionally possible that some migrating individuals return to Skid Row, effectively representing negative migration in terms of the influence on LTBI prevalence rates.

Using the formula for the implicit growth rate presented in Eq. 20 in Section 4.4 and default model values, a 33% migration rate would imply negative annual growth in incidence in SPA-4 (-0.9%) and LAC (~2.6%), which is inconsistent with observed trends shown in Table 9. The model is initialized with a migration rate of 20%, the highest rate consistent with the data presented in Table 9.

In the status quo scenario, migration decreases LTBI prevalence because the incoming population is less infected. In the intervention scenario, migration curbs the decline in prevalence once the intervention has reduced prevalence below the rates among the incoming population.

Individuals face a weekly probability of migration equal to Migration-Rate-Annual / 52. All individuals leaving the simulation environment are replaced by new entrants. All new entrants are initially unsheltered. The epidemiological characteristics of new entrants are described in 4.3.9.

4.3 TB Morbidity and Progression

4.3.1 TB Disease Incidence and Prevalence at Model Initialization: User-Input Parameter

Users can choose the approximate initial incidence of TB disease within the target population (*TB-Incidence-Start-Approx)*. For the status quo scenario simulation, the model is initialized with an incidence rate of 95 per 100,000 person-years, the average incidence in SPA-4 in years 2007-2012 (see Table 9) using the adjusted annualized homeless population derived with methods described in

section 4.1. Users can select a value between 5 and 250 cases per 100,000 person years in increments of 5. The annual growth in TB incidence is discussed in section 4.4.2.

The total number of prevalent cases at the beginning of the simulation (*prevalent-cases*) is equal to the product of the annual incidence, the population size, and the mean duration of disease (including both the infectious period and the duration of treatment) expressed in years and rounded to the nearest integer. If the total duration of disease exceeds a year (as in the status quo scenario), TB prevalence will be greater than TB incidence. Prevalent TB cases at model initialization are assigned randomly among homeless persons aged 40-55, the inter-quartile range of age at TB diagnosis among homeless cases in LAC from 1997-2014 [76].

Because TB disease cannot be partially assigned, the computed initial incidence may differ by a few percentage points from the value set by the user due to rounding when deriving prevalent cases at initialization. Initializing the model with 95 cases per year and a population of 20,000, for example, results in 16 prevalent cases, corresponding to an exact incidence of 93 cases per year. The computed incidence is displayed as an outcome monitor on the user interface.

4.3.2 Percent of Cases due to Recent Transmission at Model Initialization: User-Input Parameter

Users can select the proportion of TB disease cases at model initialization that were due to recent transmission (*TB-Pct-Recent-Transmission-Start*). In the status quo scenario, 83% of homeless cases are due to recent transmission (range: 76%-91%), based on data from SPA-4 2007-2013 (see Table 9).[30] As described in 4.3.8, the assignment of LTBI cases to state 1 (fast progressing) and state 2 (slow progressing) is a function of this parameter: a higher percent of recent transmission cases implies a greater proportion of infections within the past year.

4.3.3 Progression to TB Disease: Assumed and User-Input Parameters

At time t, a simulated LTBI-infected individual's risk of progression is determined by the days since they were infected (DLTBI) and the associated annual risk of progression to TB disease. The lifetime risk of progression to TB disease for a person with LTBI from the general population is typically estimated at 5-10 percent based on data from the placebo arm of controlled trials on LTBI treatments and vaccines [3, 40, 41]. Estimates of the distribution of reactivation risk by time since infection are varied, but the "rule of thumb" is that about half of an individual's lifetime risk of developing TB disease occurs within the first two years after infection [2]. After this "fast progressing" period of 1-2 years the rate of activation, or "reactivation" of previously acquired TB, drops to a low but persistent reactivation rate, with estimates from 30 to 100 cases per 100,000 person years for the general population [41, 42, 43]. The risk of reactivation varies considerably by medical risk factors impacting cell mediated immunity, the host's principal defense against the progression of disease [3].

The annual risk of progression by time since infection is determined by the user-defined relative risk of progression associated with homelessness (*prog-rate-homeless-RR*) and three pre-defined parameters:

[30] We choose 83%, a value slightly lower than the estimate for SPA-4 (84%) because the percentage for LAC homeless at large (80%) suggests the SPA-4 estimate may be high.

the annual risk of progression for recently infected individuals from the general population; the annual risk of reactivated disease for previously infected individuals from the general population; and the fast progressing period (*fast-prog-period-days*). Recently infected individuals from the general population are assumed to face a 5% annual risk of progression to TB disease (5,000 per 100,000 PYs) that is uniformly distributed throughout the fast progressing period [44, 41, 19]. Following this period, the rate of reactivation drops to 72 per 100,000 person-years (95% CI, 67-77) based on a meta-analysis of five studies conducted within *the Priorities for Testing and Treating FB* paper within this series [5].[31] The definition of "recently infected", or the "fast progressing period" (*fast-prog-period-days*), is typically assumed to be 1-2 years following exposure [3]. For simplicity, the model is calibrated against the assumption of a 1-year fast progression period.

Homelessness is not an independent risk factor for progression. However, it is significantly positively associated with comorbidities such as HIV and substance abuse that compromise the immune system's defense against progression to disease. We estimate the relative risk (RR) of progression associated with homelessness based on the relative prevalence and risk of associated with HIV and alcohol abuse using the weighted RR formula given in Eq. 8, where RR_{HIV} and RR_A are the relative risks of HIV and alcohol abuse versus the general population and ΔP_{HIV} and ΔP_A are the differences in the prevalence of HIV and alcohol abuse among the homeless in LAC versus the general population.

$$RR_{Homeless} = RR_{HIV} * (\Delta P_{HIV} - \Delta P_{HIV} * \Delta P_A) + RR_A * (\Delta P_A - \Delta P_{HIV} * \Delta P_A) + RR_A * RR_A * \Delta P_{HIV} * \Delta P_A + 1 * (1 - \Delta P_A - \Delta P_{HIV}) \quad \text{Eq. 8}$$

The RR of progression versus the general population is 17.8 (95% CI, 10.7-24.5) among persons with HIV infection and 2.7 (95% CI 2-3.8) among persons suffering from alcohol abuse [5]. The rate of HIV infection among the homeless in the Los Angeles County Continuum of Care (CoC) was 0.9% in 2013 [45]. Among the general population aged 15 and older, prevalence of diagnosed HIV was 0.32% in 2012 [46]. Approximately 37% and 31% of the LAC currently homeless population reports suffering from substance abuse and alcohol abuse, respectively [47, 45].[32] Among the general population, 6.6% report heavy alcohol use [48]. These figures yield a weighted RR of progression associated with homelessness of 1.5.

4.3.4 Infectious Period

An individual *j* with active TB disease can infect uninfected individuals in the model with LTBI after progression to disease and before diagnosis ($TBState_j = \{5,6,\}$). The duration of this "infectious period" or the "waiting time to diagnosis" influences the rate of transmission; a longer infectious period will produce, on average, more secondary infections. The 2013 epidemiological assistance (EPI-AID) investigation of 45 cases linked to the GENtype 11610 outbreak conducted by the Centers for Disease Control and Prevention (CDC) found a mean infectious period of 150 days (range: 31-458).

[31] Among persons aged 15 and older.

[32] Rates of alcohol abuse were reported only for the 2007 homeless count. In 2007, 35% of survey respondents reported suffering problems with alcohol abuse, or about 83% of those reporting any substance abuse problem (LAHSA, 2007). This proportion was applied to reported substance abuse prevalence in 2013 estimate the prevalence of alcohol abuse.

Three of the 45 cases (6%) had infectious periods greater than 365 days [39]. A survey of active TB patients from the general population in Los Angeles in the mid-1990s found a mean infectious period of 74 days (standard deviation: 216 days) [77]. Following previously published simulation models we assume that the waiting time to diagnosis is exponentially distributed [19].

Each individual is assigned an infectious period by drawing from an exponential distribution with a mean of 18 weeks (126 days). Applying this parameter, approximately 6% of cases will have an infectious period greater than 1 year. Among the prevalent cases at model initialization, infectiousness is assigned stochastically with probability equal to the proportion of the total duration of disease (infectious-period + TB-treatment-duration) spent in the infectious period.

4.3.5 Treatment Duration, Hospitalization and Total Duration of Disease

Total duration of disease is the sum of the duration of treatment (*TB-treatment-duration*) and the infectious period (*infectious-period*). The duration of treatment is set to 26 weeks, the length of the standard 130-dose treatment regimen for active TB disease assuming 5 doses per week.[33] This underestimates the true average length of treatment for a homeless case due to challenges associated with treating transient populations. An analysis of 766 homeless TB patients in LAC from 1997-2014 showed an average treatment duration of 44 weeks [76]. However, because costs are allocated on a per-dose basis and because we assume that individuals undergoing treatment are not infectious, the distribution of doses over time does not influence model outcomes.

Treatment for TB disease consists of an inpatient period (TBState = 7) and subsequent period spent in "TB housing" (TBState = 8), a dedicated residential facility for homeless TB patients. The duration of hospitalization (hospitalization-days) is assigned stochastically to each TB patient from an exponential distribution with a mean of 7 weeks (49 days) based on an analysis of homeless TB patients in LAC from 1997-2014 [76].[34] All homeless patients are hospitalized at diagnosis.

All TB patients undergoing treatment are assumed to be non-infectious; likewise, all non-infectious TB patients are by definition undergoing treatment. Non-infectious TB patients at model initialization are assigned to the hospital with probability equal to the proportion of the total duration of treatment spent in the hospital (hospitalization-days / TB-treatment-duration). The remaining non-infectious patients are assigned to TB-housing.

4.3.6 TB Mortality Rate (Mortality-Rate): User-Input Parameter

Users can determine the percent of homeless TB cases that die of TB-related causes (*Mortality-Rate*). The default value is 15%, which was the mortality rate found in an analysis of LAC homeless cases based on data from the LAC DPH Tuberculosis Registry Information System (separate paper within this dissertation) [30]. The simplifying assumption is made that all TB-related deaths occur at the end of the treatment regimen.

[33] See Section 4.6 for details on the costs and resources associated with treating active disease.

[34] This figure may under-estimate the true mean LOS for the homeless population. The *Cost of a Case* paper accompanying this analysis found a mean LOS of 60 days among the patients with at least one recorded hospitalization Only 68% of the 797 cases analyzed had at least one complete hospitalization record but an additional 22% had evidence of an unrecorded hospitalization record. The mean LOS per episode was 39 days and the typical patient with a record hospitalization had 1.7 episodes.

4.3.7 Baseline LTBI Prevalence: Assumed/Implied

LTBI prevalence at model initialization is derived by fitting a theoretical model for LTBI prevalence to progression and case rate data from the SPA-4 homeless population during 2007-2013. The estimate is validated with two other data sources characterizing LTBI prevalence within the target population: results from targeted LTBI testing of contacts of cases linked to the large homeless outbreak in Skid Row and prevalence estimates from the published literature addressing the urban homeless populations in the United States.

We derive a model to predict the prevalence of LTBI from the formulas for the slow and fast progression rates (PR_{Fast}, PR_{Slow}) published in several prior studies [78, 56, 79]. The formulas are shown in Eq. 9 and Eq. 10, where $Inc_{TB-Fast}$ is the incidence of TB disease attributed to recent infection, $Inc_{TB-Slow}$ is the incidence of TB due to reactivated (previously acquired) LTBI, $P_{LTBI-Slow}$ is the prevalence of previously acquired infection and $P_{LTBI-Fast}$ is the prevalence of recently acquired infection (given our one-year definition of the fast progression period this parameter is equivalent to the annual incidence of infection). Both equations can be expressed in terms of the overall incidence of TB disease (Inc_{TB}) and the percent of cases attributed to recent infection ($\%CasesRecent$).

Overall LTBI prevalence (P_{LTBI}) is the sum of the prevalence of recently acquired infections ($P_{LTBI-Recent}$) and previously acquired infections ($P_{LTBI-old}$). Rearranging and substituting Eq. 9 and Eq. 10, P_{LTBI} can be expressed in terms of the progression rates, which are constants, Inc_{TBD} and $\%CasesRecent$ (Eq. 11).

$$PR_{Fast} = \frac{Inc_{TB-Fast}}{P_{LTBI-Recent}} = \frac{Inc_{TB} * \%CasesRecent}{P_{LTBI-Recent}} \quad \text{Eq. 9}$$

$$PR_{Slow} = \frac{Inc_{TB-Slow}}{P_{LTBI-Old}} = \frac{Inc_{TB} * (1 - \%CasesRecent)}{P_{LTBI-Old}} \quad \text{Eq. 10}$$

$$P_{LTBI} = P_{LTBI-Old} + P_{LTBI-Recent} = Inc_{TB} * \left(\frac{\%CasesRecent}{PR_{Fast}} + \frac{(1 - \%CasesRecent)}{PR_{Slow}}\right) \approx 16\% \quad \text{Eq. 11}$$

This model is applied to the data presented in Tables 8-9 to estimate LTBI prevalence among the homeless in LAC and SPA-4 during 2007-2013. Results are shown in Table 10.

An average prevalence of 12% (95% CI 9%-15%) and 16% (95% CI 10%-24%) is found for LAC and SPA-4, respectively.[35] Applying the proportion of implied infections that were recently acquired to the overall prevalence estimates suggests an annual incidence of new infections of 0.6% for the LAC homeless population and 1.1% for the SPA-4 homeless population.

[35] Confidence limits for the LTBI prevalence estimates were based on the upper and lower limits of the estimate of the percent of cases due to recent transmission.

As discussed in section 4.3.2, we initialize the model under the assumption that 83% (range: 75%-91%) of cases were due to recent transmission. This corresponds to an LTBI prevalence of 16% (range: 10%-24%) in SPA-4.

Table 10: Implied Prevalence of LTBI among the Homeless Populations in LAC and SPA-4, 2007-2013*

	2007	2008	2009	2010	2011	2012	2013	Total/ Avg×
All LAC Homeless								
Incidence – Adjusted Annualized$^{\phi}$	45	63	49	45	64	40	58	52 (44-60)
Proportion Due to Recent Transmission	79%	76%	73%	64%	83%	89%	73%	79% (74-85)
Implied LTBI Prevalence	9.1%	14.6%	12.6%	15.5%	10.8%	4.8%	15.4%	11% (8-13)
Implied Rate of New Infections	0.5%	0.6%	0.5%	0.4%	0.7%	0.5%	0.6%	0.6%
Service Planning Area (SPA) 4: Homeless Cases								
Incidence – Annualized Adjusted$^{\phi}$	94	114	70	70	120	83	101	95 (75-114)
Proportion Due to Recent Transmission	83%	84%	86%	60%	82%	87%	73%	83% (76-91)
Implied LTBI Prevalence	15.5%	18.0%	10.0%	26.3%	20.9%	11.2%	26.4%	16% (10-24)
Implied Rate of New Infections	1.0%	1.3%	0.8%	0.6%	1.3%	1.0%	1.0%	1.1%

$^{\phi}$ Using the adjusted annualized homeless population, as described in Section 4.1.

*Assuming the fast progression annual risk of 9.37% (see section 4.2.3).

$^{\phi}$ Assuming the slow progression annual risk of 0.135% (see section 4.2.3).

×Weighted average computed by, e.g., dividing total clustered cases by total cases.

This method was validated by comparing the results to estimates of LTBI prevalence within comparable populations:

- *Targeted LTBI testing of contacts of cases linked to the large homeless outbreak in LAC*. During 2013, a total of 689 contacts of 45 infectious cases linked to the GENtype 11610 outbreak in Skid Row were evaluated for LTBI, including 258 "tier I" high-prior contacts that were either HIV positive or exposed to an infectious case for more than 120 days. LTBI prevalence was 23% overall and 17% excluding the highest priority contacts [74].[36] These data suggest an average prevalence of 17-20%.
- *A review of the published literature on LTBI rates among the urban homeless in the United States*. Bock et al found a prevalence of 18% among the homeless in the mid-1990s [80]. Rates among the San Francisco homeless population were estimated to be 32% in the mid-1990s by Zola et al, 37.1% by Moss et al from 1990-1994 and 7% by Grinsdale in 2005-2011. [81, 82, 83]. Kong and colleagues found an LTBI prevalence of 12.8% (95% CI 12.2-13.5%) among the homeless within the Denver Metro TB Clinic during 1995-1998 [57]. Friedman et al reported a prevalence of 32% among welfare recipients in the Friedman et al found a prevalence of 32% among the drug abuse welfare population in NYC, which was only 1.5 times the age-matched rate for the general NYC population [84]. Adjusting for study setting (LTBI prevalence has declined over time in the general population), prior studies have found slightly lower LTBI rates among the homeless than those produced by the method proposed in this study. However, prior studies have not addressed a population experiencing an outbreak on the scale of the GENtype 11610 outbreak.

The model is initialized with an implied LTBI prevalence of 15% and a range of 11% to 29% depending on the user-defined incidence of disease and percent of cases due to recent transmission (a high

proportion of recent transmission implies lower LTBI prevalence and vice versa). Our prevalence estimate of 20% implies that the Skid Row population experiences LTBI rates approximately 4 times higher than the general population [5].

4.3.8 LTBI Incidence (Prevalence of Recently acquired LTBI) and Endogenous LTBI Incidence

The prevalence of LTBI is comprised of the prevalence of recent infections (the past year) and the prevalence of previously acquired infections. The prevalence of recently acquired LTBI ($P_{LTBI-Recent}$) is equivalent to the incidence of LTBI (Inc_{LTBI}), given our definition of "recent" as acquired within the preceding year. LTBI incidence is equal to the incidence of recent transmission disease divided by the fast progression rate (Eq. 12).

$$Inc_{LTBI} = P_{LTBI-Recent} = \frac{Inc_{TB} * \%CasesRecent}{PR_{Recent}} \approx 1.1\% \quad \text{Eq. 12}$$

Individuals in the initial cohort are assigned to the fast progressing (TBState=1) or slow progressing (TBState=2) state stochastically with probability equal to the incidence of LTBI divided by the prevalence of LTBI. Days since infection (DLTIB) is drawn from a uniform distribution 0-365 for individuals in the fast progressing period and 366 – age-in-days for individuals in the slow progressing period. During the simulation, newly infected agents enter state 1 (LTBI-positive, fast progressing) and remain in state 1 for the duration of the user-defined fast progression period unless they progress to TB disease. At the termination of the fast progression period infected agents enter state 2 (LTBI-positive, slow progressing).

The observed incidence of new LTBI infections within the simulation environment is equal to the weighted average of the incidence of new endogenous infections arising from incident TB cases within the non-departing population ($Inc_{LTBI-Endogenous} * (1 - DR - MR)$ and the incidence of new *exogenous* infections among new entrants ($Inc_{LTBI-Exogenous} * (DR + MR)$) less the loss of new infections due to progression to disease (Inc_{TB}), as described in Eq. 13. The departing population is represented by *DR+MR* where *MR* is the annual migration rate and *DR* is the annual death rate within the initial cohort, as determined by provided mortality tables and the SMR associated with homelessness (see Section 4.2.3) and the additional annual deaths attributed to TB disease (*TB DISEASE-incidence * Mortality-Rate*). At model initialization approximately 1.94% of the cohort dies annually (1.91% from non-TB related causes; 0.03% from TB disease).

$$Inc_{LTBI} = Inc_{LTBI-Endogenous} * (1 - DR - MR) + \quad Inc_{LTBI-Exogenous} * (DR + MR) - Inc_{TB} \quad \text{Eq. 13}$$

4.3.9 Disease States of New Entrants: LTBI Prevalence (Exogenous LTBI Prevalence) and Incidence (Exogenous LTBI Incidence): User-Input Parameters

[36] Five tiers were used to prioritize contacts: tier II-II contacts had between 30-120 days of exposure; tier IV contacts had between 1-29 days of exposure and tier V contacts had no exposure. Prevalence was between 17-18% for all groups except for tier I (31% prevalence) and tier V (0 cases out of 9 contacts evaluated).

The prevalence of LTBI among agents migrating into the simulation environment (replacing those that emigrate or die) is represented by the *LTBI-prev-new-entrants* ($P_{LTBI-Exogenous}$) parameter, which is the product of the implied baseline LTBI prevalence (P_{LTBI}, see 4.3.7) and the user-defined *LTBI-Prev-RR-new-entrants*($RR_{LTBI-Entrants}$), the relative risk of LTBI among those entering the simulation. The version of the model calibrated to represent SPA-4 assumes that new entrants experience LTBI at a rate equal to the LAC homeless population at large. As derived in Table 10, the LAC population had an implied prevalence of about 0.75 times the prevalence in SPA-4, the default model value.

The incidence of LTBI among new entrants($Inc_{LTBI-Exogenous}$), or the prevalence of recent infections, is equal to the product of LTBI prevalence among new entrants ($P_{LTBI-Exogenous}$), and the percent of LTBI infections that were recently acquired (%LTBIRecent). We make the simplifying assumption that the distribution of recent infections among the entering LTBI positive cohort is equal to that among the simulated cohort. This likely overestimates the true proportion of recent infections given the elevated risk of recent transmission associated with the Downtown LA outbreak. However, the overall impact on model outcomes and implied transmission parameters is small (only about 20 agents with recent infections enter the simulation environment per year) and can be balanced by slightly decreasing the overall RR of LTBI within the entering cohort.

$$Inc_{LTBI-Exog} = P_{LTBI-Exog} * \frac{Inc_{LTBI}}{P_{LTBI}} = Inc_{LTBI} * RR_{LTBI-Entrants} = \frac{Inc_{TB} * \%CasesRecent}{PR_{Recent}} * RR_{LTBI-Entrants} \quad \text{Eq. 14}$$

We assume that no new entrants have active TB disease. Likewise, active TB patients cannot migrate out of the simulation.

4.3.10 Sputum smear-positive and smear-negative active cases

Cases of active TB disease are classified as "smear positive" or "smear negative" according to whether acid fast bacilli (AFB) were identified in a smear microscopy examination of a sputum specimen. Sputum smear-positive cases are substantially more symptomatic and are 3 to 20 times as infectious as sputum smear-negative cases [18, 19, 20]. Based on data from the LAC DPH Tuberculosis Registry Information System (TRIMS), we estimate that 68% of cases in Skid Row are sputum smear positive [30].[37]

Smear-negative source cases produce approximately 22% as much transmission (range: 5-30%), producing between 0.5-4 new infectious per source case [19, 85, 86].

4.4 TB Trends over Time and Transmission of LTBI

4.4.1 Annual Growth in LTBI Prevalence

LTBI prevalence, and therefore changes in prevalence, is not directly observed. This paper proposes a new method for estimating the annual change in LTBI prevalence user-input parameters: the percent

[37] This is similar to other models. Porco et al assumes that 0.51% (3%-77%) of new cases are quickly or immediately smear-positive and that a fraction of the remaining smear-negative case will progress to smear-positive status over time. We simplify the simulation by applying the mean proportion of cases at a given time that are smear-positive.

of cases recently transmitted (Section 4.3.2), the relative risk of progression associated with homelessness and the associated fast and slow progression rates (Section 4.3.3), the annual migration rate (Section 4.2.6), and the relative risk of LTBI among new entrants (4.3.9).

As shown in Eq. 15, the annual change in LTBI prevalence is determined by the incidence of new LTBI infections attributed to infectious TB disease cases within the environment $\left(Inc_{LTBI-Endogenous}\right)$, exogenous changes in LTBI prevalence $\left(\Delta P_{LTBI-Exogenous}\right)$ caused by death and by migration in and out of the homeless population, and the incidence of LTBI cases progressing to TB disease (Inc_{TBD}):

$$\%\Delta P_{LTBI} = \frac{Inc_{LTBI-Endogenous} + \Delta P_{LTBI-Exogenous} - Inc_{TB}}{P_{LTBI}} \quad \text{Eq. 15}$$

The exogenous annual change in LTBI prevalence $\left(\Delta P_{LTBI-Exogenous}\right)$ is determined by the proportion of the population departing the simulation (DR+MR) and the difference between the endogenous and exogenous LTBI prevalence rates $\left(P_{LTBI} * (RR_{LTBI-Entrants} - 1)\right)$, as shown in Eq. **16**. As described in Section 4.2.1, we assume that all individuals that die or migrate out of the environment are replaced by new entrants.

$$\boldsymbol{\Delta P_{LTBI-Exogenous} = (DR + MR) * P_{LTBI} * (RR_{LTBI-Entrants} - 1) \approx -0.88\%} \quad \text{Eq. 16}$$

The incidence of new LTBI infections arising from endogenous infectious TB cases $\left(Inc_{LTBI-Endogenous}\right)$ can be found by rearranging the formula incidence of LTBI (Inc_{LTBI}) presented in Eq. 13 in 4.3.8, as shown below in Eq. 17. Substituting the formulas forInc_{LTBI}, $Inc_{LTBI-Exogenous}$, and P_{LTBI} allows us to express $Inc_{LTBI-Endogenous}$ in terms of user-input parameters (Eq. 18). With initialized model parameters, approximately 1.3% of the simulated population is infected by an infectious case within the simulation environment per year prior to death and migration.

$$Inc_{LTBI-Endogenous} = \frac{Inc_{LTBI} - Inc_{LTBI-Exogenous} * (DR + MR) + Inc_{TBD}}{(1 - DR - MR)} \quad \text{Eq. 17}$$

Substituting Eq. 13 for Inc_{LTBI} and Eq. 14 for $Inc_{LTBI-Exogenous}$:

$$Inc_{LTBI-Endogenous} = \frac{Inc_{TBD} * \left(\frac{\%CasesRecent}{PR_{Recent}} + 1\right) - Inc_{TBD}\frac{\%CasesRecent}{PR_{Recent}} * RR_{LTBI-Entrants} * (DR + MR)}{(1 - DR - MR)} \approx 1.3 \quad \text{Eq. 18}$$

Combining preceding equations allow us to derive a theoretical model for the annual growth in LTBI prevalence based on user-provided values for the percent of recently transmitted cases, the progression rates and migration parameters. The combined formula for the annual change in LTBI prevalence is shown in Eq. 20. Default model parameters suggest an annual growth rate of 1.74% (95% CI -0.7%-8.4%) in SPA-4 and 0.6% in LAC, which is consistent with the trends observed in incidence in Table 9.

$$\%\Delta P_{LTBI} = \frac{Inc_{LTBI-Endogenous} + \Delta P_{LTBI-Exogenous} - Inc_{TB}}{P_{LTBI}}$$

Substituting Eq. 26 $\left(Inc_{LTBI-Endogenous}\right)$ and Eq. 16 $\left(\Delta P_{LTBI-Exogenous}\right)$ into the formula for $\%\Delta P_{LTBI}$: Eq. 19

$$\%\Delta P_{LTBI} = \frac{Inc_{TB} * \left(\frac{\%CasesRecent}{PR_{Recent}}\left(1 - RR_{LTBI-Entrants} * (DR + MR)\right) + DR + MR\right)}{P_{LTBI}(1 - DR - MR)} + (DR + MR)(RR_{LTBI-Entrants} - 1)$$

Substituting equation Eq. 11 for P_{LTBI} we can solve for $\%\Delta P_{LTBI}$ in terms of user-input parameters: Eq. 20

$$\%\Delta P_{LTBI} = \frac{\frac{\%CasesRecent}{PR_{Recent}}\left(1 - RR_{LTBI-Entrants} * (DR + MR)\right) + DR + MR}{\left(\frac{\%CasesRecent}{PR_{Fast}} + \frac{(1 - \%CasesRecent)}{PR_{Slow}}\right)(1 - DR - MR)} + (DR + MR)(RR_{LTBI-Entrants} - 1)$$
$$\approx 1.74\%$$

4.4.2 Annual Growth in TB Incidence

The annual growth in TB incidence is hard to assess form the data presented in Table 9 due to significant year-to-year changes, a small sample of cases, and an unobserved denominator. This section demonstrates that the annual growth in TB disease incidence is theoretically equivalent to the annual growth in LTBI prevalence if the percent of cases due to recent transmission is approximately constant over time.

The annual incidence of TB is a function of the prevalence of LTBI (P_{LTBI}), the proportion of LTBI infections that were recently acquired (*%LTBIRecent)*, and the progression rates for recent (PR_{Fast}) and previously acquired (PR_{Fast}) LTBI (Eq. 21). The proportion of LTBI infections that were recently acquired (*%LTBIRecent)* is implied by the percent of cases attributed to recent transmission and the progression rates (Eq. 22). Substituting, incidence can be shown to be a function of LTBI prevalence, the progression rates and the percent of recent transmission cases (Eq. 23). Because the progression rate parameters are constant over time, changes in incidence are entirely determined by changes in LTBI prevalence and the percent of cases due to recent transmission. The data in Table 9 suggests that the percent of cases due to recent transmission has been approximately constant among the homeless in SPA-4 and LAC at-large. *It can thus be assumed that the annual change in incidence of TB should be equal to the annual change in prevalence of LTBI*.

$$Inc_{TB} = P_{LTBI} * \%LTBIRecent * PR_{Fast} + P_{LTBI} * (1 - \%LTBIRecent) * PR_{Slow} \quad \text{Eq. 21}$$

$$LTBIRecent = \frac{P_{LTBI-Recent}}{P_{LTBI-Recent} + P_{LTBI-Old}} = \frac{\frac{\%CasesRecent}{PR_{Recent}}}{\frac{\%CasesRecent}{PR_{Recent}} + \frac{(1 - \%CasesRecent)}{PR_{Reactivated}}} \quad \text{Eq. 22}$$

$$Inc_{TB} = P_{LTBI}\left(\frac{1}{\frac{\%CasesRecent}{PR_{Fast}} + \frac{(1 - \%CasesRecent)}{PR_{Slow}}}\right) \quad \text{Eq. 23}$$

If the % of cases due to recent transmission is constant over time, Eq. 21 and Eq. 23 imply that: Eq. 24

$$\%\Delta Inc_{TB} = \%\Delta P_{LTBI} = 1.74\%$$

This system of equations helps to validate the method described in Section 4.1 for identifying the appropriate denominator for the incidence statistic. As shown in Table 9, the "point in time" count would suggest an annual growth rate in incidence of 14% in LAC and 16% in SPA-4. The "annualized" count, by contrast, would suggest a growth rate of -3% in LAC. Our adjusted denominator yields a growth rate of 0.8% in LAC and 2.2% in SPA-4, which compare favorably to the growth rate estimates derived in this section (0.6% in LAC and 1.7% in SPA-4).

4.4.3 Transmission of LTBI

A transmission event occurs when an infectious agent with TB disease (state 3-4 for smear negative, state 5 and 6 for smear-positive) exposes or comes into contact with an uninfected agent and the exposed agent contracts latent TB infection. In the NetLogo environment, uninfected agents are exposed if they reside on the same "patch" as an infectious agent. The extent of transmission therefore depends on the average number of contacts per day, proportionate to population density (see Section4.2.5), the proportion of uninfected persons $(1 - P_{LTBI} - P_{TBD})$, the duration of the infectious period $\overline{InfPeriod}$, and the weighted average probability of becoming infected if exposed $P_{Infected|Exposed}$, also known as the "attack rate:"

$$InfectedPerCase = UninfectedContactsPerDay * \overline{InfPeriod} * P_{Infected|Exposed} \quad \text{Eq. 25}$$

This section proposes a novel method for estimating the attack rate based on user-input and implied parameters. The formulas in Eq. 26 - Eq. 27 demonstrate that the number of uninfected agents that each infectious TB patient infects (InfectedPerCase) is equal to the incidence of new LTBI infections from endogenous infectious cases $\left(Inc_{LTBI-Endogenous}\right)$ divided by the incidence of TB disease at the point in time that the new infections were transmitted. Since days since infection is uniformly distributed among the cohort infected within the past year, we assume that all recently infected agents were infected 6 months ago. The incidence of TB disease when the average individual from the recently infected cohort was infected is thus equal to $Inc_{TB}(1 - (\%\Delta Inc_{TBD}/2)$.

Substituting the formula for endogenous LTBI infections (Eq. 18), expected new infections per case can be derived from the percent of cases due to recent transmission, migration and mortality parameters, and the TB disease incidence growth rate (Eq. 27). Default model parameters yield an estimated 13.2 new infections per case on average within the simulation environment prior to death and migration.

$$Inc_{LTBI-Endogenous} = InfectedPerCase * Inc_{TB,Y-0.5} = InfectedPerCase * Inc_{TB} * (1 - \left(\frac{\%\Delta Inc_{TB}}{2}\right) \quad \text{Eq. 26}$$

$$InfectedPerCase = \frac{Inc_{LTBI-Endogenous}}{Inc_{TB}(1 - (0.5 * \%\Delta Inc_{TB})} = \frac{\frac{\%CasesRecent}{PR_{Recent}} + 1 - RR_{LTBI-Entrants} * (DR + MR)}{(1 - DR - MR)(1 - (0.5 * \%\Delta Inc_{TB})} \approx 13.2 \quad \text{Eq. 27}$$

Rearranging Eq. 25 produces a formula for the attack rate (Eq. 28), which is equal to the estimated number of new infections per case divided by the product of the average number of uninfected contacts per day and the mean infectious period (see Section 4.3.4). If smear-positive cases are 4.5 times as infectious (see Section 4.3.10), default model parameters suggest that average homeless client faces a 5.8% probability of infection if exposed to a smear-positive case and a 1.3% probability of infection if exposed to a smear-negative case [19, 85, 18, 20, 86]. In downtown Los Angeles, 68% percent of cases are smear-positive (see Section 4.3.10). Our estimate of 13.2 new infections per source case suggests that each smear-positive case produces ~18 new cases and each smear-negative source case produces ~4 new infections.

$$Attack\ Rate = P_{Infected|Exposed} = \frac{InfectedPerCase}{UninfectedContactsPerDay * \overline{InfPeriod}}$$

Where: Eq. 28

$$UninfectedContactsPerDay = ContactsPerDay * (1 - P_{LTBI} - P_{TBD}) \approx 3.5 * (1 - 0.187 - 0.0018) \approx 2.84$$

$$P_{Infected|Exposed,Overall} \approx 4.3\%$$

The method is validated by comparing our estimate of the number of new infectious per source case to estimates of secondary infections found in the published literature. Other studies have estimated that each smear-positive source case produces between three and 13 new infectious per year [19, 87]. Accounting for the shelter density factor (see section 4.2.5), our estimate suggests that each smear positive case produces ~11.5 new infections in an unsheltered environment, corresponding to the upper bounds of estimates from the published literature.

Prior to account for the annual migration and death rate, these parameters suggest that each case of active TB presenting within the downtown LA homeless population produces 1 case in the near-term and 0.34 undiscounted reactivated cases over the life expectancy of the average homeless client. In contrast, each case of TB among the general population produces approximately 0.23 cases in the near-term [25]. Among the broader LAC homeless population, each case of TB produces ~12.6 new infections per year resulting in 0.94 new cases in the near-term and 0.28 reactivated cases. These parameters are used in the *Cost of a Case* paper to estimate the number of secondary cases per active case.

4.4.4 Growth Rates, Transmission and Model Validation

The projections of the annual growth rate in LTBI prevalence and TB incidence help to validate the NetLogo simulation model. During 2007-2013 there were 136 cases of TB among the homeless within an average annual population of ~20,500. The model simulates TB over the next 10 years in SPA-4. Assuming 7 prevalent cases at model initialization the model is therefore initialized with an annual incidence of ~19 per 20,000 inhabitants (see Section 4.3.1).

TB incidence is initialized at approximately 20 cases per year (see Section 4.3.1). Assuming 7 prevalent cases at model initialization, a 1.74% annual growth rate in LTBI prevalence and TB incidence suggests that LTBI prevalence should reach 18.7% and that there should be approximately 212 undiscounted and 186 discounted cumulative cases of TB throughout the 10-year simulation. On average across the runs aggregated in Table 12, there were 200 discounted cumulative cases and LTBI prevalence grew by 1.68%.

4.5 LTBI Testing and Treatment Assumptions and Efficacy Parameters (Intervention)

4.5.1 Treatment Assumptions

All LTBI test positive homeless patients are offered treatment with a 12-dose regimen of weekly Rifapentine plus isoniazid ("3HP") administered as directly observed therapy (DOT). Because many patients successfully completing LTBI therapy remain test positive by TST or IGRA following therapy completion, LTBI testing cannot detect re-infection in "cured" patients completing LTBI therapy. Patients that have successfully completed treatment are therefore assumed to be "cleared" for the

purpose of shelter admission for the duration of the simulation and will not be offered LTBI screening at shelter admission despite the risk that they were re-infected following treatment completion.

LTBI treatment reduces but does not eliminate the risk of progression to TB disease. The relative risk of progression to TB disease among LTBI test positive patients treated with 3HP versus untreated LTBI test positive patients is represented by the risk reduction parameter (Risk-Reduction-3HP). In the 2011 Sterling trial, the annual risk of progression was 0.05% for those completing 9+ 3HP doses versus 0.36 for patients completing 90 or less doses of 9H. Risk reduction associated with completing 3HP is estimated to be 86%. Partial completion, defined as 5-9 doses, is assumed to confer 50% protection relative to complete treatment (43% risk reduction). Patients completing 4 or less doses are assumed to experience no risk reduction.

4.5.2 LTBI Test (IGRA or TST): User-Input

Users can choose whether agents are tested with the interferon-γ release assay (IGRA) or the Tuberculin Skin Test (TST). The TST is cheaper and more sensitive than the IGRA. However, it is less specific and, most important, requires that that patients return to have the test read, which can reduce the efficacy of the intervention. If users select the IGRA test, the simulation assumes that the QuantiFERON®-TB Gold In-Tube test (QFT-GIT) test is used.

4.5.3 Compliance: Shelters-Complying, Percent Shelter Non-Compliers and Percent Shelter Refusers: User Input

The total number of shelters, out of 8, implementing the mandatory screening intervention is defined by the Shelters-Complying user-input parameters. In the base case intervention scenario, 4 shelters adopt the recommendation.

The percent of clients that will submit to screening by a compliant shelter is a function of the proportion of homeless persons that do not participate in the shelter system (Pct-Shelter-Refusers) and the fraction of clients that will not comply with screening when referred (Pct-Shelter-NonCompliers). Individuals are indexed as compliers or non-compliers when they enter the simulation in order to avoid reaching unrealistic compliance rates with repeat admission attempts. The maximum proportion of screened clients is therefore equal to (1 – Pct-Shelter-Refusers) * (1 – Pct-Shelter-NonCompliers).

A study by Kong and colleagues of a mandatory TST screening program in 4 shelters and 6 residential drug and alcohol treatment programs in Denver during 1995-1998 found a screening ratio (number of completed TSTs divided by the estimated homeless population) of 67% after four years. Among the 33% that failed to complete a TST, we assume that 20% were due to failure to return for reading. This implies that approximately 25% of the population will either not participate in the shelters or not comply with initial screening. We assume that 10% are shelter-refusers and 17% are non-compliers with the testing referral.

4.5.4 TST Percent Returning to Read: User Input

The proportion of clients that, after having a TST placed, will return to have the test read is represented by the TST-Pct-Return-Read parameter. The default value is 65%, based on a study conducted by Bock et al on the prevalence of LTBI among the homeless in the mid-1990s [80]. Individuals are indexed as "TST-returners" when they enter the simulation.

4.5.5 Test Sensitivity and Specificity

The IGRA test is assumed to be 83% sensitive and 99% specific [88, 89, 90]. The TST 99% sensitive [90]. TST is 92% specific in U.S. born individuals and 98% specific in U.S. bon individuals [90]. Assuming that 30% of the homeless population is foreign born yields an average TST sensitivity of 96%. The false-positives-treated monitor tracks the total number of false positive clients that completed LTBI treatment.

4.5.6 Clearance Period: User Input Parameter

The user-defined Clearance-period-wks parameter defines the duration of time, measured in weeks, that an agent is granted admission to a shelter following a negative LTBI test or LTBI treatment initiation. While LAC DPH refers to this intervention as "annual screening" in reality the clearance duration is closer to 15 months due to shelter program timing [66].

4.5.7 Treatment Capacity: User-Input Parameter

There are constraints on the total number of homeless clients that can be tested and treated for LTBI in downtown LA. Treatment is the capacity bottleneck given relatively high prevalence of test positive patients and the costs and personnel requirements associated with 3HP administered by DOT. The Treat-Capacity-Starts-Annual parameter captures the total number of homeless clients that LAC-DPH can treat with 3HP per year in addition to the homeless clients already treated under the status quo scenario. Capacity is defined in terms of treatment initiation (treatment "starts") rather than successfully completed treatment. Analysts at LAC-DPH Community Health Services (CHS) and TBCP stated that about 100 homeless clients are currently treated. If resources were scaled significantly, about 300 homeless clients could initiate treatment with 3HP in SPA-4 per year, suggesting a marginal capacity of approximately 200 clients [91]. The model is initialized with 200 treatment starts per year as the capacity limit, enforced on a per-month basis.

If the capacity limit has been reached, clients are not tested. However, clients are still screened and referred to testing at shelter intake due to anticipated difficulties associated with updating shelter operators on the status of treatment resources. I assume that patients turned away from testing for capacity-related reasons are permitted re-entry into the shelter.

This capacity limit parameter significantly influences model outcomes. With an estimated prevalence of 16% and a population of 20,000, there are more than 15 times as many LTBI positive clients as there are 'slots' for treatment initiation in the first year of the simulation. Given fixed and annual implementation costs and the pre-admission cost of the shelter-screen, capacity limits not only curtail program effects but create cost inefficiencies. Further, it is unclear to what extent the capacity

constraint is variable. Further study is needed into whether and at what cost LAC-DPH could redirect resources to augment capacity.

4.5.8 Treatment Initiation Rate: User Input Parameter

The proportion of homeless clients that initiate treatment with 3HP if it is offered to them is represented by the Initiation-Rate-3HP parameter. Published studies assessing initiation rates among the homeless population have found initiation rates between 64% and 82%. In Horsburgh et al, 70.6% initiated treatment (95% CI, 64%-77%); Miller et al observed an initiation rate of 79% (95% CI, 76%-82%) [36, 92]. LAC DPH found an initiation rate of 54% out of 215 contacts of outbreak cases offered LTBI treatment. The number of initiators was highest among those on the 3HP regiment but a rate could not be determined because the treatment offers by regimen (the denominator) was not reported [93]. We initialize the model with an initiation rate of 65%. Users can choose a value between 40 and 95%.

4.5.9 Treatment Completion Rate: User Input Parameter

The proportion of homeless clients that take all 12 doses of the 3HP treatment regimen, among those that initiate treatment, is represented by the Completion-Rate-3HP parameter. No published studies have assessed 3HP completion among homeless subjects. Horsburgh et al found low completion rates among homeless shelter participants (31%, 95% CI 26%-35%). However, the majority of subjects were treated with a 9-month course of isoniazid ("9H") taken as self-administered therapy (SAT), which has been found to have low completion rates overall [36]. Horsburgh found an odds ratio for failure to complete treatment associated with homelessness of 2.9 (95% CI 1.6-5.6) [25, 36]. The Sterling 2011 trial found an overall 3HP completion rate of 81% [25, 94, 36]. Applying the relative risk from Horsburgh to the completion rates in Sterling yields an estimate completion rate of 53% among homeless clients. However, LAC DPH has reported slightly higher rates among homeless initiators: 69% for 3HP and 57% overall [93]. We therefore initialize the 3HP completion rate at 61%, the midpoint between the literature estimate and the rate reported by LAC DPH. Users can choose a completion rate between 40 and 95%.

We assume that the risk of treatment non-compliance among initiators is probabilistic and independent from week to week rather than an indexed propensity. All treatment initiators therefore face an equal risk of quitting equal to (1 – Completion-Rate-3HP). This implies that agents that initiate but fail to complete treatment in one year have the opportunity to complete treatment in subsequent years. The risk of quitting is assumed to be evenly distributed through the duration of 3HP treatment. It is also assumed that the risk is independent such that an agent's probability of completing treatment is unrelated to whether they have initiated and quit in the past. This is in contrast to treatment initiation, a propensity assigned to each agent. In other words, agents have a propensity to initiate treatment but, once initiated, whether or not they quit on any given week is random. The assumption of independence decreases the influence of the treatment completion parameter because quitters have subsequent opportunities to complete. The weekly risk of quitting is therefore (1-Completion-Rate-3HP)/Duration-3HP.

4.5.10 3HP Risk Reduction

In the 2011 sterling trial, progression rate for individuals on 9H that failed to complete more than 90 treatments was 0.36% per year and the progression rate individuals completing at least 9 doses of 3HP was 0.05%. We therefore assume a risk reduction of 86% for individuals completing the 3HP regiment (1- 0.05/0.36). Risk reduction for partial completers is proportionate to the portion of doses completed.

4.5.11 3HP Toxicity

Agents undoing treatment for LTBI with 3HP face a risk of treatment-related toxicity or other adverse events. In the 2011 Sterling trial of the 3HP treatment regiment, 8.2% of treatment subjects experienced treatment-related adverse events and 0.3% required hospitalization. The risk of death from treatment-related toxicity was observed to be 0.014% in a study of a 12 month course of isoniazid [95, 96, 25]. Because toxicity-related discontinuity is already incorporated into our treatment compliance parameter and because this model is not considering quality adjustments, only severe adverse events (hospitalizations or death) are modeled. Homeless agents experiencing severe toxicity spend two weeks in the hospital. Models simulating the general population typically assume that toxicity-related hospitalizations last 1 week [25].

4.6 Cost Inputs and Aggregation Methods

Each agent is assigned a cost and attribute that tracks the cumulative costs incurred by the agent, including costs associated with the intervention and those incurred if they develop TB disease. Cost data were gathered from the published literature, interviews with LAC-DPH officials, published salary information for LAC officials and personnel and the 2011 Centers for Medicare and Medicaid (CMS) physician fee schedule [97, 14]. The costs per case of active TB among the homeless were analyzed within the *Cost of a Case of TB among the Homeless* paper submitted within this dissertation series. [76]. All costs are reported in 2014 U.S. dollars using medical cost inflation (MCI) rates [98]. All future costs were discounted at 3%. Cost input variables, default values, and description of the cost components and implicit assumptions are detailed in Table 11.

Table 11: Cost Inputs

Cost Variable	Value (Range)	Costs Included / Description	Sources
LTBI Shelter Screening Costs			
Cost to Check Clearance Status (C-Shelter-Screen)	$3 ($1-$10)	10 Minute Shelter Worker Time @ $24/Hour. This cost is incurred regardless of the agent's clearance status and available treatment resources.	[99]
Cost to adopt the intervention (C-Shelters-Adopt)	$4,000/Shelter	Up-front cost to implement the policy per participating shelter: system upgrades and initial training.	*N/A**
Annual Cost to Train Staff (C-Annual-Training)	$500/Shelter	Annual cost per participating to train new shelter employees on the LTBI intake screening. ~20Hrs @ $24/Hour.	*N/A**
LTBI Testing			
IGRA Cost: QFT Gold-In Tube	$56 (28-113)	Phlebotomist time and supplies, nurse time to screen, QFT-GIT kit, lab scientist time and supplies,	[100, 56, 98]

		clerical time	
TST: Placement	$24	TST Reagent + Nurse Visit	[14]
TST: Reading	$21	Nurse Visit ~ 5 Minutes	[14]
Evaluation if IGRA Positive	$115 (87-154)	MD visit, Chest X-ray (CXR)	[100, 98]
LTBI Treatment (3HP) Costs			
Drug Costs / Week	$14		[25, 98]
DOT Costs / Week	$31	0.5 hours of PHN time	
Physician Clinic Visits / Month	$81	1 Initial Visit and 1 Per Month of Treatment. 1 Hour of RN Time / Visit. First visit amortized	[25, 97]
Diagnostic Costs / Month	$62	2 Cultures, 2 Liver Enzymes. 2011 costs with 8.4% MCI.	[14]
Treatment Adherence Incentives	$12	Meal Vouchers	[66]
Total 3HP Cost / Week	$94($50-150)	Derived	
Costs of a Case: Inpatient			
Diagnostic Costs	$400 / Case	3 Sputum Smears + 3 Cultures + 2 Chest Radiographs + Physician and Nurse time	[76]
Mean Hospitalization LOS	49 Days	Described in Section 4.3.5	[76]
Hospitalization Cost / Day	$2,888 / Day	General ward average cost per day for homeless TB patient at LAC+USC hospital.	[76]
Cost of a Case: Outpatient Treatment & Case Mgmt.			
Mean Outpatient Duration	26 Weeks	8 weeks of isoniazid (INH), rifampin (RMP), pyrazinamide and ethambutol followed by 18 weeks of INH and RMP.	4.3.5 [25, 98]
Drug Costs Per Week	$18 / Week	5 doses per week. 130 dose regiment was $390 in 2008 dollars = $467 in 2014 w/20% MCI.	[25, 98]
DOT Costs Per Week	$155 / Week	0.5 hours of PHN time. $31 per dose.	[25, 97]
Physician Clinic Visits	$122 / Month	1 hour of MD time per month on treatment.	[25, 97]
Diagnostics During Treatment	$107 / Case	2 CXRs, 2 Cultures, 2 Liver Enzymes. 2011 CMS Carrier file costs with 8.4% MCI.	[56, 14]
TB Housing / Lodging	$3,750 / Case	Average per case – 57% received vouchers.	[76, 30]
Food & Transportation Vouchers	$1,400 / Case	Average per case – 65% received vouchers.	[76, 30]
Total Outpatient Treat & Mgmt. Cost	$479 / Week	Total costs are amortized on a per-week basis assuming the average patient spends 19 weeks in outpatient treatment (26 – 7 inpatient weeks).	Derived
Contact Investigation Cost / Case	$16,000 / Case	Methods described in the *Cost of a Case* paper	[76]
Average Cost Per Case	$180,914		

PHN: Public Health Nurse; DOT: Directly Observed Therapy; 3HP: 3 months of weekly Rifapentine plus isoniazid;
LOS: Inpatient Length of Stay; MCI: Medical Cost Inflation
*Fixed and annual shelter implementation costs have not been validated. Further study is needed.

5 Results and Policy Implications

With ample treatment resources (~ 600 treatment start per year), the intervention typically generates cost savings by the 5th-68h year post implementation owing to the high cost of averted cases. However, the cost effectiveness of the intervention varies considerably with the treatment capacity parameter due to the fixed costs incurred by each participating shelter. As discussed in Section 4.5.7, although clients are not tested if capacity is reached, each participating shelter incurs an up-front cost to implement the policy, an annual training cost, and a small intake screening cost per client seeking admission regardless of available treatment resources. As a consequence, once capacity has been

reached, the capacity constraint creates inefficiencies that increase with the number of participating shelters.

5.1 Simulation Results with Default Parameters with Varying Capacity Constraint

Simulated costs and benefits over a 10-year period associated with three treatment initiation capacity scenarios – 200, 600 and 2,500 – are shown in Table 12. If LAC-DPH could have treatment for at least 600 LTBI positive homeless clients in SPA-4 each year, the intervention would typically yield cost savings. Due to fixed costs and the time-lag between LTBI treatment and averted cases, cost savings would not typically appear until the 5^{th}-8^{th} year post-implementation, as cost savings are driven by the high cost of averted cases, specifically by long inpatient LOS. With a cost per case of ~$170,000 and steady-state gross annual program costs of ~$80 per person, the intervention is theoretically cost saving, with discounting, when 7-8 cases are averted per year, representing a drop in incidence of ~40%. Pursuant to the equations in 4.4, this reduction will be achieved after LTBI prevalence drops by approximately the same degree. These dynamics for a typical simulation are illustrated in Figure 4.

The intervention is not typically cost saving under the 200-starts-per-year capacity scenario because LTBI prevalence and incident TB cases will not drop far enough to recoup the fixed costs and inefficiencies generated by the shelter-screen. On average, the intervention will cost approximately $17,000 per averted case after 10 years. With a baseline LTBI prevalence of 16% and a population of 20,000, only about 7% of the LTBI positive population can be tested and treated per year. Cost inefficiencies decrease moderately over time as the fraction of treated clients increases. By the tenth year post-adoption, approximately 16% of the population will be 'cleared' (test negative or test positive and treated). However, the policy when implemented under this capacity constraint is essentially equivalent to randomly testing 7% of the population annually, which inherently fails to meet the intent of a mandatory or "universal" approach to screening. Moreover, ran*dom testing may be a less effective use of limited testing and treatment resources than a prioritized approach targeting groups at higher risk of progression.* Further study is needed into the relative effectiveness of allocating limited treatment spots to groups facing an elevated risk of progression, particularly those that were recently exposed (e.g., close contacts to infectious cases) given the high rate of progression in the period immediately following infection.

There are diminishing returns to increasing annual treatment capacity beyond 600 starts per year. As shown in Table 12, the average number of actual treatment starts per year over the 10-year period will not exceed 600 per year even under the scenario with no treatment capacity because the fraction of 'cleared' clients will converge, under default model parameters, to a steady-state level of about 57%. Lifting the capacity constraint shortens the time to generating cost savings and causes a modest increase in total cases averted and a decrease in net costs over the 10-year period due to the large number of patients that are treated immediately. However, the absence of a capacity constraint would overwhelm DPH resources in the early stages of the program and would place uneven demands on the program over time, complicating planning efforts: on average over 600 clients would present for testing and over 60 for treatment per week during the first several months of the program. As the fraction of cleared clients increased, demands on the system would eventually decline to ~100 tested and 11 treated per week.

Trends in TB incidence, LTBI prevalence, cost and health outcomes by week for a typical 10-year simulation under the 200-starts-per-year and 600-starts-per-year capacity scenarios are illustrated in Figure 4. These plots are displayed on the NetLogo user interface. Under the 600-starts scenario, the intervention became cost saving during the 5th year (week 249) when LTBI prevalence in the intervention cohort reached 7.5%, approximate 60% less that LTBI prevalence in the status quo cohort. The point at which the intervention became cost saving is represented by the green line.

Table 12: Costs, Benefits and Cost Effectiveness of Mandatory Annual Shelter Screening in SPA-4 with Default Model Parameters and Varying Capacity (10-Year Simulation)

Treatment Capacity Constraint	Cost[d] / Case[d] Averted	Cases[d] Averted	Net Costs[d] Per Capita	LYs Gained	Annual Program Costs[d] Per Capita	NNS to prevent 1 Case[d]	Percent Cleared	Actual Treatment Starts/Year	Severe Toxicity Events	Active Case Yield
200 Starts/Year, Mean	**17,180**	**45**	**38**	**119**	**44**	**375**	**16%**	**207***	**5**	**4**
25th Quartile	Cost Saving	-1	(401)	4	42	250	14%	207*	3	3
75th Quartile	↑ in Cases	101	490	214	44	↑ in Cases	17%	207*	6	6
600 Starts/Year, Mean	**Cost Saving**	**108**	**(97)**	**263**	**79**	**1,206**	**57%**	**531**	**12**	**15**
25th Quartile	Cost Saving	59	(401)	144	77	657	57%	513	9	11
75th Quartile	46,516	144	334	346	80	1549	57%	541	14	19
No Capacity Constraint, Mean	**Cost Saving**	**141**	**(280)**	**310**	**87**	**30,301**	**57%**	**558**	**13**	**18**
25th Quartile	Cost Saving	93	(590)	218	88	577	51%	553	8	13
75th Quartile	20,679	187	193	446	101	553	59%	592	15	22

Cost[d]: Discounted Net Costs: Cases:[d] Discounted Cases.
*The treatment capacity constraint is implemented on a monthly basis. Due to rounding, the exact number of treatment starts per year is slightly over 200/year for the 200-starts-per-year scenario.

Figure 4: Trends in TB and Discounted Health and Cost Outcomes Over Time for a 10-Year Simulation

Figure 4A: 200 Treatment Starts Per Year

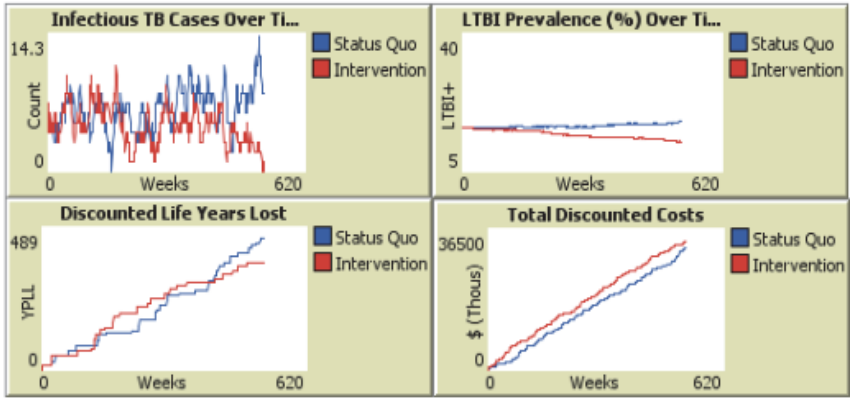
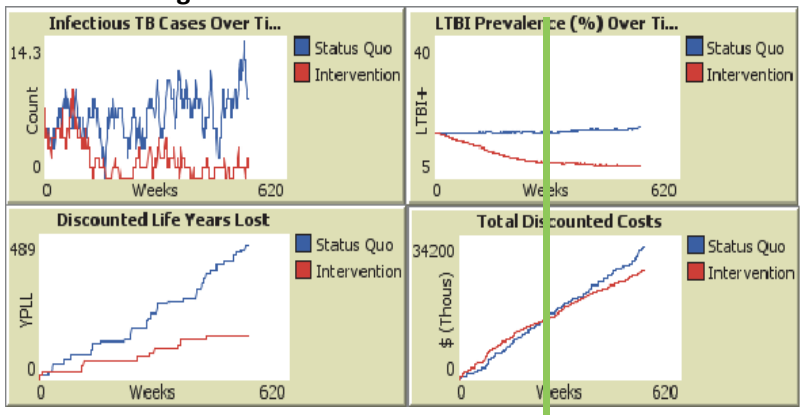


Figure 4B: 600 Treatment Starts Per Year



Results generated with seed -832191. The week the intervention becomes cost saving is represented by the green line (week 249 for the 600-starts scenario).

5.2 Univariate Sensitivity Analysis

Univariate sensitivity analysis was conducted to evaluate the influence of individual cost and intervention efficacy parameters on cost effectiveness over the 10-year simulation while holding all other inputs at their default value. Separate sensitivity analyses were performed for the 200-starts-per-year and 600-starts-per-year scenarios. Results are shown in Table 13. Arrows denote the practical significance of the parameter to effectiveness outputs, defined as a percentage change equal to or greater than 10%. The most influential factor in the cost effectiveness of the intervention is the cost of treating and managing a case of active TB within the homeless population, driven primary by the average inpatient length of stay (LOS). The intervention is no longer cost saving under the 600-starts-per-year scenario if the average homeless case spends less than approximately 35 days in the hospital.

Sensitivity analysis revealed that increased shelter participation (the proportion of complying shelters) may not be cost effective under either treatment capacity assumption. If capacity is constrained, it is more effective to have one out of eight shelters participating because only 7% of the LTBI positive population can be tested and there are fixed costs per participating shelter. If capacity is unconstrained or flexible (~600 starts/year), the intervention can "reach" approximately the same proportion of clients by ensuring or increasing churn or throughput through participating shelters. If 36% of the population is sheltered and the average shelter stay is 6 weeks long and the client's choice of shelter is random and independent, the typical client will transition through approximately 3 shelters per year. If 2 out of 8 shelters are participating and if the client enters a different shelter at each transition, the client will face a ~60% probability of encountering the intervention in a given year and a 90% chance within 2 years. Thus, policymakers can ensure 'coverage' and avoid implementation and other costs by focusing on policies that limit repeat stays rather policies that increase shelter participation/compliance.

With 600 treatments per year the intervention is cost saving under a wide range of initiation, compliance, completion and intervention cost parameters. Improving initiation rates will save some resources due to less wasteful tests but will have a small influence on health outcomes because patients failing to initiate treatment lose their clearance status and are "replaced" in the following week by new agents seeking admission into the shelter (demand for beds always exceeds supply of beds as documented in Section 4.2.4). Similarly, increasing the proportion of clients that comply with the screening referral (decreasing the percent of non-compliers) results in a slight gain in cost savings but does not considerably improve the yield of the intervention because non-compliers are replaced with new shelter seeker. A higher 3HP completion rate saves resources by reducing ineffective treatment costs and also decreases the time until the intervention shows cost savings. Over time, however, completion rates have a minimal impact on the total yield of the intervention because quitters can initiate and complete treatment in subsequent years given our assumption that attrition risk is probabilistic and independent over time (see Section 4.5.9). A 50% cut in the cost of the IGRA test has a larger impact on net costs than equivalent cuts to the cost of treatment or the costs to screen and refer at shelter intake.

Table 13: Results of Univariate Sensitivity Analysis Varying Intervention Efficacy and Cost Characteristics: 10-Year Simulation*

	200 Treatment Starts Per Year					600 Treatment Starts Per Year				
Parameter (Base case)*	**Effectiveness vs Base Case***	**Cases[d] Averted**	**Costs[d] Per Capita**	**Gross Annual Costs/Capita**	**% Clients Cleared**	**Effectiveness vs Base Case***	**Cases[d] Averted**	**Costs[d] Per Capita**	**Gross Annual Costs/Capita**	**% Clients Cleared**
Intervention Efficacy										
Shelters-Complying (4)										
1 (13%)	More Effective	--	↓	↓	--		↓	↓	↓	↓
2 (25%)	More Effective	--	↓	↓	--		--	↓	↓	--
8 (100%)	Less Effective	--	↑	↑	--	Less Effective	--	↑	↑	--
Client Non-Compliance										
35% (65% compliance)		--	--	--	--		--	--	--	--
5% (95% compliance)		--	--	--	--		--	--	--	--
Initiation-Rate-3HP (65%)										
30%		--	--	--	--		--	--	--	--
85%		--	--	--	--		--	--	--	--
Completion-Rate (61%)										
30%	Less Effective	↓	--	--	↓	Less Effective	↓	--	--	↓
85%		--	--	--	--		--	--	--	--
Test (IGRA)										
TST		--	--	--	--		--	--	--	--
Clearance-Period-Wks (65)										
52 Weeks		--	--	--	--		↑	↑	↑	↓
78 Weeks		--	--	--	--		↓	↓	↓	↑
Cost Parameters										
Hosp-Days-Average (49)										
20 Days / Case	Less Effective	--	↑	--	--	Less Effective	--	↑	--	--
75 Days / Case	More Effective	--	↓	--	--	More Effective	--	↓	--	--
C-Shelter-Screen ($4)										
$1	More Effective	--	↓	↓	--	More Effective	--	↓	↓	--
$10	Less Effective	--	↑	↑	--	Less Effective	--	↑	↑	--
C-IGRA ($56)										
$30	More Effective	--	↓	↓	--	More Effective	--	↓	↓	--
$80	Less Effective	--	↑	↑	--	Less Effective	--	↑	↑	--
C-3HP-Weekly ($94)										
$50	More Effective	--	↓	↓	--	More Effective	--	↓	↓	--
$150	Less Effective	--	↑	↑	--	Less Effective	--	↑	↑	--

* Up arrow on green field = significantly increased, operationally defined as a greater than 10% increase in the outcome in question; Down arrows on red field = significantly decreased, operationally defined as a greater than 10% decrease in the outcome in question; Dash on grey field = no change.

*Cost effectiveness relative to base case parameters. "More effective" denotes a parameter configuration that either saves costs and health, saves health at no cost, or saves costs at no loss of health. "Less Effective" denotes a parameter configuration that either costs health and resources, costs health with no cost savings, or costs resources with no gain in health. If the cell is blank the parameter configuration either gains health at cost or saves cost and loses health.

5.3 Discussion

This study set out to characterize the transmission of TB among the homeless in downtown Los Angeles and to assess the costs and benefits associated with mandatory annual LTBI screening in the homeless shelters serving the downtown Los Angeles homeless population. Based on TB surveillance and genotyping data collected during 2007-2013 and a weighted analysis of the annualized and point-in-time LAC homeless counts, this study estimates the prevalence of LTBI to be 16% among the downtown LA homeless population (SPA-4) and 11.5% among the broader LAC homeless population. Incorporating estimates of migration, these data suggest that each case of active TB produces approximately 13.2 new Mtb infections in SPA-4 and ~12.6 new Mtb infections in LAC.

The efficacy of a mandatory annual shelter screening intervention is complicated by treatment capacity constraints. With a population of 20,000 homeless and an LTBI prevalence of 16%, over 3,000 persons experiencing chronic or transient homelessness are estimated to be living with LTBI in downtown LA. However, public health clinics serving the population may only have the capacity to initiate treatment for about 7% of the LTBI infected population per year. *Under this constraint, the mandatory screening initiative is equivalent to randomly testing 7% of the population per year, which may be a less effective use of limited treatment resources than targeting groups facing an elevated risk of progression (in particular, close contacts of infectious cases).*

LAC-DPH should focus on increasing treatment capacity to approximately 600 treatment starts per year before requiring other shelters to adopt the mandatory screening intervention. The county should not screen or treat persons that they cannot afford to treat. Because there are up-front and annual fixed costs per participating shelter, it is more cost effective to have one out of eight shelters participate than to expand the program. *There are diminishing returns to increasing annual treatment capacity beyond 600 starts per year* because default model compliance and migration parameters cause the percentage of clients screened to converge to a steady-state of approximately 57% even when capacity is unconstrained.

If capacity were to expand to 600 starts per year, the intervention would typically generate cost savings between the fifth and ninth year post-implementation, driven by the high cost of averted cases. The efficacy of the intervention under this scenario is robust to a wide range of compliance and treatment initiation parameter values if non-compliers are denied entry and demand for beds always exceeds supply. Moreover, cost effectiveness may be optimized at less than full shelter participation under any capacity scenario, particularly when considering non-financial implementation hurdles: the county can “reach” approximately the same fraction of the population by facilitating churn through participating shelters through measures such as enforcing limits on repeat stays.

Due to migration, the intervention is unlikely to end the transmission of TB in downtown Los Angeles under any capacity scenario. However, with 50% of shelters complying LTBI prevalence and TB disease incidence can reach steady-state levels approximating those within Los Angeles County at large.

Finally, strategies to control the transmission of TB among the homeless can be improved with better data collection. The TB registration forms submitted by health care providers upon diagnosis of an active case should include a field for "currently homeless" in addition to the field "homeless within the past 12 months." In addition, migration in and out of a homeless population has a large impact on the epidemiology of infectious disease. The Los Angeles Homeless Services Authority (LAHSA) should use data from the Homeless Management Information System to track migration patterns in and out of Los Angeles service planning areas (SPAs) to measure and predict the spread of infectious diseases.

The results presented in this study are subject to a number of limitations that should be addressed in subsequent research. Most importantly, further study is needed into the relative cost effectiveness of alternative uses of limited treatment resources – particularly intensified contact investigations or other approaches that target groups facing an elevated risk of progression.

The model assumes that, among shelter participants, agents randomly transition between shelters without shelter participation propensities and without preferences for particular shelters. In reality, clients may have a range of shelter participation propensities and may only transition in and out of only one of two shelters which would decrease the reach of the intervention. Moreover, a client's propensity to comply may be correlated with the percent of shelters participating in the intervention. For example, if Shelter A is requesting that a client be screened and the client knows that Shelter B does not require screening, a client who would otherwise comply with screening may refuse and seek admission at Shelter B. The model does not account for this possibility, which could under-estimate the influence of shelter compliance on intervention outcomes.

There are several potential advantages to the implementation that are not captured by the model. The model does not account for discounted cases presenting after the end of the 10 year simulation. Moreover, the intervention will avert TB cases outside of downtown Los Angeles due to lower rates of LTBI among the population migrating out of SPA-4. The present model cannot capture the health and economic gains associated with those averted cases. The model does not capture ancillary benefits to the screening program such as improved relationships between DPH and the homeless shelters, better surveillance data and improved capacity to link homeless clients to other services [82].

Appendix: Supplemental Figures and Tables

Table A.1: Model States

Variable	State: Interpretation of state in day t [NetLogo Turtle Color, If Applicable]	Weeks in State
$TBState_j$	**Tuberculosis Status of Person j**	
	0: Uninfected [Color = Blue]	1-∞
	1: LTBI, recently infected (fast progressing) [Color = Yellow]	52
	2: LTBI, previously acquired (slow progressing) [Color = Yellow]	1-∞
	3: LTBI treatment partially completed, partial residual risk of TB [Color=Yellow]	1-∞
	4: LTBI treatment completed, small residual TB risk [Color = Blue]	1-∞
	5: Infectious TB: Smear-negative TB, undiagnosed [Color = Red]	18[Y]
	6: Infectious TB: Smear-positive TB, undiagnosed [Color = Red]	18[Y]
	7: Hospitalized for TB, on TB Treatment [Color = Green]	7[Y]
	8: TB Housing, on TB Treatment [Color = Green]	19[Y]
	9 Dead from TB	
$EvalState_j$	**LTBI Evaluation and Shelter Admission Clearance Status of Person j**	
	0: Not Cleared: Never tested or treated for LTBI	1-∞
	1: Not Cleared: Screened and test-negative > 1 Year Ago	1-∞
	2: Not Cleared: Test-positive, failed to initiate or failed to complete treatment	
	3: Cleared: Test-negative within the past year	365
	4: Cleared: Test-positive and undergoing or completed treatment in the past	1-∞
$LTBIRxState_j$	**LTBI Treatment status of person j**	
	0: Not currently receiving LTBI treatment	1-∞
	1: Currently undergoing treatment for LTBI (3HP)	1-90
	2: Hospitalized from LTBI treatment Toxicity	1
$Sheltered_j$	**Shelter Status of Person j**	
	0: Unsheltered	1-∞
	1-X: In Shelter 1-X	6
	Other Continuous and Binary Variables	
$Complier_j$	Indicator for whether the agent will comply with the testing referral	
$Refuser_j$	Indicator for whether the agent refuses to participate in shelter programs	
$DLTBI_j$	Days since infection with LTBI	0-90
DRx_j	Days of LTBI Treatment Completed	1-∞
LS_j	Indicator for participation in long-duration shelter stay program	
Age_j	Age of Person j	
$Cost_j$	TB-Related Costs Accrued by person j	

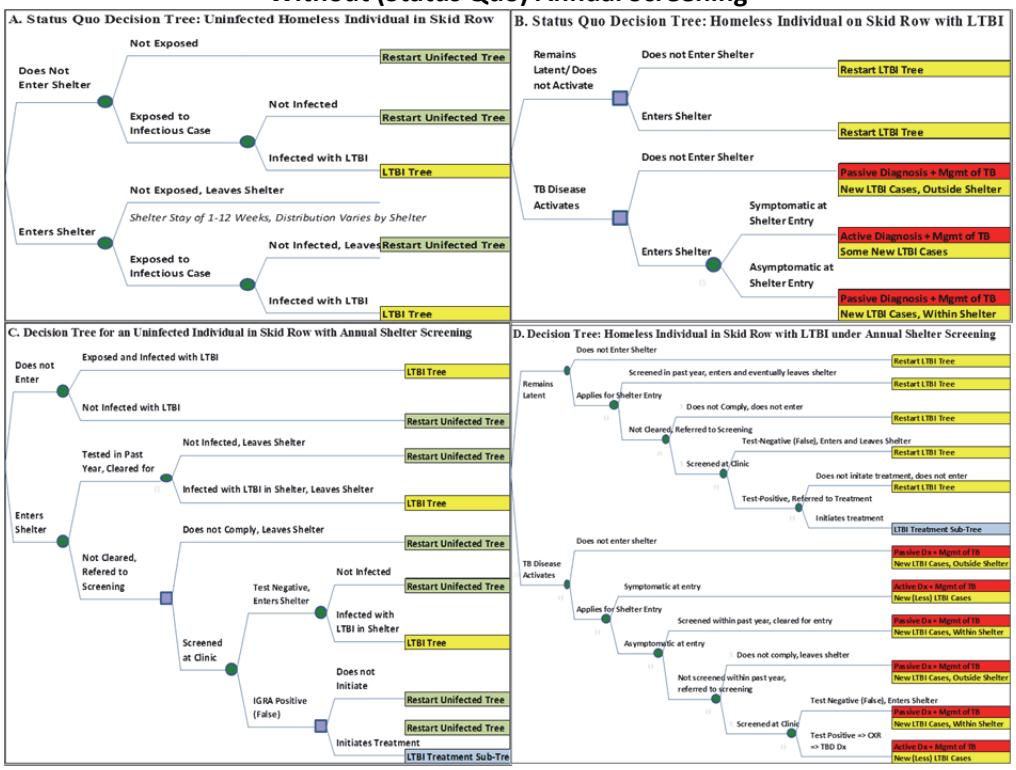
[Y] Mean values. The infectious period and hospitalization days are exponentially distributed.

TB: Tuberculosis Disease; LTBI: Latent Tuberculosis Infection

Table A.2: Possible Transitions between States

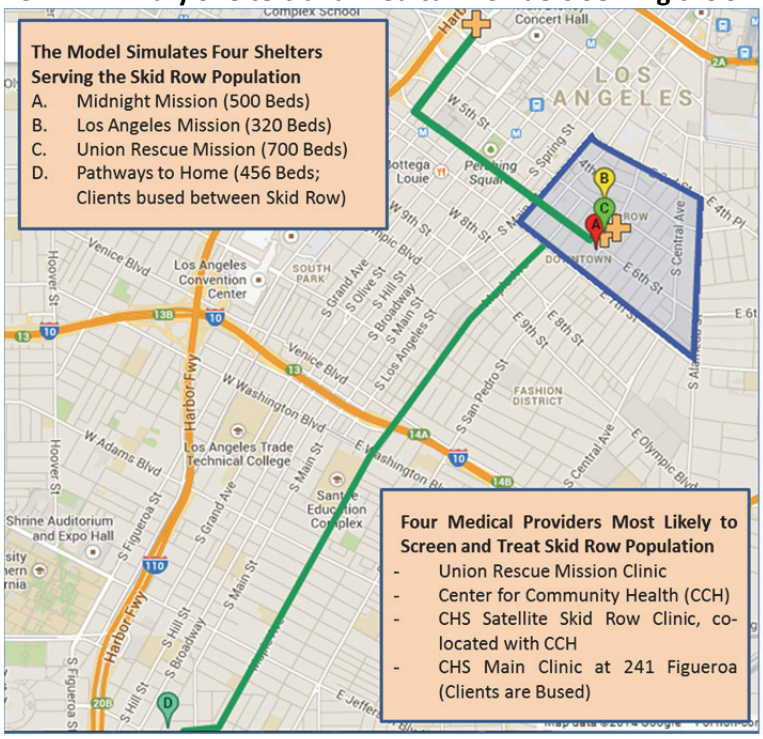
Variable	State 1	State 2	Transition Interpretation
T_j	**0**	1	Acquire LTBI Infection; become "Recently Infected"
	1	2	LTBI Status changes" to "Previously Acquired/Slow Progressing"
	1,2	5,6	TB Activation
	1,2	3	5 Weeks of Treatment Completed, Activation Risk Reduced
	1,2	4	12 Weeks of Treatment Completed, Activation Risk Reduced
	3,4	1	Re-infection with LTBI After Partial or Complete Treatment
	5,6	7	Diagnosed with TB at Hospital, Rendered Non-Infectious, Treated
	7	8	Leave Hospital for TB Housing for Homeless
	8	0	Complete TB Treatment, Cured
	5,6	9	Die from TB Before Diagnosis
	7,8	9	Die from TB During Treatment
E_j	0,1,2	3	Tested for LTBI and test-negative, cleared
	0,1,2	4	Tested for LTBI and test-positive, initiate treatment, cleared
	0,1	2	Tested for LTBI and test-positive, fail to initiate treatment, not cleared
	4	2	Quit LTBI treatment, lose clearance
R_j	**0**	1	LTBI treatment initiation
	1	0	LTBI treatment discontinuation
	1	2	Severe Adverse Reaction to LTBI Treatment Requiring Hospitalization
S_j	0-5	0-5	Transition between the five shelters and the street

Figure A.1: Decision Trees for Infected and Uninfected Homeless Individuals in Skid Row With and Without (Status Quo) Annual Screening



These shelters, and the medical clinics that serve their populations, are illustrated on the map presented in Figure A.2.

Figure A.2: Primary Shelters and Medical Providers Serving the Skid Row Population



NOTE: The first cases associated with the large homeless outbreak were reported from the Pathways to Home/New Image shelter, located south of Skid Row, near Compton CA. This led public health officials to initially identify Compton as the locus of the outbreak Later, it was discover that these clients were being bused daily to and from Skid Row

Priorities for Targeted Testing for Latent Tuberculosis Infection among Foreign-Born Adults in the United States

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Abstract

Setting: Over half of all TB cases in the United States are attributable to reactivation of previously acquired latent TB infection (LTBI) among the foreign born. Recent studies have found that testing and treating all foreign born persons (the "universal approach") would be cost effective. However, with limited treatment resources and an estimated 7.5 million foreign born persons living with LTBI this approach may not be feasible.

Objectives: To identify subpopulations among the foreign-born that should be prioritized for targeted LTBI testing and treatment.

Methods: The prevalence of LTBI overall and by risk group is estimated using the results from the interferon-γ release assay (IGRA) examination on the 2011-2012 National Health and Nutrition Examination Survey (NHANES). The annual risk of progression to TB disease overall and by age and medical risk factor group is estimated with meta-analyses and an analysis of the exposure-adjusted relative risk of disease during 2011-2013 from CDC surveillance reporting. Population prevalence of each FB risk group is estimated with NHANES, the American Community Survey and other surveillance datasets. Discounted cases averted and quality adjusted life years (QALYs) gained by targeting each foreign-born subpopulation are derived from the aggregate risk of TB, life tables and parameter estimates from the published literature.

Results: With base case model parameters, testing and treating the average foreign born person costs $58,000 per QALY gained. Targeted testing is cost saving for foreign-born persons in the following categories: HIV-infected, end-stage renal disease, transplant recipients, immunosuppressive therapy, hematologic cancer, low bodyweight, and injection drug use. Targeted testing is more cost-effective than the universal approach for foreign-born persons with solid organ cancer, current tobacco use, and alcohol abuse, as well as those from countries with extremely elevated TB prevalence (e.g., Ethiopia, Haiti). Targeted testing is less cost-effective than the universal approach for foreign-born persons with diabetes mellitus and those over 55 years old.

Conclusions: Targeting foreign-born risk groups can dramatically improve the impact of LTBI testing and treating in the United States. Forty-five percent of all potential QALYs gained from testing the foreign born can be captured by targeting 10% of the foreign-born population.

1 Introduction

1.1 Background/Context

In 2013, 65% of all cases of TB disease in the United States were among foreign-born (FB) persons [37]. Among them, approximately 84% were likely due to reactivation of previously acquired latent TB infection (LTBI) [101]. Detecting and treating LTBI in FB populations has thus become a centerpiece of TB control policy in the United States.

A recent analysis found that testing and treatment for LTBI among all FB persons would be cost-effective at an incremental cost effectiveness ratio (ICER) of less than $100,000 per quality adjusted life-year (QALY) saved [56]. However, with more than 41 million foreign born in the United States, this approach may not be feasible given limited resources and competing priorities within public health departments and other healthcare settings [102]. Prior guidelines recommended testing and treating all FB within the first 5 years after U.S. entry, based upon the assumption that the elevated case rates of TB disease noted among recently arrived persons is due to greater rates of reactivation, which decline over time [3, 103, 104]. However, recent studies have questioned this assumption, finding that elevated case rates may instead be due to increased rate of prevalent TB disease at U.S. entry and that, among the previously infected, the risk of progression does not significantly decline over time [105, 43].

Other than foreign birth and time since entry, there are several other potential factors which could be used to prioritize testing and treatment for FB persons living in the United States, including the person's age and the presence of a medical risk factor for progression to TB disease. The risk of progression to TB disease has been reported to be associated with several risk factors, including HIV infection, diabetes mellitus, chronic renal failure, leukemia, lymphoma, immunosuppressive therapy, smoking, abusing alcohol, and other factors identified in Table 8 [90]. However, the cost-effectiveness of utilizing these risk factors to prioritize FB persons for targeted testing and treatment has not been previously studied.

Using the 2011-2012 National Health and Nutrition Examination Survey (NHANES), CDC TB surveillance data, and published estimates of relative risk of TB progression, this analysis will propose an overall model of TB risk to help local policymakers prioritize FB subpopulations for LTBI testing and treatment. LTBI treatment capacity is the rate-limiting step with respect to resources and capacity for LTBI testing and treating within health jurisdictions. As a result, we hypothesize that it is more effective to prioritize groups facing an elevated risks of progression to TB (minimizing the *number needed to treat* to avert a case) rather than groups facing an elevated risk of infection (minimizing the *number needed to test* to treat a case).

1.2 Policy Relevance and Decision Context

Several state and local jurisdictions are actively pursuing strategies to increase the efficiency and cost-effectiveness of targeted LTBI testing and treatment. This analysis will help to shape the design

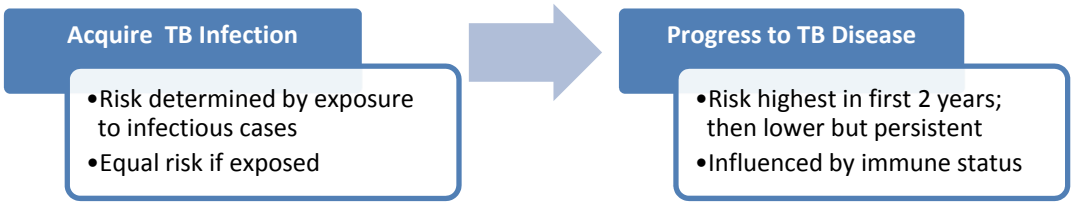
and/or re-design of guidelines issued by state and local governments to guide primary care providers in selecting patients for LTBI testing. California, for example, is currently seeking expert input into the design of a practical tool for providers to identify high-risk groups.

Patients infected with LTBI are typically infected for a lifetime. As a consequence, although the prevalence of infection can be high among certain risk groups the incidence of new infections on an annual basis is low. The analysis therefore informs whether to conduct a one-off test of a patient belonging to priority risk groups, rather than annual or periodic testing.

1.3 Overview of Methods

Overall risk for TB disease depends on the risk of infection with LTBI and the probability that LTBI will progress to TB disease (see Figure 1). While infection risk is assumed to primarily depend on exposure to infectious cases, the risk of progression is influenced by immune status [6, 7].[38] Once an individual acquires LTBI, they are typically infected for a lifetime. An individual's lifetime risk of TB disease is therefore the product of social and demographic factors that predispose them to infection (foreign birth, age, race, and poverty), life expectancy, and the presence of medical risk factors that compromise the host's immune function, the primary defense against the activation of disease.

Figure 1: Conceptual Model for the Overall Risk of TB



The study synthesizes these risk components to compare the lifetime risk of TB and associated benefits to testing and treating by FB age and risk factor subgroups. Candidate risk factors for progression included HIV infection, end-stage renal disease, smoking, diabetes, immunosuppressive therapy, alcohol and injection drug use, low bodyweight, and select malignancies. Potential LTBI risk factors among the FB included age, race, country of origin, smoking, and proxies for socioeconomic status (e.g., diabetes).

For each risk group, we compare total cases averted, quality-adjusted life years (QALYs) gained, and the incremental cost effectiveness ratio (ICER) of targeted testing and treating to those associated with testing and treating an average FB person. The analysis took part in the following steps. Methods for each study component are described in the corresponding section:

[38] This assumption deviates from the 2004 review of progression rates by Horsburgh et al, which assumed that immunosuppressive conditions including insulin-dependent diabetes, chronic renal failure and immunosuppressive therapy increase the risk of infection and disease by a similar degree. Horsburgh assumed that the risk of progression was equal to the square root of the risk of disease for these groups.

- LTBI prevalence overall and by foreign birth is estimated using the results of the interferon-γ release assay (IGRA) test on the 2011-2012 NHANES survey among persons aged 15 and above.
- The relative risk for TB infection on NHANES by FB socioeconomic risk group is identified with multivariate logistic regression.
- The relative risk for previously acquired TB infection by country of origin is estimated with CDC surveillance data during 2011-2013, population prevalence by country of origin, and literature estimates of the percent of FB cases due to reactivation.
- The annual, overall risk of progression to TB disease among those with latent infection is estimated with a meta-analysis and an original estimate synthesizing CDC reported rates of reactivated disease during 2011-2013 with LTBI prevalence estimated from NHANES.
- Relative risks for progression to TB disease were derived from meta-analyses and an analysis of the exposure-adjusted relative risk of disease based on CDC reported cases during 2011-2013.
- Estimate the population prevalence of each FB risk group using NHANES and other surveillance datasets (e.g., U.S. Renal Data System).
- Project the total discounted cases averted and associated health and economic outcomes by FB subgroup from a one-time testing and treatment initiative by combining our estimate of the lifetime risk of TB with life expectancy data and parameter estimates from the published literature.
- Propose a final prioritization tool incorporating risk, population size and testing and treatment capacity.

The analysis considers all future discounted costs and health outcomes associated with testing and treating FB subpopulations in the present time period. Costs are expressed in 2014 U.S. dollars and all future costs and health outcomes were discounted at a 3% rate [17]. The study addresses the FB population aged 15 and older. We exclude children because there are already clear guidelines in place for testing and treating children for LTBI and because the progression rate is very high in young children which could bias our overall estimates.

LTBI treatment capacity is the rate limiting step with respect to resources and capacity for testing and treating LTBI within health jurisdictions. We therefore assume that capacity for LTBI testing and treatment is wholly determined by the jurisdiction's capacity for treatment and that jurisdictions can always test the requisite number needed to treat those for whom they have capacity.

2 LTBI Prevalence and Risk Factors

2.1 LTBI Prevalence by Select Characteristic: Univariate Analysis

We calculated the prevalence of LTBI based on the 5,628 participants aged 15 or older in the 2011-2012 National Health and Nutrition Examination Survey (NHANES) with positive or negative results

from the QuantiFERON®-TB Gold In-Tube test (QFT-GIT) [106]. QFT-GIT is one of the recently developed interferon-γ release assay (IGRA) tests for LTBI, which measure the immune response to TB proteins in a serum sample. Among FB persons, IGRA tests are more specific than the traditional TST (0.99 versus 0.92) because BCG vaccination, common among FB persons, may trigger a false positive TST reaction [90]. The last NHANES survey wave to include an LTBI test, NHANES 1999-2000, measured LTBI rates with TST examination. All Medical Examination Survey (MEC) examination participants aged 6 and older were eligible for the IGRA test.[39]

LTBI prevalence was estimated according to the methods described in the NHANES Analytic Guidelines for the 2011-2012 survey wave [107]. Data management and analysis were conducted in SAS 9.3 (SAS Institute, Cary, NC). LTBI prevalence estimates for the overall U.S. population and for subgroups were adjusted using the NHANES 2011-2012 MEC 2-year sampling weights to account for unequal probability of selection due to complex survey design, including oversampling, and for nonresponse to the medical examination center (MEC) component of the survey. Following methods described by Bennett and colleagues, we constructed an additional weight adjustment to account for nonparticipation in the IGRA test [108].

For the 2011-2012 NHANES survey wave, 13,431 individuals were selected. Among them, 9,756 completed the interview portion and 9,338 participated in the medical examination. Using the MEC 2-year sample weights, these 9,338 persons represent a total U.S. civilian non-institutionalized population of 306,590,681 based on population totals provided by the 2011 American Community survey [107].[40] Participants aged 0-5 were ineligible for the IGRA examination and persons age 6-14 were excluded from this analysis.[41] The residual 6,059 MEC participants represent a target population of 244,540,589 persons aged 15 and older. IGRA results were available for 5,628 of these respondents, representing a population of 230,994,360 prior to the weight adjustment for IGRA nonparticipation.

Previous studies have shown that LTBI risk factors such as age and place of birth can be predictors of non-participation LTBI testing. We therefore constructed a subsequent adjustment to the 2-year MEC weights to control for bias from nonparticipation in the IGRA test subsample. Our treatment of observations with missing variables is discussed in Appendix A.

A logistic regression reweighting approach was used to identify and adjust for predictors of nonparticipation in the IGRA examination [108, 109]. We constructed a logistic regression to predict the probability of participation based on demographic factors and socioeconomic indicators.

[39] In addition to the health an nutrition questionnaire, a large subset of NHANES respondents take part in several physical tests and measurements at a Mobile Examination Center (MEC), a mobile clinic comprised of five trailers that travel to randomly selected parts of the country. The IGRA test is conducted within the MEC.

[40] NHANES used the 2011 U.S. civilian noninstitutionalized population as the target population for weighting the sample and projecting IGRA positive weights. This population (306,590,681) is a subset of the population denominator used to calculate TB rates in the CDC's surveillance reporting on TB in the United States (319,743,925), which was based on the resident population for the United States and Puerto Rico as of July 2013 based on the 2010 U.S. census [263, 37]. We therefore applied the derived LTBI prevalence rates to the CDC population denominators to derive total case load parameters.

[41] Although we excluded ages 6-14 from the overall estimates of LTBI prevalence, we considered the full sample in some of our meta analyses that required synthesizing results from this and other studies without an age restriction.

Race and age were found to be significant predictors of nonparticipation. Weight adjustment factors, equivalent to the *inverse of the respondent's predicted IGRA participation probabilit*y, were calculated for each sampling unit and applied to the original MEC 2-year weights [109]. Using the adjusted 2 year MEC weights the 5,238 IGRA participants represent the target population of 244,540,589. Detailed discussions of our reweighting method and our treatment of missing data are included at Appendix A.

Variances for the weighted binomial proportions were estimated using the Taylor Series linearization method using the 2-year MEC weights and masked variance pseudo-stratum and pseudo- primary sampling unit (PSU) variables. Although we were are only concerned with the subpopulation over age 6, our variance and error estimates accounted for the full structure of the complex sample by specifying that observations missing from the IGRA sample subpopulation were not completely missing at random (NOMCAR). Confidence intervals were calculated using Wilson's method [110]. Formulas used to compute variance, standard errors and confidence intervals for our weighted estimates can be found at Appendix A.

Our estimates of IGRA-positive prevalence overall and among the foreign born are displayed in Table 1. Our analysis estimates that 5.7% (95% CI, 4.9 to 6.7) of the U.S. civilian non-institutionalized population aged 15 and older was infected with TB during 2011-2012, as measured by the IGRA test. Prevalence was 16.7% (95% CI, 14.1 to 19.6) among the foreign born and 3% (95% CI, 2.2 to 4%) among the US born population. Assuming that the IGRA test is 99% specific and 83% sensitive, this corresponds to an estimated LTBI prevalence of 4.8% overall and 18.2% among the foreign born. LTBI prevalence was derived from our estimates of IGRA positive prevalence using Equation 1:

$$LTBI_Prev = \frac{(IGRA_Pos_Prev + Specificity - 1)}{(Sensitivity + Specificity - 1)} \qquad \text{Equation 1}$$

The last published study assessing LTBI prevalence rates in the United States found a TST positive prevalence of 4.2% overall and 18.7% among FB persons aged on NHANES 1999-2000 [108]. Adjusting for TST specificity and sensitivity and excluding those aged 6-14, the estimated prevalence of LTBI among those aged 15 and older was 3.3% overall and 13.8% among the foreign born during 1999-2000 [108].[42]

Our analysis therefore suggests that the prevalence of LTBI grew overall and among FB persons between 1999 and 2010.

[42] Assuming that the TST is 89% sensitive and 98% and 92% specific for the overall and foreign born, respectively [56].

Table 1: Estimated LTBI Prevalence among the U.S. Civilian Non-Institutionalized Population Aged 15 and Older Stratified by Nativity from NHANES 2011-2012

	Overall Population			Foreign Born Population		
Characteristic	**IGRA Pos. Prevalence (95% CI)**	**LTBI Prevalence (95% CI)[d]**	**IGRA Sample Size**	**IGRA Pos. Prevalence (95% CI)**	**LTBI Prevalence (95% CI)**	**IGRA Sample Size**
Overall U.S. Population	5.7 (4.9-6.7)	5.8 (4.7-7)	5628	16.7 (14.1-19.6)	19.1 (16-22.7)	1651
US Born	3.4 (2.5-4.6)	2.9 (1.9-4.4)	3974			
Female	4.9 (3.9-6.1)	4.7 (3.6-6.2)	2846	15.1 (12.3-18.4)	17.2 (13.7-21.2)	819
Male	6.6 (5.6-7.9)	6.9 (5.6-8.4)	2782	18.3 (15.3-21.7)	21.1 (17.5-25.3)	832
Age 15 to 24	2.7 (1.9-4)	2.1 (1-3.6)	1154	7.5 (3.7-14.7)	7.9 (3.3-16.6)	228
Age 25 to 44	4.3 (3.4-5.3)	4 (2.9-5.3)	1695	11.5 (8.9-14.9)	12.9 (9.6-16.9)	580
Age 45 to 64	7.2 (5.3-9.7)	7.5 (5.2-10.6)	1706	23.3 (18-29.7)	27.2 (20.7-35)	588
Age 65 or Older	9 (7-11.4)	9.7 (7.4-12.6)	1073	32.1 (24-41.5)	37.9 (28-49.4)	255
Black	7.3 (5.7-9.4)	7.7 (5.7-10.2)	1483	22.9 (16.1-31.4)	26.7 (18.5-37.1)	147
Hispanic	11.7 (9.8-14)	13 (10.7-15.8)	1178	15.9 (12.8-19.7)	18.2 (14.4-22.8)	755
Asian or Other Race	13.4 (11.2-16.1)	15.1 (12.4-18.4)	960	21.7 (18.7-25)	25.2 (21.6-29.3)	659
White	3.2 (2.3-4.3)	2.6 (1.6-4.1)	2007	8.3 (4.1-16)	8.9 (3.8-18.3)	90
Below the Poverty Threshold	7.9 (6.4-9.8)	8.4 (6.5-10.7)	1350	16.7 (12-22.8)	19.2 (13.4-26.5)	427
Above the Poverty Threshold	5.1 (4.1-6.2)	5 (3.8-6.3)	3815	16 (13.4-18.9)	18.2 (15.2-21.8)	1022
Close Contact to Infectious Case	16.6 (11.7-23)	19 (13-26.8)	185	29.6 (14.3-51.5)	34.9 (16.2-61.6)	57
HIV Positive±	6.8 (1.4-27.4)	7 (0.5-32.2)	18			2
Diabetes Mellitus, Diagnosed	10.9 (7.9-14.8)	12 (8.4-16.9)	630	27.4 (18.3-38.8)	32.1 (21.1-46.1)	188
End Stage Renal Disease±	5.5 (1-24.9) ±	5.5 (0-29.2)	19	53.8 (10.8-91.8)±	64.4 (11.9-110.7)	2
Immunosuppressive or Prolonged Corticosteroids* [ɣ]	6 (1.7-18.8)	6 (0.9-21.8)	67	16.6 (3.7-50.9)	19 (3.3-60.9)	11
Cancer, Ever: Hematological or Solid Organ	12.8 (6.9-22.6)	14.4 (7.2-26.4)	116			5
Underweight	5.5 (2.7-10.9)	5.5 (2.1-12)	159	11.9 (5.2-24.8)	13.3 (5.1-29)	43
Current Smoker: Daily	6.5 (4.3-9.8)	6.7 (4-10.7)	815	17 (10.5-26.2)	19.5 (11.6-30.8)	134
Current Smoker: >= Some Days	6.8 (4.7-9.6)	7 (4.5-10.5)	989	16.2 (10.4-24.3)	18.5 (11.4-28.4)	182
Alcohol Abuse, Ever	5.1 (3.6-7.2)	5 (3.2-7.5)	610	14.1 (8.8-22)	16 (9.5-25.6)	107
Alcohol Abuse, Current	3.8 (1.8-7.6)	3.4 (1-8.1)	270	22.4 (9.4-44.3)	26 (10.3-52.8)	34
Injection Drug Use, Ever±	4.7 (1.4-14.3) ±	4.5 (0.5-16.2)	70			1
Injection Drug Use, Current±	10.6 (2-41.1) ±	11.73 (1.2-48.93)	10			5

± Point estimates and confidence intervals are unstable due to small sample sizes associated with these risk groups. The relative risk of LTBI for these groups was assessed with a combined analysis of the 2011-2012 and 1999-2000 NHANES waves. Methods and results are presented in 0.

[ɣ] LTBI Prevalence estimate based on all prolonged (30+ days) corticosteroid users independent of dose because dosage data is not available. Population prevalence based on numbers provided in Appendix D. Includes the four categories of immunosuppressive therapy defined in Appendix D: long-term corticosteroids, post-SOT immunosuppression, TNF-alpha blockers, and 'other.'

[d] Calculated using the formula presented in Equation 1.

2.2 LTBI Risk Factors

An individual's overall risk for TB disease is a product of their risk of infection and their risk for progression to disease. Progression to disease is influenced by immune status. Infection, however, is assumed to primarily depend on exposure to infectious cases [6, 7]. The risk of LTBI can therefore be theoretically modeled as a function of environmental and social factors that predispose an individual to exposure. Risk factors for a positive IGRA result were examined using univariate and multivariate logistic regression. Separate analyses were performed for the overall U.S. population and for the US and FB subpopulations. Predictor variables included gender, age, race/ethnicity, poverty, foreign birth, diabetes and current cigarette smoking. In the multivariate (adjusted) analysis, separate regressions were conducted for each race/ethnicity category excluding the remaining race/ethnicity variables. In multivariate analysis of non-race/ethnicity variables, all variables were included except for white race. Because the policy context is to evaluate the efficacy of targeted testing and treatments over a random or universal approach, odds ratios (ORs) are expressed versus the general population and were converted using Equation B.12 in Appendix B.

Our LTBI risk factor model overall and among the foreign born is presented in Table 2. In the analysis of the overall U.S. population, age, family income, male sex, and all race/ethnicity categories are significant predictors of a positive IGRA test in weighted univariate and multivariate analysis. Whites are less likely to be infected; blacks, Hispanics and Asians are significantly more likely. When restricting the sample to the FB population, white race, Hispanic race, and family income are no longer significant in adjusted analysis. However, this model may under-estimate the influence of poverty among the foreign born because country of birth is omitted. As discussed in the following section, the demographics associated with relocating to the United States vary by country and countries with a high TB burden (e.g., India) may export relatively more affluent individuals.

Diagnosed Diabetes Mellitus (DM) is significantly predictive in univariate analysis overall (RR: 2.2, 95% CI 1.5-2.8) and among the foreign born (RR: 2, 95% CI 1.2-2.9). However, LTBI and Diabetes share many risk factors (poverty, age, race, etc.) As hypothesized, the significance of DM is removed when adjusting for poverty and race (its significance remains when adjusting for age, as discussed in Appendix A). This suggests that DM is more appropriately conceptualized as a proxy for LTBI risk factors. A detailed analysis of the relationship between DM, TB disease and LTBI can be found in Appendix A.

Table 2: Risk Factor for LTBI by Nativity among Persons Aged 15 and older on NHANES, 2011-2012 with Univariate and Multivariate Analysis*

	All United States		Foreign Born	
Characteristic	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**
Foreign Born	5.7 (3.7-8.6)	4.2 (2.9-6.1)		
Age, Per 10 Yr. Increase ±	1.3 (1.2-1.3)	1.4 (1.3-1.5)	1.4 (1.3-1.7)	1.5 (1.3-1.7)
Male Sex	1.4 (1.1-1.3)	1.2 (1.1-1.4)	1.2 (1.1-1.3)	1.2 (1.1-1.3)
Race/Ethnicity				
White	0.3 (0.2-0.7)	0.7 (0.6-0.8)	0.4 (0.2-0.9)	0.5 (0.2-1.1)
Black	1.4 (1-1.7)	2.1 (1.5-2.7)	1.3 (1-1.8)	2.5 (1-5.7)
Asian or Other Race	2.9 (2.2-3.1)	2 (1.4-2.8)	2 (1.7-2.2)	1.9 (1.1-2.8)
Hispanic	2.7 (1.9-2.7)	1.6 (1.1-2.2)	1.4 (1.3-1.5)	1.3 (0.9-1.6)
Below the Poverty Threshold	1.6 (1.2-1.8)	1.3 (1-1.7)	1.4 (1.2-1.6)	1.2 (0.8-1.5)
Diagnosed Diabetes Mellitus	2.2 (1.5-2.8)	1.3 (0.8-2)	1.9 (1.2-2.9)	1.3 (0.8-2)
Current Smoker, Daily	1.1 (0.7-1.6)	1.4 (0.9-1.9)	1 (0.6-1.5)	1.4 (0.9-2.1)

* The reference category for all characteristics except age is the general population. ORs were converted using Equation B.12 in Appendix B.

± The mean age on NHANES among IGRA test subjects was 44 from the general population and 42 from the FB population. With the ORs presented in this table, the predicted IGRA positive probability 5.4% for a 44 year old from the general population and 16.8% for a 42 year old from the FB population.

The indicator for whether or not a respondent recalled living with a person with active TB disease ("close contact") was excluded from the risk factor analysis for several reasons. First, it is a less policy relevant risk factor because close contacts are already prioritized for testing and treatment by local health departments and are typically deliberately targeted for testing during contact investigations surrounding infectious cases. As such, these patients would be assessed for testing in a primary care setting. Second, even if the contact was not previously targeted during a contact investigation, whether or not a patient was a close contact is a *less useful screen* because it is difficult to observe or assess in a clinical setting. Third, there is a small sample size of FB known close contacts (N=64) and a disproportionate number of FB respondents did not know whether they had lived with someone with TB[43]

2.3 Imputing the Relative Risk of LTBI by Country of Origin

Policymakers or practitioners may wish to prioritize FB persons for LTBI testing by country of origin. It can be inferred from the difference in LTBI prevalence among US born and FB persons (3.4% versus 16.7%) that an individual's risk of infection, and therefore of TB disease, is influenced by the country in which they were born.

Sixty three percent of TB cases among the foreign born reported to the CDC during 2011-2013 occurred in persons originating from one of eight countries: Mexico, the Philippines, India, Viet Nam, China, Guatemala, Haiti and Ethiopia [37]. Among these countries of origin, the case rate within the U.S. varies from 11 (Mexico) to 27 (India) to 92 (Ethiopia) per 100,000 (see Table 3)

[43] 1.4% of the FB sample reported not knowing whether they lived with someone with TB versus 0.3% among native born respondents. This is considerable given that only 2.8% reported living with someone with TB.

[102].[44] Recent studies have shown that variation in TB rates by nativity is attributable to higher prevalence of LTBI, rather than variation in the relative risk of progression [43, 105].

We imputed the rate of LTBI prevalence by country of origin by dividing the average annual number of presumably reactivated TB cases reported to the CDC during 2011-2013 by our estimate of the annual risk of progression to TB disease among the foreign born (see Table 4), with an adjustment for the population prevalence of HIV in the country of origin. The percent of cases due to reactivation by country of origin was taken from a cross-sectional study of genotyped FB TB patients from 2005-2009 [101].

Results are presented in Table 3. Relative to the overall foreign born population, our analysis suggests that the risk of infection is highest among persons born in Ethiopian (RR: 5.9), Philippines (RR: 2.5), Viet Nam (RR: 2.6), and India (RR: 2.0), and is slightly lower among persons born in Mexico (RR=0.7). We find a particularly high rate of LTBI among persons born in Ethiopia (~84%). However, this method does not account for differences in progression risk factor prevalence other than HIV (e.g., malnutrition) or in prevalent TB cases at arrival by country of origin. The cases from Ethiopia, for example, may be more likely to have been prevalent at arrival and therefore misclassified as reactivated due to the lack of genotypically related or clustered cases in the CDC surveillance dataset.

We were unable to control for race in this analysis due to data availability limitations. It is therefore difficult to combine these RRs with the LTBI RR found in our NHANES logistic regression risk factor analysis because country or origin is presumably confounding our estimated RRs by race/ethnicity. Moreover, country of origin is not included in the final risk assessment because it does not influence progression risk, or the number needed to treat among LTBI test positive patients to avert a case. We can, however, compare LTBI rates across countries with similar racial/ethnic composition to inform projections of the number needed to test (NNTest) to diagnose a case of LTBI among the foreign born.[45] Among Asian FB, NNTest will be lower among those from Viet Nam or the Philippines; among black FB, NNTest will be lower among those from Ethiopia; and among Hispanic FB, NNTest will be lower among those from Guatemala than among those from Mexico. Guatemala has over twice the rate as Mexico and India; Ethiopia three times the rate of Haiti; and Viet Nam and the Philippines have rates 2-3 times that of China.

We also compared the case rates among US-dwelling FB persons to TB case rates within the country of origin reported by the World Health Organization (WHO) (see Table 3). As other studies have shown, WHO reported case rates do not predict case rates by country reported by the CDC, which could be explained by WHO underreporting in several countries of origin [111, 112]. However, a plausible explanation is that there is significant variance by country of origin in the characteristics of

[44] Case rates were calculated by dividing the number of cases from the country of origin by the population of foreign born persons living in the United States born in the country.

[45] The number needed to test measure is more commonly referred to as the Number Needed to test (NNTest). However, "screening" in this context refers to the risk assessment whereby high priority groups are identified and recommended for testing.

persons that move to the United States relative to those that do not. There are only twice as many cases per person in Mexico as there are among Mexican-born persons living in the United States, suggesting that persons that re-locate are close to representative of the population at large. Likewise, the case rate in Ethiopia is only three times the case rate among the Ethiopian-born. India, by contrast, has 20 times as many cases per year as Indian-born persons living in the United States (537 versus 27 per 100,000 people), suggesting that the individuals that relocate to the United States are more immuno-competent and less likely to be exposed to infectious cases than their Indian-born counterparts that remain in India.

Table 3: Imputed LTBI Prevalence among the Foreign Born by top 8 County of Origin Contributing to US TB Cases

	All FB	Mexico	Guatemala	Philippines	India	Viet Nam	China	Haiti	Ethiopia	All Others	Source±
TB Cases Reported to CDC, 2011-2013	18,635	4,000	579	2,311	1,537	1,460	1,108	558	468	6,614	
U.S. Population (Thous.)	39,159	11,477	814	1,778	1,820	1,234	2,186	575	164	19,110	[102]
Percent Reactivated[δ] (%)	83%	82%	83%	76%	95%	87%	85%	85%	81%	82%	[37, 101]
Reactivated Cases, 2011-2013*	15,597	3,280	479	1,754	1,463	1,266	938	475	380	15,597	[37]
HIV Prevalence in Country, 2000-2014*	0.3%	0.2%	0.6%	0.1%	0.3%	0.4%	0.1%	2.1%	1.4%	0.3%	[113]
RR of Progression with HIV Adjustment*	1.00	0.98	1.04	0.96	1.00	1.01	0.96	1.28	1.16	1.00	
Persons with LTBI (Thous.)[ɣ]	19,619	4,206	577	2,287	1,846	1,572	1,223	468	411	7,745	
LTBI Prevalence, 2011-2013^	17%	12%	24%	43%	34%	42%	19%	27%	84%	14%	
LTBI Relative Risk (vs overall FB)	1 (Ref.)	0.7	1.4	2.6	2.0	2.5	1.1	1.6	5.0	0.8	
Avg Cases Per Year in US per 100,000	15	11	22	41	27	37	16	31	92		
Avg TB Cases/Year Per 100,000 in Country of Origin		27	114	299	537	250	116	325	289		[114]

[ɣ] Previously acquired LTBI. Imputed assuming a reactivation rate among the FB of 80 per 100,000 PYs based on the methods in Table 5. The reactivation rate for the FB is higher than our summary estimate for the general population (72 per 100,000) presented in subsequent sections (72 per 100,000).

[δ] Baseline rate reactivated from 2011-2013 per CDC 2014 report times 1 less the relative risk of percent clustered of origin from Ricks 2009

± Source for population prevalence. Case counts within the United States were taken from CDC surveillance reports, 2011-2013 [37, 115]. Case rates within the country of origin from WHO Tuberculosis report [114].

^May underestimate total prevalence because this estimated number of people with LTBI excludes those with recently acquired infection.

*Average prevalence in country of origin during 2000-2014 among persons aged 15 and older. Assuming HIV prevalence among the FB overall is equivalent to that among the United States general population, as demonstrated with NHANES data in 0. The RR of progression assumes 0.32% of the overall population is infected with HIV and that HIV is associated with an RR of progression of 17 (see Appendix C).

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3 TB Progression Rate Overall and by Age

The lifetime risk of progression to TB disease for a person with LTBI is typically estimated at 5-10 percent based on data from studies conducted prior to routine treatment of LTBI [3]. Estimates of the distribution of reactivation risk are varied, but the "rule of thumb" is that about half of an individual's lifetime risk of developing TB disease occurs within the first two years after infection [2]. The risk is highest in the first year, at 1,290 cases per 100,000 person years [3]. After this "fast progressing" period, the rate of activation, or "reactivation" of previously acquired TB, drops to a low but persistent reactivation rate, with estimates from 30 to 100 cases per 100,000 person years for the general population [41, 42, 43]. Because cell mediated immunity is the host's principal defense against the progression of disease, the risk of reactivation varies considerably by medical risk factors impacting immune status.

With respect to progression risk, this study considered three sets of parameters. First, the baseline rate of progression for a person living in the United States (foreign or native born). As discussed subsequently in this section, the baseline rate of progression for an FB person was assumed to be equal to the rate among the general population. Second, the relative risk (RR) of progression by age. Third, the RR of progression by medical risk factor, controlling for age. This section addresses our estimation of the rate of progression overall and by age.

The overall rate of progression to TB disease was estimated with a meta-analysis that synthesized the results of two studies from the published literature and our original estimate of the progression rate analysis of CDC surveillance data on reported TB cases in the United States during 2011-2013 [37].

3.1 Original Estimate of the Progression Rate Using CDC and NHANES

We derived the rate of progression to TB disease by combining our estimate of LTBI prevalence from NHANES with an analysis of active TB cases reported to the CDC during 2011-2013 [37, 115, 116]. The rate of progression to TB disease (*PR*) per person-year (PY) among individuals with a positive IGRA test (PR|IGRAPos) was calculated with Equation 2, where *TotalTBCases* is the average annual case count during 2011-2013, *TBCaseRate* is a the number of cases per person year within the population, and *%Reactivated* is the proportion of these cases attributable to reactivation of latent disease.

$$\mathrm{PR|\ IGRAPos} = \frac{ReactivatedTBCases}{IGRAPositivePop} = \frac{TotalTBCases * \%Reactivated}{Population * IGRAPosPrev} = \frac{TBCaseRate * \%Reactivated}{IGRAPosPrev} \qquad \text{Equation 2}$$

We estimate that the *%Reactivated* parameter using 2011-2013 CDC data on the proportion of cases that genotypically inked or "clustered" [37]. A cluster is defined as two or more cases with matching genotypes in the same county during a 3-year time period [37]. Non-clustered or "unique" cases are more likely attributable to reactivation of previously acquired TB infection. Following

methods described in Horsburgh et al, we use the "n-1" method wherein the percent of cases due to reactivation is presumed to equal to the total number of genotypically unique (non-clustered) cases plus the total number of *clustered index cases* divided by the total case count [36]. The cluster index case is the first chronological case in a cluster, which can be assumed to be a case of reactivated disease. We assume that the total number of index cases is equal to the total number of clusters. The CDC estimates that there were 17,077 unique cases and 4,625 clustered cases occurring in 1,532 clusters during 2011-2013 [37]. We therefore estimate that 85.7% of cases during this period were attributable to reactivation.

Because the policy context is to inform decisions governing whether to treat if test positive, and because only test outcomes are observed, we express progression rates in terms of test status rather than true infection status. However, if policymakers or other end-users of our analysis wish to modify this analysis under different LTBI tests or different sensitivity and specificity assumptions, they may do so using the conversion formula provided in Equation 1.

3.2 Progression Rate Error Estimation

Methods for characterizing the error of estimates of the progression rates derived from numerators (observed reactivated TB cases) and denominators (estimated population with LTBI) taken from different populations are not well documented in the published literature. In these "non-cohort dual-population" studies, the estimated progression rate is a *binominal proportion (TB rate over LTBI Positive) of a binomial proportion sample mean*, since the prevalence of LTBI is always estimated from a sample with error. Recent studies of this nature (Horsburgh 2010, Shea 2014) have published variance estimates treating the rate as a simple proportion wherein the denominator is observed. As a consequence, they have substantially under-estimated the sample variance and therefore the range of plausible progression rates because they have failed to account for the standard error of the LTBI prevalence estimate used to calculate the rate. For example, Horsburgh 2010 only analyzed 135 persons with LTBI (out of a sample of 447) but the denominator used for the error calculation was 38,207, the projected population with LTBI (based on the sample of 447) times 5, the number of years that numerator (TB case) data were collected [79]. Shea 2014 reports a very narrow 95% confidence interval of 83 to 85 per 100,000 person-years, using a denominator of 37,999,080 person-years of observation when only 310 people were TST positive out of a sample of 7,386.

Progression rate estimates associated with non-cohort, dual population studies do not follow a binomial proportion sampling distribution because the denominator is not part of the sample in which the numerator is observed. Because it is directly observed, the numerator (TB cases per person-year) is a constant rather than an estimator. Nearly all of the variance in the progression rate estimate arises from the denominator (persons with LTBI).[46] We therefore estimate the

[46] There is also error in the estimated percent of cases due to reactivation of previously acquired TB. However, confidence intervals for these estimates were not reported by the CDC. The confidence interval around our summary estimate may therefore underestimate true variance.

progression rate confidence interval around the upper and lower confidence limits of the LTBI estimate, with the LTBI upper limit corresponding to a progression rate lower limit and vice versa. In our meta-analysis we recomputed confidence intervals from prior studies accordingly. The methods are described in detail in Appendix B.

3.3 Meta-Analysis of the Overall Progression Rate

The overall progression rate was estimated with a meta-analysis that synthesized our original analysis with estimates identified from systematically reviewing the literature on TB progression rates. A literature search using PubMed for studies published in English from 1990 to 2014 was conducted and supplemented with a review of secondary references cited by the selected studies. Search terms used to collect estimates of the overall or baseline rate included: "tuberculosis" OR "TB infection" OR "LTBI" OR "latent tuberculosis infection" AND "progression" OR "reactivation" OR "activation." Studies that did not include an LTBI-test positive control group were excluded.

The summary estimate for the overall progression rate was derived with meta-analysis synthesizing the results of two types of studies. First, prospective *cohort studies* constructed from data from the placebo arm of randomized controlled trials on LTBI treatments (e.g., Ferebee 1963) or vaccinations (Comstock 1974). These studies observed a cohort of LTBI test positive persons over time and derived the progression rate by dividing the number of TB cases arising within the cohort by the LTBI positive person-years observed. For ethical reasons, studies with a placebo arm have not been conducted in the years since LTBI treatment was introduced. The second, broad category of studies included in the meta-analysis was *non-cohort dual-population* studies which impute the progression rate by dividing the number of presumably reactivated TB cases reported to the CDC by the projected total number of persons with LTBI in the population based on a representative sample. Because the LTBI positive cohort cannot be directly observed over time, these studies use a different data source for the numerator (TB surveillance) and denominator (survey-based estimates, typically NHANES) complicating variance estimation and the assignment of study weights in the context of meta-analysis (see section 3.2).

For cohort studies, the progression rate confidence interval (CI) is determined with Wilson's method, a variation on the normal approximation interval method for a proportion (see Equation A.5 in Appendix A). The width of the CI is therefore primarily determined by the size of the LTBI positive cohort. For non-cohort dual-population studies, by contrast, the progression rate CI is determined by the upper and lower bounds of the LTBI prevalence estimate, since the cohort of LTBI positive persons is not directly observed (see Equation B.6 in Appendix B). Since higher prevalence estimates correspond to lower progression rates, the width progression rate CI for non-cohort studies is primarily driven by the LTBI prevalence estimate, which does not reflect true variance associated with the PR estimate. A novel weight-adjustment method was developed and applied to the non-cohort studies to avoid penalizing studies with smaller prevalence estimates and to facilitate appropriate weight assignment.

The summary reactivation rate point estimate was equal to the weighted average of the five study estimates using a fixed-effects model with adjusted individual study weights. Adjusted weights were equal to the inverse *adjusted* variance of the progression rate estimate [117]. For non-cohort studies, the adjusted variance was determined by calculating and adjusted standard error based on the variance associated with the progression rate estimate if all non-cohort studies used a standardized case rate and LTBI prevalence point estimate. This method was adopted to avoid penalizing studies with relatively smaller LTBI prevalence point estimates or larger case rates. There was no adjustment applied to cohort studies. The variance of the progression rate summary estimate was equal to the inverse of the sum of the unadjusted individual study weights.[47] A detailed discussion of our meta-analysis weighting, error estimation and adjustment methods is provided in Appendix B (Adjusted Fixed-Effects Model for Estimates of the Overall Progression Rate).

Five studies, including our original estimate, were included in our meta-analysis of the overall TB progression rate, including two prospective cohort and three non-cohort, dual population studies. Table 4 illustrates our synthesis methods and summarizes the key characteristics and parameters of each examined study. Progression rate estimates are influenced by several assumptions and methodological choices: design, data source and test used to measure LTBI prevalence (progression rate denominator), data source for TB cases (progression rate numerator), and the method for determining the portion of cases attributed to reactivation.

Our meta-analysis suggests that, among LTBI test positive persons, an average of 72 (95% CI, 67-77) cases of TB active per 100,000 person years (PYs). Assigning an equal weight of evidence to each study would yield a progression rate of 77 cases per 100,000 PYs. Results are shown in Table 4 and illustrated in the forest plot in Figure 2. Forest plots were constructed with modified version of a template developed by Neyeloff and colleagues [118].

[47] As described in 0, the unadjusted study weights were used when estimating the variance of the summary estimate because the sum of the unadjusted weights reflect true variability even if individual weights do not reflect relative precision.

Table 4: Estimates of the TB Progression Rate Among persons aged 15 and older within in the United States with Study Characteristics Input Parameters

Study	Original Estimate	Shea 2014 [38][A]	Horsburgh 2010 [79][B]	Comstock 1974 [119][D]	Ferebee 1963 [120][E]
Design	Non-Cohort	Non-Cohort	Non-Cohort	Prospective Cohort	Prospective Cohort
Data Source: TB Cases (Num.)	CDC 2011-2013 [37, 115, 116]	CDC 2006-2008	Palm Beach TB Surveillance, 97-02	Puerto Rican Children, 1949-1972	Mental Health Patients, 1957-69
Data Source: LTBI (Den.)	NHANES 11-12	NHANES 99-00	TST Survey in Palm Beach, 99-00		
Subset Considered	Age 15+	Age 15+	N-1 Method	TST reactors age 13-18, excl. Years of Ob 0-4	Excl. subjects w/ prior TB & Years of Ob 0-1
LTBI Test & Induration	IGRA	TST, >9mm	TST, > 10mm	TST, >10mm	TST, >10mm
Years of Observation (TB Cases)	3	3	5	13.87	9
LTBI Test+	528	371	135	42,494	4,221
LTBI Test Sample Size	5,628	5,018	447		
LTBI Test+ Prevalence (95% CI) [¥]	5.7% (4.9 - 6.7)	4.9% (3.9 – 6.1)	24.5% (20.5 - 28.5)	N/A: Only LTBI+ Enrolled in Cohort Studies	
True LTBI Prevalence (95% CI) [¥]	5.8% (4.7-7)	3.3% (2.2-4.7)	25.9% (21.3-30.4)		
TB Cases Analyzed	28,481	37,543	72	393	30
TB Case Rate Per 100,000	4.37	5.24	41.43	N/A - Cohort Study	
% TB Cases Reactivated	86%	81%	53%	N/A: Progression was observed/100%	
Progression Rate Per 100,000 PYs	65	84	90	67	79.0
Progression Rate 95% CI [¥]	56-77	71-105	77-108	60 - 74	59 - 113
Adjusted S.E. of Prog. Rate Est.±	3.5	4.1	23.9	3.2	10.1
Adjusted Weight of Evidence±	0.082	0.058	0.002	0.098	0.010
Progression Rate if LTBI Test+, Summary Estimate (95% CI):		**72 (67-77)**			

[A] Rates for age 15+ from the Shea 2014 study were imputed. LTBI prevalence was 4.2% for all ages and was 1.1% for ages 1-14.Persons aged 1-14 represent 21% of the population and 6% of total TB cases. .

[B] We are using results from Horsburgh derived from the N-1 method, which attributes the first case in a cluster to reactivated, previously acquired infection. Because Horsburgh published results associated with the "N" method, some figures were imputed.

[D] Reported reactivation rates from Comstock are exclude non-reactors. 39,775 subjects aged 1-12, and all cases presenting within the first 5 years of observation. The full study included 82,269 TST reactors observed for an average of 18.87 years.

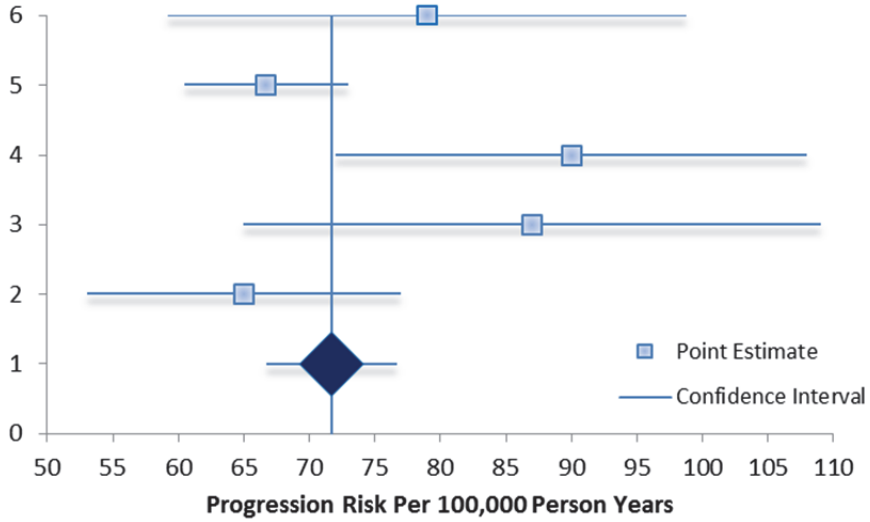
[E] Reported reactivation rates from Ferebee are from the placebo group in years 2-10 following treatment. We exclude subjects with evidence of prior TB and with TST indurations less than 10mm. The total LTBI+ cohort size was 5,674 with 53 cases of TB observed. Figures were imputed for the cross-section of subjects with an induration greater than 10mm without evidence of prior TB.

[H] The LTBI estimate sample size is the number of persons with known positive or negative LTBI test results.

[¥] Confidence intervals were derived with Wilson's method. Confidence intervals for the progression rate estimate were recalculated based on the methods described in this section.

± Per the weighting and adjustment methods described in 0, which includes a description of the met analysis methods used to generate a summary estimate of the progression rate.

Figure 2: Forest Plot of Results of 6 Studies Examining the Overall TB Progression Rate per 100,000 Person Years



NOTE: 1=Summary estimate; 2=Original; 3=Shea, 4=Horsburgh, 5=Comstock, 6=Ferebee.

3.4 Progression among the Foreign Born

The overall rate of progression for an FB person was assumed to be equal to the overall rate for a person living in the United States, independent of birthplace. We made this assumption for three reasons. First, there is no known clinical rationale by which progression risk varies by birthplace other than the through confounding risk factor variables captured by our model. Second, a case control analysis of 188 patients with reactivated TB disease compared to age-matched LTBI control subjects showed that the occurrence of reactivated TB is not associated with foreign birth with controlling for the underlying risk of LTBI [105]. Third, the relative risk (RR) of progression associated with foreign birth varies greatly across the three non-cohort, dual-population studies examined in our meta-analysis.[48] As shown in Table 5, the RR of foreign birth is positive but not significant in any of the three studies. Moreover, the method used in our original analysis and in Shea does not exclude prevalent cases diagnosed within a year of arrival (approximate 949 out of the 6,193 FB cases in 2013, for example), which may inflate the estimated progression rate both because the cases do not contribute to reactivation within the United States and they may be inaccurately classified as non-clustered. Confidence intervals for the RRs were found using the formula for standard errors associated with the ratios of two independent estimators given in Equation B.9 in Appendix B.[49]

[48] The two cohort studies, Comstock 1974 and Ferebee 1963, do not address the foreign born population.
[49] We cannot compute the RR standard errors directly because the two progression rates used to compute the RR ratio are not observed with a single sample.

Table 5: Estimates of the Relative Risk of TB Progression Rate associate with Foreign Birth from Three Studies[¥]

Study	Original Estimate	Shea 2014	Horsburgh 2010
Subset Considered	FB Age 15+	FB Age 15+	FB, N-1 Method
Years of Observation (TB Cases)	3	3	5
LTBI Test+ / LTBI Sample Size	341 /1,651	220 / 1,230	67 / 137 ±
LTBI Prevalence (95% CI)	16.7% (14.1-19.6)	19.1% (14-25.6)	44.5% (36.2-52.9)
LTBI True Prevalence (95% CI)	19.1% (16-22.7)	22.1% (15.9-30)	53.1% (42.9-63.2)
TB Cases Analyzed	18,635	22,406	37
TB Case Rate Per 100,000	15.86	21.94	69.93
% TB Cases Reactivated	84%[ϕ]	87%	53%
Progression Rate Per 100,000 PYs (95% CI)	80 (68-94)	100 (76 – 136)	84 (70 – 90)
RR of Progression vs Baseline (95% CI)*	**1.22 (0.9-1.53)**	**1.15 (0.64-1.66)**	**0.93 (0.74-1.13)**

[¥] Same study characteristics as those annotated in Table 4.
± Data on foreign bon sample sizes were not published. These figures were estimated based on other published parameters.
* Relative risk standard errors were found using the formula for standard errors associated with the ratios of two estimators given in Equation B.9 in 0 using unadjusted S.E.s of the progression rate.
[ϕ] Estimated in a cross-sectional study of 2005-2009 CDC genotyping data [101].

3.5 Relative Risk of Progression by Age

We analyzed the relative risk of TB progression by age band (15-24, 25-44, 45-64, and 65 plus) by synthesizing the results from our original analysis with those from Shea 2014. Only these two studies assessed TB progression by equivalent age bands.[50] We derived summary RRs by comparing the weighted average progression rate associated from each age band to the weighted average baseline progression rate between the two studies (75, 95% CI 70-80). Confidence intervals for the summary RRs were estimated with the formula for the standard error of a ratio of two independent estimators given in Equation B.9 in Appendix B. Except where noted, our weighting methods followed those summarized above and detailed in Appendix B.

Our summary RR estimates from the two studies are shown in Table 6. Based on these studies alone, the risk of progression is significantly higher for persons aged 15-24 (RR: 1.19, 95% CI 1.09-1.29) and significantly lower for those aged 45-64 (RR: 0.7, 95% CI 0.62-0.77). However, these results do not control for medical risk factors associated with both age and the risk of progression. Moreover, four other studies shown in Table 6 examining the relative risk of progression according to different age bands have reached conflicting conclusions. A small cross sectional study by Horsburgh et al found a positive and significant association between progression and age ≥ 50, which contradicts our finding of lower progression rates for age 45-65. Age was not a significant predictor in the remaining three studies. Progressively older ages were negatively associated with progression in the two largest cohort studies (Sterling et al and Ferebee et al). Although these

[50] Horsburgh et al and Patel et al published RRs associated only with age 50+ and 45+, respective. Ferebee et al 1963 and Ferebee et al 1962 published progression rates for age 15-34, age 35-54 and age 55+. The Sterling trial published relative risk by age per 10-year increase.

results were not significant, the range and inconsistency of results suggest that there is insufficient evidence to support our earlier finding that progression varies by age.

Table 6: Relative Risk of TB Progression by Age Band

Progression Rates by Age Group	LTBI Test+ Prevalence (95% CI)	TB Case Rate Per 100,000	% Reactivated	Progression Rate (95% CI)	RR (95% CI)
Original: CDC 2011-2013/NHANES 2011-2012					
Reference (All: Age 15+)	5.7% (4.9-6.7)	4.37	85.7%	65 (56-77)	1 (Ref)
Age 15-24	2.7% (1.9-4)	2.30	78.5%	67 (45-95)	1.02 (0.56-1.49)
Age 25-44	4.3% (3.4-5.3)	3.75	85.7%	75 (61-95)	1.14 (0.78-1.51)
Age 45-64	7.2% (5.3-9.7)	3.71	82.3%	42 (31-58)	0.65 (0.39-0.91)
Age 65 Plus	9% (7-11.4)	4.87	95.2%	52 (41-66)	0.79 (0.52-1.05)
Shea 2014					
Reference (All: Age 15+)	5% (4-5.9)	5.24	80.8%	84 (71-105)	1 (Ref)
Age 15-24	2.4% (1.9-4)	3.57	77.0%	115 (69-145)	1.32 (0.84-1.8)
Age 24-55	5% (3.7-6.6)	5.16	79.1%	82 (62-110)	0.94 (0.45-1.43)
Age 45-65	6.5% (4.5-9.5)	5.41	76.7%	64 (44-92)	0.73 (0.27-1.2)
Age 65 Plus	5.6% (3.7-8.4)	7.06	88.8%	112 (75-169)	1.29 (0.36-2.22)
Summary Estimate: Shea and Original*					
Reference (All: Age 15+)				75 (70-80)	1 (Ref)
Age 15-24				**91 (86-96)**	**1.19 (1.09-1.29)**
Age 24-44				78 (74-83)	1.03 (0.94-1.11)
Age 45-64				**53 (49-57)**	**0.7 (0.62-0.77)**
Age 65 Plus				82 (71-92)	1.07 (0.92-1.23)
Other Studies Assessing RR of Progression by Age Controlling for LTBI Status					
Horsburgh 2010: Age ≤ 50	20.2% (16.6-24.2)	40	100%	43 (24-78)	Ref.
Horsburgh 2010: Age > 50	41.5% (33.2-50)	223	100%	120 (73-190)	**2.7 (1.3-5.9)**
Ferebee 1970: All Age 15+†				43 (35-51)	Ref.
Ferebee 1970: Age 15-34 †	N/A: Cohort of LTBI Positive			39 (28-49)	0.9 (0.63-1.26)
Ferebee 1970: Age 35-54 †	subjects			61 (39-82)	1.41 (0.94-2.13)
Ferebee 1970: Age 55+ †				38 (22-54)	0.88 (0.54-1.41)
Sterling 2011: Per 10-Yr Increase	N/A: Cohort Study / trial of LTBI treatment				0.87 (0.65-1.17)
Patel 2007: Age < 45	N/A: Case Control			N/A	Ref.
Patel 2007: Age ≥ 45				N/A	1.0 (0.8-1.3)

*For the summary estimate, we assigned an equal weight to both studies given an approximately equal adjusted weight of evidence in our meta-analysis of the overall progression rate (see Table 4). Unadjusted weights were used to calculate the SEs of the weighted RR estimates.
† Ferebee 1970 includes results from the Ferebee et al 1962 trial (household contacts) and the Ferebee et al 1963 trial (mental institution). Progression rates and standard errors were imputed from published data on cases by year.

4 Risk Factors for TB Progression and TB Disease: Relative Risks and Population Prevalence

In addition to age and country of origin, the presence of one or more of one or more risk factors for progression to TB disease may be used to prioritize FB persons for LTBI testing and treatment. [90]. This section presents the relative risk of progression to TB disease among IGRA test positive persons

associated with the following risk factors identified by the joint statement by the CDC and the American Thoracic Society.[51] Precise definitions of each risk factor can be found in Appendix D.

- HIV Infection.
- Diabetes Mellitus (DM), operationally defined as diagnosed DM.
- End-stage renal disease, defined as receiving dialysis.
- Immunosuppressive therapy, including TNF-alpha inhibitors, and long-term high-dose corticosteroids.
- Immunosuppressive therapy associated with solid organ transplantation (SOT), including recent SOT recipients and those that have ever received an SOT.
- Hematological and Solid Organ Cancers.
- Malnutrition associated with low bodyweight, defined as having a body mass index less than 18.5.
- Cigarette smoking, alcohol abuse and use of injection drugs.

4.1 Relative Risk of TB Disease and Progression Associated with each Medical Risk Factor

We derived the RRs of progression associated with each medical risk factor with meta-analyses synthesizing estimates from the published literature and an original analysis of relative risk for select risk factors based 2012-2013 CDC surveillance data. A literature search using PubMed for studies published in English from 1990 to 2014 was conducted and supplemented with a review of secondary references cited by the selected studies. Search terms used to collect estimates of the relative risk of progression or disease included: "tuberculosis disease" AND "diabetes" OR "cigarette smoking" OR "HIV" or "renal disease" and so forth. In addition to surveying the literature, we derived RRs of disease associated HIV, renal disease, diabetes, post-organ transplantation and immunosuppression using 2012-2013 CDC surveillance data.

Forest plots were created for each risk factor and summary effect estimates were calculated using either the fixed- or random-effects model described in Appendix B. If there was substantial between-study heterogeneity, a random-effects model was used. If heterogeneity was low, a fixed-effect model was used [121, 118]. Heterogeneity was assessed with Cochran's Q test [122]. This section presents only a summary of the RRs associated with each risk factor. The individual meta-analyses of each risk factor are presented in Appendix C.

As described previously and illustrated in Figure 1, the risk of TB disease is the product of the risk of infection and the risk of progression to disease, where the risk of infection is wholly determined by exposure to infectious cases. The RR of progression is therefore equal to *the RR of disease divided by the risk of exposure*. Our meta-analyses of each risk factor therefore considered two types of studies:

[51] Other risk factors have been identified, including age and evidence of prior TB. Age was accounted for in the prior section. Evidence of prior, healed TB is not included as a risk factor because patients it is a less useful screen because it is difficult to observe and patients may not know whether they had TB.

1. Studies that explicitly calculated the RR of progression by comparing progression rates among subjects with the risk factor to a group of LTBI test positive controls without the risk factor. Also considered within this category were studies designed such that the level of exposure (and therefore, of LTBI) could be assumed to have been equal for persons with and without the risk factor.[52] Given the availability of LTBI treatment, only a handful of studies included a group of untreated LTBI test positive controls. When synthesizing estimates from these studies, the RR of progression was equal to the RR of disease.
2. Studies that estimated the RR of disease without controlling for LTBI status, including our original analysis of 2012-2013 CDC surveillance data on TB case count by risk factor. For these studies, we derived the RR of progression by dividing the RR of disease by the RR of infection (LTBI) associated with the risk factor population, as shown in with Equation 3. Methods for determining the RR of LTBI are discussed in the following section. In addition, we adjusted for the difference in the likelihood of reactivated disease versus disease due to recent transmission (RR_Reactivated), if the literature suggested this parameter varied with the risk factor (e.g., HIV). If we did not find a significant association between LTBI status and the risk factor, we assumed the RR of progression was equal to the RR of reactivated disease.

$$RRofProgression_RF = \frac{RR_ReactivatedDisease_RF}{RR_Infection_RF} = \frac{RRofDisease_{RF}}{\left(\frac{LTBIPosPrevRF}{LTBIPrevOverall}\right)} * RR_Reactivated \qquad \text{Equation 3}$$

If a significant association was found between LTBI and the risk factor, the confidence interval for the RR of progression was calculated with the formula for the standard error of a ratio of two estimators provided in Equation B.9 in Appendix B. The final estimate of the progression rate was found by multiplying the baseline progression rate, **72 (67-77)**, by the RR of progression. The confidence interval was calculated using the formula for the standard error of the product of two estimators provided in Equation B.10 in Appendix B.

Because the policy context is to compare the efficacy of testing and treating a high risk FB subpopulation to a random FB individual, our estimates of RR used the overall population as the reference category, rather than the population without the risk factor to derive the RR versus the general population, we converted RRs versus the population without the risk factor to RRs versus the general population with the formula provided in Equation B.12 in Appendix B. Because the incidence of tuberculosis was below 10 percent for all risk groups, we assumed that relative risks were equivalent to published odds ratios [123, 78].

4.1.1 Estimating the Relative Risk of LTBI

The relative risk of LTBI was determined by a meta-analysis of the published literature and an analysis of the age and birthplace-adjusted association between LTBI and each of the medical risk factors on NHANES. To enhance the statistical reliability of the estimated RRs associated with risk factor subdomains we combined the 2011-2012 NHANES with the 1999-2000 NHANES, the last

[52] For example, Moss 2000 evaluated relative risk among the homeless, a population that can be assumed to have an equal risk of exposure independent of medical risk factor.

survey wave with an LTBI test result available. On NHANES 1999-2000 LTBI was assessed with the Tuberculin Skin Test (TST). LTBI was indicated if the subjected had a TST induration greater or equal to 10mm.

We computed estimate of the RR of LTBI associated with each risk factor with and without adjustments for age and nativity. We did not adjust for poverty or race because studies on the RR of disease typically do not control for those factors. Whether we used the adjusted or unadjusted LTBI RR estimates to derive the RR of progression depended on the design of the study that estimated the RR of disease. Age-adjusted disease RR estimates were divided by age-adjusted LTBI RR estimates. Likewise, unadjusted disease RR estimates were divided by unadjusted LTBI RR estimates, in effect, controlling for confounding factors influencing both LTBI and disease risk.

The reference category for the RRs presented in the following section is the population lacking the risk factor. The reference category was subsequently converted to the general population using Equation B.12 in Appendix B. We assumed that relative risks were equivalent to odds ratios due to the relatively low prevalence of LTBI [123, 78].

4.1.2 Original Estimates of the RR of Disease Using 2012-2013 CDC Surveillance Data

The CDC reports on tuberculosis in the United States in 2012 and 2013 provide data on the total number of cases by nativity occurring in persons reported to have one of the following risk factors: diabetes mellitus, end-stage renal disease, recently taking TNF-alpha inhibitors, recently taking other immunosuppressant therapy, and receipt of a solid organ transplant [37, 115].[53] Data are also provided on HIV status for a subset of cases (not stratified by nativity). We combined these case counts with risk factor population prevalence estimates to compute the relative risk of TB disease associated with each of the five risk factors tracked by the CDC. Because the CDC report does not provide case counts by risk factor and age we assessed relative risk across all ages. Population prevalence was estimated by risk factor across all ages with the same methods as those documented in Appendix D.

Equation 4 displays the formula for computing the relative risk point estimate:[54]

	Tuberculosis Disease	
Risk Factor	Present	Absent
Has Risk Factor	A	B
Lacks Risk Factor	C	D

$$= \frac{CaseRateRF}{CaseRateGeneral}$$

RR Point Estimate

$$RR = \frac{A/(A+B)}{C/(C+D)}$$

Equation 4

Confidence intervals for the RR estimates were estimated with two methods, depending on the population prevalence data source:

[53] Rates by medical risk factor were not published in years prior to 2012.

[54] Because these RR estimates were synthesized with other studies, we first calculated the RR versus the population lacking the risk factor, to facilitate comparisons across studies. The summary RR estimate from the meta analysis was then converted to an RR versus the general population.

1. If population prevalence was estimated (e.g., Diabetes, immunosuppressive therapy, post-SOT), the lower and upper bound of the confidence interval were equal to the RR associated with the upper and lower bounds of the risk factor population prevalence 95% confidence interval. For a given case count, smaller population prevalence corresponds to a higher case rate and thus a higher RR and vice versa.
2. If population prevalence was observed (e.g., HIV, ESRD) the confidence interval for the estimate was found using Equation 5, where ln(RR) is the log relative risk. The standard error of the log relative risk, SE(ln(RR)), was defined Equation 6 [124].

$$95\%\ CI = e^{\ln(RR) \pm 1.96 * SE(\ln(RR))} \quad \text{Equation 5}$$

$$SE(\ln(RR)) = \sqrt{\left(\frac{1}{A} + \frac{1}{C}\right) - \left(\frac{1}{A+B}\right) - \left(\frac{1}{C+D}\right)} \quad \text{Equation 6}$$

Our estimates of the case rate, population prevalence and RR of disease for each risk factor are presented in Table 7. As hypothesized, all of the RR estimates for the FB population overlap with those from the general population, suggesting relative risk does not vary by foreign birth. These estimates were synthesized with estimates from the published literature in the meta-analyses presented in the following sections.

Table 7: Relative Risk of TB Disease by Nativity and Risk Factor in the United States, 2012-2013

	Cases with Risk Factor: 2012-2013	Population Prev. (95% CI) ¥	Case Rate: 2012-2013	RR of Disease (95% CI)[E]
Overall U.S. Population				
All Cases	19,501	100%	3.1*	1 (Ref)
Diabetes	2,850	6.9% (6-7.9)	6.6 (5.8-7.5)	2.31 (2-2.6)
HIV Infection ±	1,347	0.298%*	72.8*	25.18 (23.8-26.6)
ESRD	406	0.2%*	31.9*	10.49 (9.5-11.6)
Immunosuppressive therapy	898	0.65% (0.49-0.87)	22.1 (16.3-29)	7.41 (5.5-9.8)
Post-SOT (ever, including recent)	98	0.1% (0.1-0.11)	15.9 (15-16.7)	5.15 (4.9-5.4)
TNF-Alpha	110	0.09% (0.05-0.14)	20.1 (12.5-32.3)	6.52 (4.1-10.5)
Other	690	0.52% (0.41-0.64)	21.3 (17.1-26.5)	7.09 (5.7-8.8)
Foreign Born Population				
All Foreign Born Cases	12,467	100%	17*	1 (Ref)
Diabetes	1,991	8% (7-9.1)	34 (29.8-38.8)	2.21 (1.9-2.5)
HIV Infection	N/A	N/A	N/A	N/A
ESRD	263	0.2%*	177.7*	10.63 (9.4-12)
Immunosuppressive therapy	455	0.4% (0.3-0.6)	158.9 (112.6-218.5)	8.87 (5.1-15.5)
Post-SOT (ever, including recent)	59	0.05% (0.02-0.09)	172 (88.1-336)	10.13 (5.2-19.8)
TNF-Alpha	70	0.09% (0.05-0.14)	110.1 (68.6-176.9)	6.49 (4-10.4)
Other	326	0.29% (0.17-0.51)	153 (86.8-269.9)	9.2 (5.2-16.2)

*Prevalence of HIV and ESRD is observed/ not estimated.

± The HIV case rate is imputed based on the subset of cases with HIV status available. In 2013, 6.5% of all cases with HIV status available were HIV positive. In 2012, 7.2% of all cases with HIV status available were HIV positive.

¥ Population prevalence for all ages. These figures differ from those presented in 0 for ages 15+. The CDC report does not provide case count by risk factor by age.

[E] Versus the population lacking the risk factor

4.1.3 Summary Estimates

We synthesized our original estimate of relative risk with estimates from the literature with meta-analyses of each risk factor, adjusting for LTBI relative risk. The meta-analyses are presented in Appendix C and the fixed and random-effects model methodologies are documented in Appendix B. Our pooled estimates of the relative risk of LTBI, the relative risk of progression, and the progression rate per 100,000 person years are shown in Table 8.

The reference category for the relative risk is the general population. The progression rate point estimate was found by multiplying the baseline rate by the relative risk associated with the risk factor. The confidence interval was found using the standard error of the product of two estimators given in Equation B.10 in Appendix B.

A significant association was found between LTBI and diabetes (RR: 1.5, 95% CI 1.1-2), current cigarette smoking (RR: 1.5, 95% CI 1.4-1.7) and injection drug use (RR: 3, 95% CI 2.1-4). For these risk factors, the cumulative risk of disease is equal to the product of the RR of LTBI and the RR of progression. In all three cases, we were unable to find a statistically significant RR of progression when adjusting for elevated LTBI risk. This finding challenges the conventional assumption that both

diabetes and cigarette smoking increase the risk of progression. For the remaining risk factors, the risk of disease is assumed to equal the risk of progression.

LTBI positive persons at the greatest risk for progression to TB disease include those with HIV infection (RR: 17.8, 95% CI 10.7-24.5), end-stage renal disease (RR: 12, 95% CI 8.4-15.6), hematological malignances (RR: 11.1, 95% CI 6-11.7) and recent recipients of a solid organ transplant (RR: 31.9, 95% CI 25-40). The relative risk of progression associated with solid organ transplantation persists but appears to decline markedly after the first one to two years (RR: 7.6%, 95% CI 3.5-8.3). We also found significant positive associations between TB progression and TNF-alpha antagonists, long-term high-dose corticosteroids, low bodyweight, solid organ malignancies and alcohol abuse.

Table 8: Relative Risk (RR) for TB Progression by Medical Risk Factor: Summary Results from Individual Meta-Analyses

Risk Group	RR of LTBI±	RR of Progression*	Progression Rate Per 100,000 PYs	No. Studies	References
Baseline: US Average, FB or US-Born	1 (Ref)	1	72 (67-77)	5	Table 4
HIV Infection	1	17.8 (10.7-24.5)	1276 (760-1792)	7	Table C.2
Diagnosed Diabetes Mellitus	1.5 (1.1-2)	1.3 (0.8-1.7)	90 (56-125)	14	Table C.4
End Stage Renal Disease	1	12 (8.4-15.6)	863 (596-1131)	9	Table C.5
Recent SOT Recipient	1	31.9 (25.3-40.3)	2291 (1789-2793)	4	Table C.7Figure C.5. Table C.7
Immunosuppressive therapy					
TNF-Alpha Antagonists	1	4.7 (2.4-5.3)	340 (203-476)	8	Table C.6
Prolonged High-Dose Corticosteroids	1	3.3 (1.8-3.9)	334 (174-495)	5	
Post-SOT Maintenance Therapy	1	7.6 (3.5-8.3)	239 (128-350)	2	
Other Immunosuppressant	1	1.2 (1-1.4)	542 (247-837)	1	
Any Immunosuppressant[ɣ]	1	4.7 (2.9-5.2)	350 (207-493)	13	
Cancers Associated with TB					
Hematological	1	11.1 (6-11.7)	798 (427-1169)	5	Table C.11
Solid Organ	1	4.3 (2.1-5)	305 (148-462)	6	
All TB-Related		7.36 (3.8-8)	528 (273-783)	7	
Underweight (BMI < 18.5)[x]	1	2.9 (2.2-3.6)[x]	208 (156-259)	6	Table C.9
Cigarette Smoking (Current)	1	1.8 (1.4-2)	225 (171-279)	7	Table C.14
Alcohol Abuse (Current)	1	2.8 (1.9-3.8)	272 (101-443)	3	Table C.16
Injection Drug Use (Current)	3 (2.1-4)	3.8 (1.4-10.1)	72 (67-77)	3	Table C.19

± The reference category for these RR is the general population rather than the population lacking the characteristic. These were derived from the RRs versus the population lacking the characteristic shown in 0 using Equation B.12 in Appendix B.

[ɣ] Excluding Recent SOT

[x] Individuals are classified as underweight if they have a body mass index (BMI) under 18.5 kg/m². However, evidence suggests there is a log-linear relationship between body mass index (BMI) and tuberculosis incidence [125].

4.2 Population Prevalence of Medical Risk Factors for Progression

We derived prevalence estimates for the US overall and FB population aged 15 and above from five waves of NHANES spanning a 10 year period from 2003-2012, supplemented with published statistics from secondary sources (detailed methods by risk factor provided in Appendix D). Prevalence for the overall population was estimated as follows. For risk factors with relative high prevalence that may have grown over the past decade, such as diabetes mellitus, the estimate was taken from the 2011-2012 NHANES and validated with an external source (e.g., the CDC National Diabetes Statistics Report). For risk factors with relatively low prevalence lacking a reliable external source, such as immunosuppressant therapy and hematological malignancies, we estimated

prevalence with five waves of NHANES surveys. For risk factors with relatively low prevalence with a more reliable external source, such as the U.S Renal Data System or CDC HIV Surveillance, we used figures published by the external source.

None of the external population prevalence sources provided prevalence data by nativity. Prevalence among the foreign born was therefore estimated by multiplying the overall risk factor prevalence by the relative risk of foreign birth associated with the risk factor by 13.1%, the fraction of the US population that is foreign born. [55] For each risk factor, the relative risk associated with foreign birth was estimated with bivariate logistic regression of the difference in prevalence by nativity across fives waves of NHANES (2003 – 2012). If the 95% confidence interval of the odds ratio estimate included the null, prevalence among the FB population was assumed to be the same as the general population. Specific methods associated with each risk factor are described in the following subsections.

Table C.12 identifies the estimated risk factor prevalence overall and among the foreign born for each of the medical risk factors considered in this study. Detailed descriptions of the methods for defining and eliciting the population prevalence associated with each risk factor are provided in Appendix D.

The population basis is 39,159,000, the estimated number of FB persons over the age of living in the United States in 2014 [102].

[55] In 2013 the resident population of the United States was estimated to be 316,128,839 (Census Bureau, 2013). The foreign born population was estimated to be 41,366,734 (CPS, 2014)

Table 9: Prevalence of Medical Risk Factors for Progression to TB Disease among Persons Aged 15 and Older in the United States

Risk Factor	Population Prevalence (% Overall)	Prevalence 95% CI (%)	RR of Foreign Birth	FB with Risk Factor	Sources and Appendix D Table
All Foreign Born Aged 15+			N/A	32,034,817	[106, 102]
Diagnosed HIV infection	0.32%	N/A	1	102,511	[126], Table D.9
Diagnosed Diabetes mellitus	8.54%	7.46-9.75	1	2,735,773	[127, 128], Table D.6
End State Renal Disease	0.25%	N/A	1	80,087	[129], Table D.8
Recent SOT Recipient	0.01%	N/A	1	3,203	[130], Table D.4
Immunosuppressive therapy*					Table D.4, Table D.3
TNF-Alpha Antagonists	0.11%	0.07-0.18	1	35,238	
Long-Term Corticosteroids	0.18%	0.15-0.22	0.43	24,795	[131, 132]
SOT Recipient (ever)	0.09%	0.09-0.094	1	28,831	Table D.4, Table D.3Table D.3.
Other Immunosuppressant	0.44%	0.34-0.57	0.48	67,658	
Any Immunosuppressant *	0.79%	0.59-0.86	0.59	149,314	Table D.3
Cancers Associated with TB±					
Hematological Malignancies	0.17%	N/A	1	54,459	Table D.10, Table D.11 [133]
Solid Organ Malignancies	0.71%	N/A	0.32	72,783	
All TB-Related Cancers	0.17%	N/A	0.35	19,061	
Underweight (BMI < 18.5)	2.32%	2.06-2.63	1	743,208	Table D.12, Table D.13
Cigarette Smoking (Current)	16.45%	14.48-18.61	0.51	2,687,561	[134, 135] Table D.15
Heavy Alcohol Use (Current)	6.6%	N/A	0.8	1,691,438	[48] Table D.17
Injection Drug Use (Current)	0.37%	024-0.56	0.32	37,929	[106], Table D.18

± Diagnosed in the last 5 years, see Appendix D.

*Associated therapies are defined in Appendix D. Any immunosuppressant' excludes Recent SOT, which is analyzed separately.

5 LTBI Testing and Treatment Parameters

This section presents our remaining model inputs: LTBI test performance and cost; LTBI treatment adherence, efficacy and cost; financial and non-financial costs of a case of TB; and LTBI treatment capacity within health jurisdictions. We make the following assumptions:

1. All patients are tested for LTBI with the QuantiFERON Gold In-Tube IGRA test (QFT-GIT).
2. Only one test is required per patient because the first test is always determinant [100].
3. All test positive patients are offered LTBI treatment.
4. LTBI is treated with a 4-month course of daily Rifampin 600mg by SAT, also known as "4R."[56]
5. The foreign born initiate and complete treatment at the same rate as the general population [36, 136].
6. A patient is considered to have completed therapy if they took 80% of more of their prescribed doses within approximately 20 weeks [137].
7. 4H efficacy by proportion of doses completed is equivalent to that observed in trials of daily 9-month isoniazid therapy ("9H") [138, 139].
8. LTBI treatment capacity is the rate limiting step with respect to testing and treating LTBI within health jurisdictions; jurisdictions have the capacity to test as many as needed to hit their treatment capacity limits.

5.1 LTBI Test Performance, Treatment Adherence and Treatment Efficacy Parameters

Initiation, adherence and efficacy parameters for the 4R LTBI treatment regimen as well as IGRA sensitivity and specific parameters are presented in Table 10. Test performance parameters and treatment initiation rates were obtained from the published literature.

The LTBI treatment initiation rate was estimated to be 50% based on the results of three studies. In a survey of 720 patients offered LTBI treatment, Horsburgh et al found an initiation rate of 83% (95% CI, 80-86) that did not significantly vary by treatment regimen or medical risk factor [36]. In Goswami et al, 130 out of 496 (26%) persons in Raleigh, North Carolina initiated LTBI treatment [140]. In Los Angeles County, approximately 40% of contacts of infectious cases initiate treatment [141].

Treatment completion rates were estimated with a meta-analysis of six studies from the published literature, including three randomized trials, two retrospective chart reviews and a random cross-sectional survey. Using a random effects model, our summary estimate of the 4R treatment completion rate is 77% (95% CI 74%-80%). Selected studies and a forest plot of results are shown in Appendix E.

[56] There is an increasing move toward 4R within public health jurisdictions. While recent studies have found 3HP to be more effective, the requirement that 3HP be administered with directly observed therapy (DOT) renders it infeasible for many jurisdictions.

Treatment efficacy of risk reduction is typically expressed in terms of proportion of doses completed. We therefore surveyed the literature for estimates of 4R completion by week or dose. Page et al. also reported partial completion rates. Among patients failing to complete at least 80% of doses, 55% discontinued in the first, 12% discontinued between months 1-2 and 33% discontinued between months 3-4 [142].[57] We impute the proportion of treatment completion by month interval by applying these rates to the overall complete rate derived through meta-analysis (see Table 10).

We considered whether treatment initiation and completion varied by age or medical risk factor for progression. Horsburgh et al examined several potential risk factors, including age, foreign birth, diabetes, ESRD, HIV Infection, immunosuppression and injection drug use. Significant risk factors for failure to complete treatment included injection drug use (OR: 2.13, 95% CI 1.04-4.35) and age ≥ 15 (OR: 1.49, 95% CI 1.14-1.94) [36]. None of the variables significantly predicted treatment initiation. Page et al found that completion rates were significantly lower among patients age 18-35 (OR: 0.48, 95% CI 0.33-0.71) [142]. Odds Ratios were converted to relative risks using the formula given in Equation B.12 in Appendix B.

Data suggest that the efficacy or risk reduction of 4R is similar to that of INH but no data are available on precise risk reduction by treatment adherence [139]. We use estimates of 4R efficacy interpolated in a 2009 cost effectiveness analysis published by Holland and colleagues [138].

[57] Proportion by time interval among drop outs derived from published completion rates by month.

Table 10: Model Inputs for LTBI Treatment Adherence, Efficacy and Cost

Parameter	Point Estimate	95% CI/ Range	Sources
IGRA Test Performance			
QFT-GIT Sensitivity	0.83	0.64-0.93	[90, 88, 89]
QFT-GIT Specificity	0.99	0.99-1.0	[90]
4R Treatment Initiation			
Initiation Rate: All / All FB	50%	26%-83%	[36]
4R Adherence			
0-4 Weeks/0%-25% Complete	12.8%	13.7%-11.9%	Table E., [142]
5-9 Weeks/26%-49% Complete	2.8%	3%-2.6%	Table E., [142]
10-15 Weeks/50%-79% Complete	7.6%	8.1%-7%	Table E., [142]
16-20 Weeks/80%-100% Complete	76.8%	75.2%-78.5%	Table E., [142]
Risk Factors for Completion			
Age 18-35, Multivariate RR	0.80	0.67-0.91	[142]
Injection Drug Use, Multivariate RR	0.75	0.64-0.98	[142]
4R Treatment Risk Reduction			
0-4 Weeks/0%-25% Complete	0	N/A	[138]
5-9 Weeks/26%-49% Complete	40%	26%-40%	[138]
10-15 Weeks/50%-79% Complete	47%	30%-47%	[138]
16-20 Weeks/80%-100% Complete	93%	60%-93%	[138]
Avg. Risk Reduction Per Patient Initiating 4R[ɣ]	*76%*	*48%-77%*	*Derived*

[ɣ] Average risk reduction per patient initiation treatment is the product of the adherence and risk reduction arrays.

5.2 Cost Inputs

Model inputs for the costs of LTBI testing and treatment and the costs of an active case of TB, including TB and drug-related mortality, are shown in Table 11. Cost inputs were derived from the published literature. Costs were converted to 2014 U.S. dollars, with medical costs adjusted according to consumer price index changes for medical care for urban consumers [98]. Societal costs include household out-of-pocket costs and the value of lost productivity. Patient time is valued at $14.08 based on 2013 U.S. per capita income adjusted for inflation [143].

Table 11: Direct and Indirect Cost Parameters

Parameter	Health System Cost	Societal Costs	Included Costs / Assumptions	Sources
IGRA (QFT-GIT) Costs				
QFT-GIT Administration	$56	$14	Phlebotomist time and supplies, nurse time to test, QFT-GIT kit, lab scientist time and supplies, clerical time	[100, 98, 56]
Evaluation if IGRA Positive	$115	$28	MD visit, Chest X-ray (CXR)	[100, 98]
4R Treatment Costs: Financial				
4R Cost Per Month	$64	$42	Drug costs, monthly nurse visit	[138, 98]
Probability of Drug Toxicity	3%		Adverse Events requiring discontinuation	[137]
Cost of Drug Toxicity	$493	$58	Lab monitoring + 1.5% risk of severe toxicity requiring 7-day hospitalization,	[144, 138, 25]
Avg. Cost Per Patient Initiating 4R	$273	$80	Product of treatment adherence array and monthly cost plus toxicity risk	*Derived*
4R Treatment Costs: Non-Financial				
Prob. Death from Toxicity	.01%			[144, 138]
Deaths Per 100,000 Initiating 4R	0.3			*Derived*
Costs Per Active TB Case: Financial				
Diagnostic Costs	$291	$42	CX-R, Sputum Smears	[25, 98]
Outpatient Treatment	$3,056	$404	9-months treatment. 6 monthly visits	[25, 98]
Cost of Hosp.: General Pop.	$27,000	$1,521	45% of cases require hospitalization with a mean LOS of 20 days. Cost per day $2,500.	[145, 98, 25, 146, 56]
Cost of Hosp.: Comorbidities	$39,000	$3,690	65% of cases require 24 days of hospitalization.	[56, 145, 98]
Costs Per Active TB Case: Non-Financial				
Prob. Death: General Population	5.1%			[25, 37]
Prob. Death: Comorbidities	6.1%			[37, 100, 56]
Secondary TB Cases Per Case	0.46		Per Shepardson and Linas, ¼ occur immediately following the primary case, ¼ occur in 10 years, 1/4 occur in 20 years, ¼ occur in 40 years. Assume secondary cases share characteristics (age, etc.) with primary case.	[25, 49, 50]
Discounted Secondary TB Cases*	0.304			
Quality Adjustments				
Active TB (Per Year)	0.13		Quality adjustment for treatment (0.1) and hospitalization (0.03). Adjustment for treatment is 0.2 per year for 6 months = 0.2*(6/12)=0.01. 49% are hospitalized for 20 days. Quality adjustment per year for hospitalization = 0.5*(20/365)=0.03.	[56, 25, 147]
LTBI Drug Toxicity / Year	0.01		2 weeks of toxicity at 0.25 per year.	[25]
LTBI Treatment/ Year	0.008		3 months of treatment, 0.03 quality adjusts per year = 0.03*(3/12)=0.008.	[25]

*For cases occurring in year 1. Secondary cases arising from active cases that develop in subsequent years are further discounted. We do not consider tertiary cases.

5.3 Treatment Capacity

Because LTBI treatment is the cost and capacity bottleneck for testing and treating LTBI, we assume that capacity for LTBI testing and treatment is wholly determined by the jurisdiction's capacity for treatment. We evaluate the yield of the program under a range of capacity assumptions informed by a review of the published literature on the scope of LTBI treatment in the United States.

A 2002 survey of the Tuberculosis Epidemiologic Studies Consortium estimated the rate of LTBI treatment starts per capita at 19 sites across the United States representing 12.7% of all TB cases. Treatment start rates ranged from 40 per 100,000 at the Seattle-King County Department of Health to 1,584 per 100,000 at the Minnesota Department of Health [148]. The authors estimated that in

2002 between 291,000 and 433,000 individuals initiated treatment for LTBI and that FB persons accounted for 56.2% of all persons receiving treatment [148]. With 1% population growth since 2002 these figures suggest that between 165,000 and 246,000 FB persons can initiate LTBI treatment per year in the United States. Assuming that 50% of patients offered treatment initiate, this implies that treatment is offered to between 330,000 and 492,000 FB persons per year, between 0.8% and 1.3% of the overall FB population and between 5.1% and 7.5% of the FB IGRA positive population. Without prioritized or targeted testing and with an average IGRA positive prevalence of 16.7%, the Sterling study suggests that between 2 and 2.9 million foreign born should be tested annually to meet current treatment levels. These estimates comprise the lower bounds of our capacity assumptions because they reflect the number of LTBI cases that presented without targeted testing. If the yield of LTBI testing was higher, more patients would be offered and initiate treatment.

Synthesizing these estimates, we evaluate the yield of the intervention under four scenarios concerning the annual capacity to treat FB IGRA positive patients: 175,000 (~ lower bound in Sterling et al), 250,000 (~ upper bound in Sterling et al), 500,000 (two times the Sterling upper bound) and 750,000 treatment starts per year (four times the Sterling upper bound).

5.4 Reach of LTBI Targeted Testing

Targeting a particular risk group does not ensure that the testing initiative will reach all members belonging to the risk group. The 'reach' parameter characterizes the percent of the risk factor population prevalence that the targeted testing intervention can actually test in the near-term. We estimate this parameter based on the projected number of foreign born with health insurance, as these individuals are more likely to have routine encounters with the health care system. The Pew research center estimates that in 2012 67.3% of the foreign born have public or private health insurance [149].

6 Aggregate Risk of TB and Life Expectancy by Risk Group

6.1 Total Potential Cases Averted by Risk Group

To provide an upper bound for the total number of TB cases that could be averted by testing and treating LTBI, this section projects the total number of TB cases annually and cumulatively over the life expectancy of the average person belonging to each of the FB risk groups given status quo LTBI prevalence rates. Because the annual risk of TB disease reactivation is assumed to be constant over time after the initial "fast progressing" period, we assume that future cases will be evenly distributed throughout the time horizon (t) (e.g., LTBI positive individuals face an equal risk of progression in each of their future life years).

Patients infected with LTBI are typically infected for a lifetime. As a consequence, the risk of acquiring infection within the United States on an annual basis is very low even among groups with

high prevalence rates. The analysis therefore informs whether to conduct a one-time test of patient belonging to each risk group, rather than annual or periodic testing. Because this analysis informs the decision of whether to test and treat LTBI in the present time period, our calculation of an individual's lifetime risk of TB does not account for the risk of future infections. Successfully treated patients could be re-infected and could develop active TB in the future.

The cumulative undiscounted number of TB cases arising over the remaining life years of the average person belong to each FB risk group g ($TotalTBCases_g$) is equal to the product of the size of the LTBI test positive population (LTBIPosPop), the risk group's annual progression rate (PR) and the life expectancy associated with the mean age of a person belonging to the risk group (LE_g), plus discounted secondary cases arising for each primary case (see Equation 7).

Following methods described in Shepardson et al and Linas et al, each case of TB produces 0.46 secondary cases with one third of the cases occurring immediately, one third occurring in 10 years, and the remaining third occurring in 25 years (see Section 5.2) [25]. We do not include costs and health outcomes associated with transmission beyond secondary cases. Total discounted cases arising from each primary case presenting *in the present time period* is therefore equal to (1/4)*0.46+(1/4)*(0.46/(1.03^10))+(0.46*(1.03^20)+(0.46*(1.03^40)=0.30. Secondary cases are discounted twice to account for the fact that they occur after the primary cases, which is also discounted.

Because these cases are assumed to be equally likely to present in each of the average individual's remaining life years, discounted total cases is defined using the formula in Equation 8, where *r* is the discount rate (3%). Implicit in this formula is the assumption that future cases will be evenly distributed over time. Confidence intervals were based on the standard errors of the estimate for the number of cases per year, computed using the formula for the product of two estimators given in Equation B.12 in Appendix B. The lifetime risk of TB for an LTBI test positive individual is equal to the product of the individual's remaining life expectancy (LE) and the annual progression rate (formula not shown.

$$TotalTBCases_g = LE_g * LTBIPosPop_g * PR_g * (1 + 0.30) \quad \text{Equation 7}$$

$$DTotalTBCases_g = \frac{TotalTBCases_g}{LE_g} * \frac{1 - (1 + r)^{-LE}}{r} \quad \text{Equation 8}$$

6.2 Age and Risk Group Specific Life Expectancies

Lifetime and cumulative risk over the time horizon were calculated with age- and risk-group specific life expectancies. Life expectancy is particularly important to this analysis because it influences not only the quality adjusted life years gained per averted case but also the likelihood that a case will present at all. Age-group specific life expectancies were found using 2010 life tables [51]. Life expectancy adjustments by risk factor were found by applying the standardized mortality ratio (SMR) associated with the risk factor to the annual probability of death at each prevalent age, under the simplifying assumptions that the SMR is constant across ages and equal to the relative

risk of death at each prevalent age of the risk factor. Detailed methods for estimating each of the risk-group specific life expectancies (LE) are described in Appendix D.

Population by age band, poverty status and nativity was found using the 2014 CPS Annual Social and Economic Supplement [102]. Except where noted, mean age among persons aged 15 and older for each risk group was derived from a weighted analysis of combined NHANES 2003-2012 (PROC SURVEYMEANS, SAS 9.3). Mean age overall was calculated from the FB subsample. Mean age by medical risk group was calculated from the overall sample due to small sample sizes among the FB subsample.

6.3 Discounted Life Expectancy Gains Per Case Averted Over the Time Horizon: A Model of Annual TB Morbidity and Mortality Risk

We assume that individuals developing active TB either die or fully recover. Quality-adjusted life expectancy gained per case averted *in the present period* is therefore equal to the product of the mortality rate (m) and the individual's discounted life expectancy ($LE_{Di.}$] plus the quality-adjusted life years (QALYs) lost from the 6 months of treatment for active TB $(QALYL_{TB})$. We assume the risk of activation is constant throughout each of the individual's remaining life years.

Average discounted QALYs lost per undiscounted case $(E[QALYsLostPerCase])$ was therefore found using Equation 9, where m_g is the mortality rate for the risk group, E[Age] is the mean age of an individual belonging to the risk group that develops TB disease in year 1, LE_g is the number of future life years lived by the average member of the risk group, and $DLE_{,i}$ is the discounted life expectancy (LE) of the average person belonging to the risk group in year *i*. Total discounted QALYs lost per case averted is the sum of the discounted QALYS lost from the case itself (the primary case) and secondary case arising from the primary case within time horizon. [58]

$$E[QALYsLostPerCase] = \frac{1}{LE_g} * \sum_{i=E[Age]}^{E[Age]+LE-1} \left(m_g * DLE_i + QALYL_{TB}\right) * (1-r)^i \qquad \text{Equation 9}$$

Discounted life expectancy (DLE_D) was found using the "Mixed DEALE" method proposed by Keeler and Bell [53]. The mixed DEALE method sets discounted LE equal to the weighed sum of LE under the declining exponential approximation of life expectancy (DEALE) method and the fixed lifetime approximation of life expectancy (FLALE) method. The DEALE method, proposed by Beck et al, adjusts LE for a constant hazard r [70], as shown in shown in Equation 10, where r is the discount rate and ULE is the undiscounted life expectancy.[59] The DEALE constant hazard assumption under-estimates life expectancy because, except for the severely ill, mortality increases exponentially with age. The FLALE method, by contrast, over-estimates discounted LE by assuming that everyone lives

[58] We do not account for tertiary cases or transmission beyond the second case.
[59] Accounting for disease-related mortality with a constant hazard r is equivalent to discounting at rate r [53].

out their full LE (Equation 11). The combined, weighted discounted LE is shown in Equation 12, where p is the weight assigned to the DEALE computed LE, which is set equal to 0.3 based on life table analysis conducted in a study of breast cancer effectiveness [71]. Pursuant to guidance from *the Panel on Cost-Effectiveness in Health and Medicine*, LE is discounted at a 3% rate [17].

$$DLE_{DEALE} = \frac{ULE}{(1 + r * ULE\ \ )} \quad \text{Equation 10}$$

$$LE_{FLALE} = \frac{(1 - \exp(-r * ULE)}{r} \quad \text{Equation 11}$$

$$DLE = \frac{p * LE_U}{(1 + r * ULE)} + \frac{(1 - p) * (1 - \exp(-r * ULE)}{r} \quad \text{Equation 12}$$

Lifetime risk of TB, years of potential life (LE), discounted projected case counts, and QALYs lost per case among the foreign born are shown in Table 12 by age and medical risk factor. The final column, future reactivated TB cases among LTBI positive, reflects the total number of cases that could be prevented if all persons belonging to the specified risk group were tested today under the assumption of perfect test sensitivity and treatment compliance. The next section incorporates test sensitivity, specific and treatment compliance parameters.

Table 12: Lifetime Reactivated TB Cases and Discounted Life Expectancy Lost By Foreign Born Risk Group

Risk Group	Mean Age	Discounted LE	Lifetime Risk of TB if LTBI+ (%)*	No. LTBI Positive Among Foreign Born (Thous.) ᵚ	Lifetime Reactivated TB Cases †	Avg QALY Lost Per Case®	Sources
All Foreign Born Age 15+	42	21.6	2.8 (2.6-3)	6,540 (5,521-7,675)	237,866 (206,209-269,522)	0.93	[128, 51, 106]
All Foreign Born By Age ᵞ							
Age 15-24 (Age 20)	20	26.0	4.2 (4-4.5)	295 (249-346)	16,234 (14,057-18,410)	1.09	[51, 102]
Age 25-34 (Age 30)	30	24.3	3.6 (3.3-3.8)	829 (700-973)	38,608 (33,449-43,767)	1.02	[51, 102]
Age 35-44 (Age 40)	40	22.1	2.9 (2.7-3.1)	1,407 (1188-1,651)	53,549 (46,418-60,681)	0.94	[51, 102]
Age 45-54 (Age 50)	50	19.4	2.3 (2.1-2.4)	1,819 (1,536-2,135)	54,168 (46,977-61,358)	0.85	[51, 102]
Age 55-64 (Age 60)	60	16.1	1.7 (1.6-1.8)	993 (839-1,166)	21,901 (19,003-24,800)	0.75	[51, 102]
Age 65-74 (Age 70)	70	12.2	1.2 (1.1-1.2)	1,159 (978-1,360)	17,353 (15,063-19,643)	0.62	[51, 102]
Age 75 Plus (Age 80)	80	8.1	0.7 (0.6-0.7)	1,589 (1,341-1,865)	14,229 (12,356-16,103)	0.51	[51, 102]
Foreign Born by Medical Risk Group							
HIV Infected	46*	13.9	20.9 (15.7-25.8)	24.5 (20.7-28.8)	6,654 (4,878-8,429)	1.04	[46, 150]
Diagnosed Diabetes Mellitus	59	12.5	1.5 (0.9-2.1)	1,650 (1,319-1,981)	32,098 (21,383-42,813)	0.88	[128, 151, 152]
End Stage Renal Disease	60*	4.1	3.5 (2.2-4.8)	31.9 (26.9-37.4)	1,467 (1,006-1,928)	0.87	[128, 153, 153]
Immunosuppressive therapy							
Recent SOT ᵠ	49*	8.9	23.2 (16.2-29.7)	0.9 (0.7-1)	261 (179-343)	1.00	[130]
Post-SOT Maintenance	56*	6.9	4.3 (2-6.5)	11.4 (9.6-13.2)	630 (351-910)	0.88	[130]
TNF-Alpha Antagonists	50	18.6	9.6 (5.1-13.8)	9.9 (6-13.8)	1227 (611-1843)	0.99	[128, 154]
Prolonged High-Dose Steroids	58	15.9	5.4 (3-7.9)	9.3 (7.2-11.5)	660 (391-929)	0.88	[128, 154]
Other	59	15.5	1.9 (1.6-2.3)	26.2 (19-33.4)	654 (487-821)	0.88	[128, 154]
TB-Related Cancers							
Hematological Cancer	61	11.6	9.7 (5.1-14.1)	23.6 (19.9-27.7)	2,968 (1,738-4,197)	0.85	[128, 133]
Solid Organ Cancer	65	7.5	2.7 (1.3-4)	35.8 (30.2-42)	1235 (719-1751)	0.80	[128, 133]
Underweight (BMI < 18.5)	34	22.0	8.8 (6.7-10.8)	115.4 (93.3-137.6)	13,154 (9,896-16,412)	1.16	[128, 155]
Cigarette Smoking (Current)	43	18.1	3.6 (2.9-4.4)	578 (468-688)	27,206 (21,187-33,225)	1.08	[128, 156]
Alcohol Abuse (Current)	39	18.8	5.9 (4.1-7.7)	318 (268-373)	24,542 (17,740-31,344)	1.11	[128, 157]
Injection Drug Use (Current)	37	19.4	8.4 (3.2-13.4)	6.6 (4.1-9.1)	720 (294-1147)	1.13	[128, 158]

*Derived with survival analysis. Lifetime Risk = 1-(1-PR) ^LE-U, where PR is the annual progression rate and LE-U is undiscounted life expectancy.

† Undiscounted total future cases assuming current LTBI infection status / prevalence associated with each risk group. Including discounted secondary cases.

ᵚ Prevalence by age is derived from the univariate RR estimate per 10 year increase presented in Table 2. CIs were derived by multiplying the upper and lower CI of the overall prevalence estimate by the RR associated with the age band. Prevalence by medical risk factors assumes the mean age among persons with the risk factor and incorporates the LTBI RRs found in 0.

® Average QALY lost per case is the sum of the discounted QALYs lost per primary case and the discounted QALYs lost per secondary case rising from

ᵞ To simplify interpretation, mean age for each age band was assumed to progress in 10-year intervals.

* Mean age derived from surveillance data as documented in 0.

ᵠ We assume that recent SOT recipients experience elevated progression rates for 2 years. After two years, they experience progression rates equal to those that have 'ever received' a transplant.

ϯ Excluding recent SOT

LE: Life Expectancy; DLE: Discounted Life Expectancy; ULE: Undiscounted Life Expectancy; QALY = Quality Adjusted Life Year

7 Prioritization Tool: Cost Effectiveness of Testing and Treating Foreign Born Risk Groups

7.1 Policy Decision Context: One-Time Testing

This section presents priorities for testing and treating FB subpopulations for LTBI. Because the annual rate of new infections in the U.S. is low, annual or routine testing is not recommended. Rather, FB persons with prioritized risk factors ought to be tested as soon as they present in a primary care setting, presumably within the year following adoption of these recommendations. If the person is test negative, subsequent testing is not indicated because transmission is rare within the United States. However, some testing will be required in subsequent years to capture 1) newly arrived immigrants and 2) FB persons that acquire priority risk factors after the initial risk assessment or *screen*.[60] To account for the fact that risk factors change over time and that many are more likely to present as the person ages, the appropriateness of LTBI testing for a person with an initial negative screen (low priority for testing) should be reassessed on a routine or annual basis.

7.2 Cost Effectiveness Analysis Methods

For each FB age and risk group we estimated total discounted costs and quality adjusted life years (QALY) gained per 1,000 persons tested. From these estimates we derived for each group the base case incremental cost effectiveness ratio (ICER) of testing and treatment versus no testing or treatment, which was defined as the discounted net costs per discounted QALY gained.

The average risk reduction (ARR) per patient initiating treatment is equal to the sum of the products of the completion rate (CompRate) and risk reduction rate (RR) for months (m) 1-4. The ARR formula is shown in Equation 13. Because the estimates of ARR from the published literature assessed risk reduction among LTBI test positive patients, we do not need to adjust for test specificity. Using the base case parameters identified in Table 10, the ARR per patient initiating treatment is 0.76. Without initiating treatment, 72 out of every 100,000 persons infected with LTBI will progress to TB disease; with treatment initiation, only about 17 will progress.

$$ARR = \sum_{m=1}^{4} (CompRate_m * RR_m) = 0.76 \qquad \text{Equation 13}$$

The number needed to treat (NNTreat) to avert an undiscounted case (in this context defined as the number of treatment initiations needed to avert a case) is the inverse of the number of cases averted per patient that initiates treatment (Equation 15). Assuming that future reactivated cases are equally distributed across the risk group's remaining life years, total undiscounted cases averted per patient tested ($CasesAvertedifTreated^U$) is equal to product of the patient's remaining life expectancy, and the cases averted per year, which is the product of the annual progression rate

[60] Screening refers to the risk assessment process by which high priority groups are identified and recommended for testing and treatment if test positive; *testing* refers to the actual test for LTBI.

(PR) and the ARR with a factor adjustment for secondary cases (0.30 discounted cases per primary case) (Equation 15). Discounted total cases averted per patient tested is found by applying a 3% discount rate and assuming the averted cases are evenly distributed across the risk group's remaining life years (Equation 16).

$$CasesAvertedifTreated^{U} = LE_g * ARR * PR_g * (1 + 0.30) \quad \text{Equation 14}$$

$$NNT_g = \frac{1}{CasesAvertedifTreated^{U}} = \frac{1}{LE_g * ARR * PR_g * (1 + 0.30)} \quad \text{Equation 15}$$

$$CasesAvertedifTreat^{D} = \frac{CasesAverted^{U}}{\boldsymbol{LE_g}} * \frac{\mathbf{1} - (\mathbf{1} + \boldsymbol{r})^{-\boldsymbol{LE}}}{\boldsymbol{r}} \quad \text{Equation 16}$$

The *number needed to test* (NNTest) to avert an undiscounted case of TB among patients belonging to risk group g is given in Equation 17, where *InitRate* is the treatment initiation rate and *IGRAPosPrev* is the expected proportion of patients that will have a positive IGRA result. We assume that all test positive patients are offered treatment. We do not adjust for test sensitivity because our estimate of test positive prevalence accounts for both true prevalence and test sensitivity and specificity.

$$NNS_g = NNT_g \frac{1}{IGRAPosPrev_g * InitRate_g} \quad \text{Equation 17}$$

Discounted net QALYs gained (DQALYGained) per patient initiation treatment is equal to the difference between the QALYs gained from cases averted and the QALYs lost from treatment (Equation 18). Average QALYs lost per person initiating treatment is the sum of the quality adjustment for treatment, the product of the quality adjustment for drug-related toxicity and the probability of toxicity, and the product of the probability of drug-related toxicity death and the risk group's undiscounted life expectancy (Equation 19). Treatment-related QALYs are not discounted because testing and treatment occur in the present time period. The quality adjustment parameters were defined in Table 11 in Section 5.2.

$$\boldsymbol{QALYGained = CasesAverted^{U} * (E[QALYsLostPerCase]) - QALYLTreatment} \quad \text{Equation 18}$$

$$\boldsymbol{QALYLTreatment = QALYL_{Treat} + P_{Toxicity} * QALYL_{Toxicity} * LE + P_{ToxicityDeath} * LE} \quad \text{Equation 19}$$

Discounted total net costs are equal to the difference between the costs arising from testing 1,000 patients in the present period and the discounted costs avoided from future averted cases. The ICER, relative to not testing or treating, is the ratio of the discounted cost to the discounted QALY gain.

We present net cost estimates including and excluding societal costs (Table 13). For most risk groups, the absolute effectiveness declines when accounting for societal costs because the social cost margin associated with testing and treating in the present period is relative larger than that associated with future case avoidance. ICER and effectiveness rating estimates are shown only for the societal perspective. The ICER is classified as "cost saving" if discounted net costs are negative. Negative ICERs are not presented because the interpretation of the ratio changes when there are gains in both the numerator and denominator.

7.3 Results: Cost Effectiveness by Foreign Born Risk Group

The cost effectiveness of testing and treating FB age and medical risk factor groups with base case model parameters is displayed in Table 13. The final column assigns a cost effectiveness rank to each risk group based on the ascending value of the ICER. If net costs were negative the effectiveness ranking is based on net QALYs gained. Table 14 presents the cost effectiveness of testing and treating groups facing elevated LTBI prevalence rates (e.g., by race/ethnicity, poverty and country of origin). Figure 3 plots the effectiveness of both progression and LTBI risk groups with net costs per 1,000 patients tested on the horizontal axis and net discounted QALYs gained on the vertical axis. The grey diagonal line splits the northwest quadrant (groups for whom testing gains health at a cost) into groups that gain QALYs at a cost less than (blue) and greater than (purple) $50,000 per QALY. This is a conservative threshold. Most analyses consider a policy to be effective if it gains health for less than $100,000 per QALY. Under this threshold, however, testing all FB would be cost effective, which is not feasible given treatment capacity constraints.

Our base case results show that testing and treating LTBI is net cost saving among FB with the following risk factors: HIV, SOT (recent or prior), hematological cancer, receiving TNF-a inhibitors or prolonged high-dose steroids, low bodyweight, injection drug use, alcohol abuse, and ESRD. Differences in cases averted and net QALYs gained between these groups demonstrate the importance of adjusting for age and risk-group adjusted life expectancy. More health can be gained by targeting persons with low bodyweight and persons on immunosuppressive therapy than by targeting persons with ESRD despite a much higher progression RR associated with ESRD due to large differences in life expectancy. LTBI infected persons with ESRD are nearly 3 times as likely to progress in a given year than their counterparts on TNF-a inhibitors but testing 1,000 ESRD patients will avert less cases and even fewer lost QALYs because ESRD patients have about 14 less remaining life years.

Testing and treating the average FB person or all FB persons (the "universal approach") costs approximately $58,000 per QALY gained. Age, between the ages of 15 and 65, makes little difference in cost effectiveness, assuming no increase in RR of progression with increased age. Targeting diabetics is less cost effective than targeting the average FB and is not cost effective at a $100,000 per QALY gained threshold due to shorter life expectancy and a relative low risk of progression. Testing persons over the age of 65 may result in health losses due to LTBI treatment

toxicity risks and quality of life decrements coupled with short life expectancy and a non-elevated progression risk.

Targeting FB current smokers, persons with solid organ cancers, and persons born in countries with extremely high prevalence (e.g., Ethiopia, Haiti) is more effective than the universal approach. Testing persons from Mexico is less effective than the universal approach. Because of the relative high prevalence of LTBI and because treatment is significantly more resource intensive than testing, it is on average more effective to target groups at greater risk of progression (higher treatment yield) than groups at greater risk of LTBI (higher test yield).

Table 13: Cost Effectiveness of Testing and Treating Foreign Born Age and Risk Groups for Progression: Base Case

			Per 1,000 FB Persons Tested			Societal Perspective		
Risk Group	**NNTreat to Avert Case**	**NNTest to Avert a Case**	**Cases[d] Averted**	**Net QALY Gained †**	**Net Costs[d] w/ Societal ($) ¥**	**Net Costs[d]: Health System Only ($) ¥**	**ICER: $ / QALY[d] Gained ($) ±**	**Effectiveness Rank®**
All Foreign Born (FB) Age 15+	36	427	1.4	1.3	78,662	60,155	58,334	
FB By Age ¥								**Age Rank**
Age 15-24 (Age 20)	23	615	0.7	1.4	70,127	54,327	50,963	3
Age 25-34 (Age 30)	28	506	1.0	1.5	72,285	55,547	49,360	1
Age 35-44 (Age 40)	34	430	1.3	1.4	77,290	59,074	55,676	2
Age 45-54 (Age 50)	44	382	1.7	1.1	87,854	67,283	79,632	4
Age 55-64 (Age 60)	59	358	2.0	0.5	108,484	84,156	204,023	5
Age 65-74 (Age 70)	87	366	2.1	-0.5	146,752	116,441	LYs Lost	N/A
Age 75 Plus (Age 80)	146	425	2.0	-1.8	212,794	173,133	LYs Lost	N/A
FB by Medical Risk Group								**RF Rank**
HIV Infected	4	44	16.9	22.5	(515,750)	(501,024)	Cost Saving	1
Diagnosed DM	67	272	2.9	1.0	106,627	77,683	105,118	14
End Stage Renal Disease	28	173	5.3	3.7	(36,792)	(53,093)	Cost Saving	10
Immunosuppressive therapy								
Recent SOT ϕ	4	35	24.0	27.5	(777,337)	(748,160)	Cost Saving	2
Post-SOT Maintenance	23	148	5.9	4.6	(63,071)	(77,610)	Cost Saving	9
TNF-Alpha Antagonists	10	88	7.4	10.1	(144,800)	(152,366)	Cost Saving	3
Prolonged Steroids	18	118	6.0	6.0	(69,308)	(83,280)	Cost Saving	7
Other	52	330	2.2	1.2	80,289	57,460	66,839	13
Cancers								
Hematological Cancer	10	58	13.8	13.2	(353,208)	(351,786)	Cost Saving	4
Solid Organ Cancer	38	188	4.6	2.5	12,557	(8,567)	4,986	11
Underweight (BMI < 18.5)	11	174	3.3	6.0	(17,834)	(30,067)	Cost Saving	6
Cigarette Smoking, Current	27	312	2.1	2.6	40,966	24,068	15,753	12
Alcohol Abuse, Current	17	215	3.0	4.4	512	(13,472)	117	8
Injection Drug Use	12	162	3.9	6.3	(36,888)	(48,408)	Cost Saving	5

† Net discounted QALYs gained is the difference between the discounted QALYs gained from cases averted and the QALYs lost from initiating treatment.

¥ Discounted Net Costs (Costs[d]) are the discounted costs of testing and treatment associated with initiating treatment for 1,000 patients less the discounted costs of a case.

± Incremental Cost Effectiveness versus the status quo: discounted costs divided by discounted QALYs; 3% discount rate

®Effectiveness ranking among age groups and among medical risk factors. If testing group has health and cost gains ranking is determined by QALY gains

QALY: Quality-Adjusted Life Expectancy; Cases[d]: Discounted Cases, ICER: Incremental Cost Effectiveness Ratio; Net Costs[d]: Discounted Net Costs; NNTest: Number Needed to Test for LTBI to avert an undiscounted case; NNTreat: Number need to initiate treatment to avert an undiscounted case; 3% discount rate

Table 14: Cost Effectiveness of Testing and Treating Foreign Born Risk Groups for Latent Infection: Base Case

				Per 1,000 Tested			
Risk Group*	**LTBI RR**	**NNTreat Avert a Case**	**NNTest Avert a Case**	**Cases[d] Averted**	**Net QALY Gained †**	**Net Costs[d] Societal ($) ¥**	**ICER: $ / LE[d] Gained ($) ±**
Average FB	1	35	414	1.4	1.3	78,662	58,334
Poverty							
Below Threshold	1.4	35	296	1.8	1.8	81,508	45,498
Race							
Black	1.3	35	319	1.8	1.8	81,261	46,355
Asian	2	35	207	2.7	2.7	87,325	32,379
Hispanic	1.4	35	296	1.9	1.9	82,127	43,503
Country of Origin							
Mexico	0.7	35	589	1.0	0.9	76,064	80,581
Guatemala	1.5	35	275	2.0	2.0	82,994	41,031
Philippines	2.5	35	165	3.4	3.4	91,656	27,188
India	2	35	206	2.7	2.7	87,325	32,379
Viet Nam	2.6	35	159	3.5	3.5	92,522	26,389
China	1.1	35	375	1.5	1.5	79,529	53,615
Haiti	2.1	35	196	2.9	2.8	88,191	31,143
Ethiopia	4	35	103	5.4	5.4	104,650	19,401
Smoking by Country of Origin							
Smokers - Asian Race/Ethnicity	2	19	116	4.9	6.1	23,608	3,855
Smokers from Haiti	2.1	19	110	5.1	6.4	21,288	3,311
Smokers from Ethiopia	4	19	58	9.7	12.2	(22,784)	Cost Saving

*Risk profile for the average FB person in terms of age and prevalence of other medical risk factors for progression.

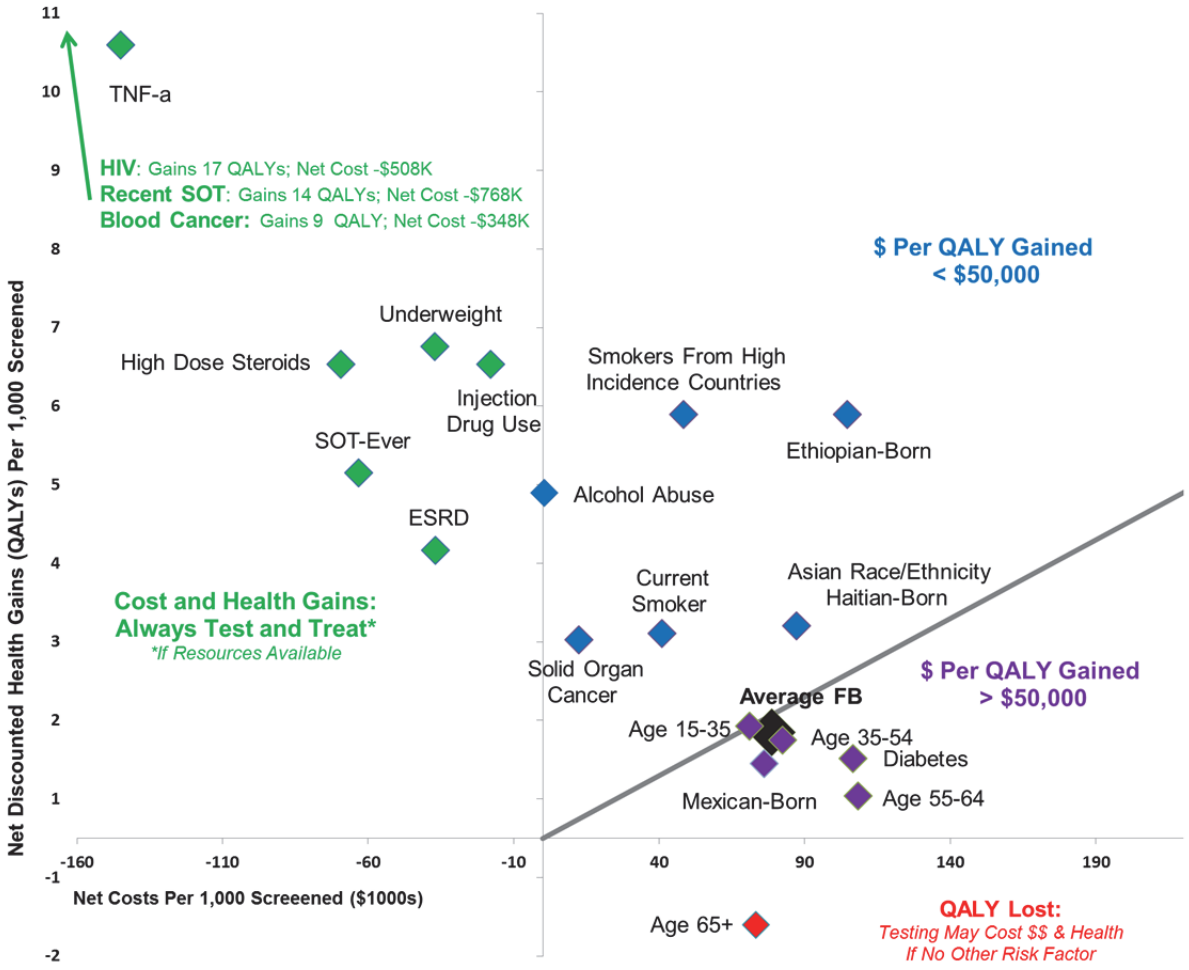
† Net discounted QALYs gained are the difference between the discounted QALYs gained from cases averted and the QALYs lost from initiating treatment.

¥ Discounted Net Costs (Costs[d]) are the discounted costs of testing and treatment associated with initiating treatment for 1,000 patients less the discounted costs of a case.

± Incremental Cost Effectiveness versus the status quo: discounted costs divided by DLE

QALY: Quality-Adjusted Life Expectancy; Cases[d]: Discounted Cases, ICER: Incremental Cost Effectiveness Ratio; Net Costs[d]:Discounted Net Costs; NNTreat: Number Needed to Test; 3% discount rate

Figure 3: Cost Effectiveness of Testing and Treating Foreign Born Subgroups for LTBI



*Discounted net costs and Quality Adjusted Life Years (QALYs) gained per 1,000 patients tested. Green diamonds represent cost-saving groups; blue diamonds represent groups that gain QALYs at a cost less than $50,000 per QALY gained; purple diamonds represent groups that gain QALYs at a cost greater than $50,000 per QALY gained; red diamonds represent groups that may lose QALYs, on average, if tested.

*FB: Foreign Born; SOT: Solid Organ Transplant; TNF-a: taking TNF-alpha inhibitor therapy; CoO: Country of Origin: Age and country of origin risk groups reflects the average FB with respect to risk factor prevalence.

7.4 Results: A Prioritization Tool for Testing and Treating FB Subgroups under Capacity Constraints

Capacity limitations impose an upper bound on the total number of risk groups that can be targeted for LTBI testing and treatment. Treatment is the rate limiting step with respect to testing and treatment costs and resources. We therefore assume that jurisdictions can always test the requisite number needed to treat those for whom they have capacity. If a jurisdiction can treat 1,000 FB persons, for example, we assume that have at least enough capacity to test (1/IGRAPositivePrevalence)*(1/Initiation_Rate)*1000 = 11,976 FB individuals.

We analyze the risk groups that can feasibly be targeted for LTBI testing and treatment in the United States during the next year under four capacity scenarios, as described in Section 5.3: 175,000, 250,000, 500,000 and 750,000 FB treatment starts. We assume that 50% of patients offered treatment will initiate (Section 5.1) and that targeting a risk group for testing will 'reach' 67.3% of the population prevalence of the risk group based on the percent of FB with health insurance (Section 5.4).

The cumulative number of treatment starts, cases averted, net costs and QALYs gained associated with targeting progressively less cost effective groups is shown in Table 15 and illustrated in Figure 4. *These results show that targeted testing can dramatically improve the impact and efficacy of testing.* Without targeting and assuming unlimited capacity, a total of 2.2 million FB would need to initiate treatment to gain about 35,800 QALYs. Targeting the top 10 risk groups (Recent SOT through Alcohol Abuse) captures 42% of those QALYs while targeting less than 10% of the overall FB population.

Table 15: Priority Risk Groups to Test and Treat Given Treatment Capacity Constraint

		If Target Entire FB Risk Group Population*				
Characteristic	**Adjusted FB Pop (Thous) †**	**Treatment Starts**	**Treatment Starts: Cumulative**	**Cases[d] Averted**	**QALYs[d] Gained**	**Net Costs[d] ($1000s)**
All FB	39,159	2,200,560	35,817	35,538	2,073,070	,073,070
Risk Groups Targeted Under Lower-Bound Capacity Scenario (175,000)						
Recent SOT	4	291	291	63	72	(2,048)
HIV Infection	125	8,222	8,512	1,422	1,890	(44,888)
Hematological Cancers	68	7,929	16,441	632	602	(33,527)
TNF-Alpha Antagonists	43	3,322	19,763	215	292	(24,947)
Injection Drug Use	144	6,894	26,657	380	608	(13,856)
Underweight	887	37,939	64,596	1,966	3,602	(18,134)
High-Dose Steroids	70	7,297	71,893	286	286	(32,333)
Post-SOT (Ever)	36	3,830	75,723	144	113	(30,210)
ESRD	98	10,700	86,423	350	241	(19,530)
Risk Groups Targeted Under the $250,000 / Year Capacity Scenario						
Alcohol Abuse	2,414	124,812	211,235	4,900	7,143	1,409
Risk Groups Targeted Under the $500,000 / Year Capacity Scenario						
Current Smokers from High Incidence Countries	1,842	204,081	415,316	4,931	4,891	122,056
Solid Organ Cancers	277	37,404	452,720	860	469	28,316
Risk Groups Targeted Under the $750,000 / Year Capacity Scenario						
Smokers – Other	5,382	318,567	771,287	7,697	9,419	359,249
CoO: Ethiopia	169	38,047	809,334	619	614	253,582
Other Priority Groups						
CoO: Viet Nam	1,260	184,044	993,378	2,996	2,972	423,351
CoO: Philippines	1,788	251,185	1,244,563	4,088	4,056	546,451
CoO: Haiti	599	70,636	1,315,199	1,150	1,141	661,470
CoO: India	1,829	205,514	1,520,714	3,345	3,319	795,186

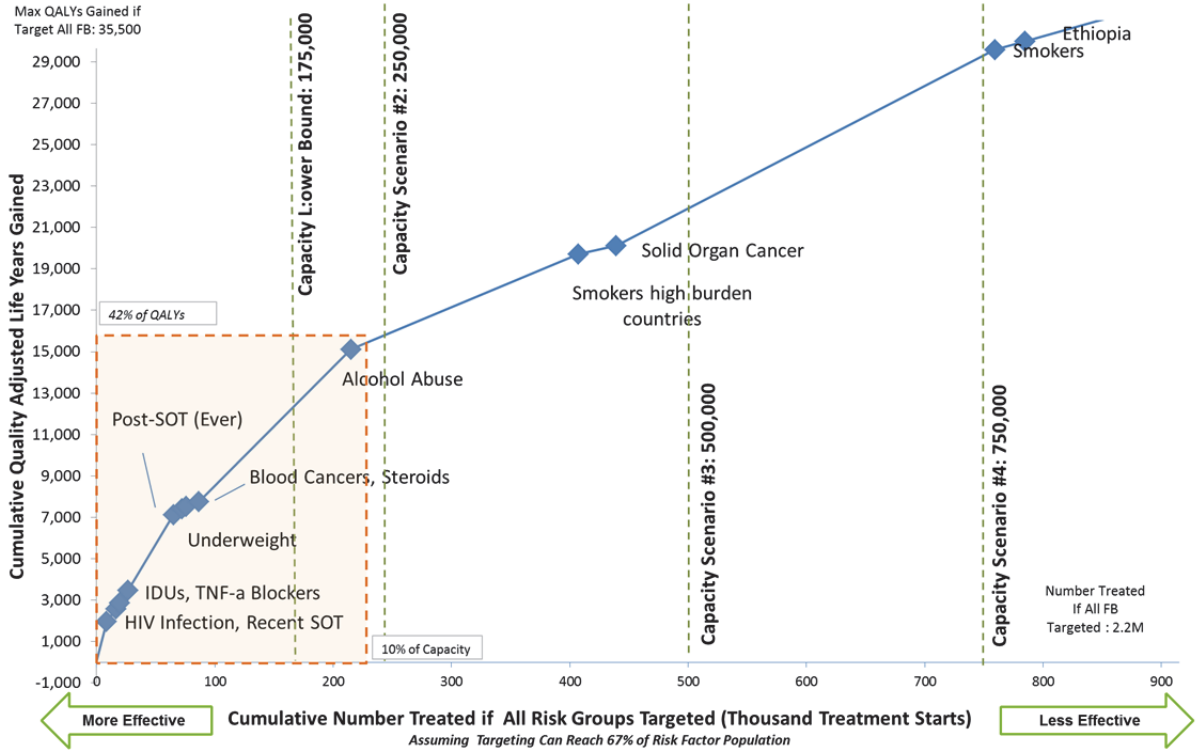
* Assuming 67.3% "reach" (for every 100 persons belonging to the risk group, targeting can test 67) and 50% treatment initiation if IGRA positive.

† Adjusting for prevalence of higher priority risk factors (e.g., Ethiopian-born without HIV and other high priority risk factors). We make the simplifying assumption that risk factor prevalence is equally distributed among the risk groups.

CoO: Country of Origin; QALY: Quality Adjusted Life Year [y]; **Net Costs[d]: Discounted Net Costs**

Figure 4 is designed to help policymakers decide which FB groups to target for LTBI testing under resource constraints. The horizontal axis is the cumulative number of persons that would initiate treatment if all risk groups to the left were targeted. The vertical axis is the cumulative amount of health gained if all groups were targeted, expressed in terms of QALYs. Risk groups are plotted according to their cost effectiveness ranking presented in Figure 4, with the higher-ranking groups appearing to the left. As such, there are diminishing returns in terms of health gained per dollar spent as policymakers move right along the horizontal axis, targeting progressively less effective groups. If capacity is limited, policymakers should target groups to the left of the capacity limit; as capacity expands, they should target the closet group to the right of that constraint, and so forth.

Figure 4: Treatment Capacity and Incremental QALYs Gained Per Risk Group Targeted*



*Groups are plotted in order of the cost effectiveness ranking presented in Table 13. Because this ranking incorporates the cost of testing, groups with exceptionally high LTBI prevalence that do not face an elevated risk of progression (e.g., Ethiopia) are included and the slope is not always progressively steeper.

7.5 Discussion

Testing and treating all FB persons in the United States is cost effective under a $100,000 per QALY gained threshold but this "universal approach" may not be feasible given limited resources for LTBI treatment and competing priorities within local health jurisdictions. Due to significant variability in the cost-effectiveness of testing and treating FB subpopulations, targeted testing can dramatically improve the impact of LTBI testing and treating among the foreign born in the United States. Forty-five percent of all potential QALYs gained from testing the foreign born can be captured by targeting approximately 10% of the FB population, including those belonging to the following subpopulations: HIV-infected, ESRD, transplant recipients, immunosuppressive therapy, hematologic cancer, low bodyweight, and injection drug use. This analysis demonstrates that testing and treating LTBI positive persons belonging to these subpopulations will generate net cost savings due to the high cost of averted cases.

Our results suggest that targeting persons with solid organ cancer, current tobacco use, alcohol abuse, as well as those from countries with extremely elevated prevalence (e.g., Ethiopia, Haiti) is more cost effective than the universal approach. Targeting diabetics is less effective than the universal approach due to shorter life expectancy and a relatively small relative risk of progression. Between the ages of 15 and 64, targeting based on age will significantly affect QALYs or cost

effectiveness: the increasing risk of LTBI with age is offset by declining life expectancy. We did not find a significant association between progression risk and age group. Testing and treating persons aged 65 and older may result in QALY losses due to short life expectancy and QALY decrements from LTBI treatment and potential toxicity. Targeting FB persons from Mexico is less effective than the universal approach given relatively low estimated LTBI prevalence.

Overall, we found that it is more effective to target groups facing an elevated risk of progression (minimizing the number needed to treat) than to target groups facing an elevated risk of infection (minimizing the number needed to test). HIV infected persons and recent SOT recipients were among the most cost-effective subpopulations, for example, due to extremely high rates of progression. Testing current smokers, while more effective than testing the average FB, was found to be less cost-effective than targeting most medical risk factor groups due to a relatively low RR of progression among smokers.

Life expectancy played an important role in our analysis. Groups facing elevated rates of progression but significantly shorter life expectancy were found to be less cost effective. For example, more health can be gained by targeting persons with low bodyweight than by targeting persons with ESRD despite a much higher progression RR associated with ESRD (RR: 12) than low bodyweight (RR: 2.9). Importantly, in the context of LTBI treatment, life expectancy matters not only due to QALY gains per case averted but also because shorter life expectancy reduces the total number of future cases that will activate within the cohort.

7.6 Limitations

This study has several limitations that should be addressed in future research. Our treatment of risk factors as binary ignores important differences in the severity or nature of the risk factor that may influence the relative risk of progression and therefore the effectiveness of testing and treating. For example, persons with insulin-dependent or poorly controlled diabetes may face an elevated risk of progression even if the average diabetic patient does not. Evidence also suggests there is a log-linear relationship between BMI and relative risk of progression. Similarly, the estimates of the RR associated with smoking and with alcohol abuse are sensitive to how these risk factors are defined. Our summary estimate synthesized studies using slightly different definitions.

Sensitivity analysis is needed to assess the influence of model parameters and assumptions on cost effectiveness. The confidence intervals surrounding our estimates of both the relative risk of progression and of LTBI prevalence by risk group are wide. Effectiveness should be assessed at the upper and lower bounds of these intervals. Moreover, the mean age of a person belonging to each risk group had a large influence on estimated effectiveness due to declining life expectancy with age. Future research should present the effectiveness of targeting risk groups stratified by age. Our assumptions regarding the LTBI treatment regimen should also be varied in sensitivity analysis to include a 9H and 3HP administered via SAT regimen. A 9H regimen, for example, may lower the

overall cost effectiveness due to poor adherence and may favor younger patients due to elevated toxicity among older patients.

The study did not adequately account for the extent to which mortality and other adverse events vary by risk factor. Our simplifying assignment of an elevated mortality and hospitalization risk to persons with *any* medical risk factor ignores important variation between risk factor groups. Moreover, we did not account for the relative risk of genotype clustering by risk group. Cases among HIV infected or younger patients, for example, may be more likely to be clustered (and therefore less likely to be attributable to reactivated disease).

Our methods for synthesizing the literature on DM and TB may have under-estimated the RR of progression associated with DM. We derived the summary estimate of the RR of progression by dividing the RR of disease derived through meta-analysis (which was positive and statistically significant) for the RR of LTBI among diabetes found on NHANES. However, some of the studies included in our meta-analysis of the RR of disease had already adjusted for covariates that increase the risk of exposure. Thus, our method may have double-counted the influence of those variables. Future research should adjust for exposure on a per-study basis prior to deriving the summary estimate.

Our estimates of the relative risk of LTBI by country of origin and our original study of relative risk of disease using CDC surveillance reports are imprecise. Due to data availability limitations, our estimates are derived from aggregate case counts and do not control for other covariates. Further study should conduct this analysis with the complete CDC dataset to control for other risk factors for exposure and/or disease.

Appendix A: NHANES Analysis Technical Appendix

IGRA Examination Subsample Weight Adjustment: Weight Adjustment to Control for Bias from Nonparticipation in the IGRA Sample

Among the 6,059 respondents to the MEC examination aged 15 and older, 5,628 responded to the survey. In un-weighted analysis, there was a 92.9% chance of participating in the IGRA examination. Applying the MEC 2-year sample weights, a representative population of 230,994,360 individuals were represented on the IGRA examination out of 244,540,589 individuals in the MEC subset aged 15 and older (the target population), corresponding to a 94.5% chance of participating in the IGRA examination.

Simple t tests of the difference in the weighted means of the IGRA subsample indicator show that the probability of participating in the IGRA tests varied significantly by MEC weight, race, age and poverty status. Aggregated test statistics for each characteristic are shown in Table A.2. Without controlling for other factors, Black and Asian respondents and respondents below the poverty threshold were significantly less likely to participate in the IGRA test while white respondents and respondents aged 25-65 were significantly overrepresented.

A logistic regression reweighting approach was used to identify and adjust for demographic and socioeconomic predictors of nonparticipation in the IGRA examination. This method involves constructing a logistic regression, using MEC 2- to predict the probability of participation based on demographic factors and socioeconomic indicators, and assign a weight to each predictor that is equal to the *inverse of the respondent's predicted IGRA participation probability*, as specified in Equation given a set of binary predictors $X_1 \ldots X_N$ [109]. The adjusted weights for respondent *i* were calculated using Equation A.2.

$$Weight_Adjustment_i = \frac{1}{P(\text{IGRA_Participation})} = \frac{1+\exp(b_0 + b_1X_1 + b_2X_2 + \cdots + b_NX_N)}{\exp(b_0 + b_1X_1 + b_2X_2 + \cdots + b_NX_N)} \quad \text{Equation A.1}$$

$$Adjusted_Weight_i = MEC_2Yr_Weight_i * Weight_Adjustment_i \quad \text{Equation A.2}$$

The original pool of variables to predict IGRA nonparticipation included MEC 2 year sample weights, the masked PSU variable, age (age 25 to 44, age 45 to 64, age 65 plus), race (Hispanic Mexican-American, Hispanic Other, Non-Hispanic Black, Non-Hispanic White and Non-Hispanic Asian), gender, foreign birth, falling below the poverty threshold, and first-order interactions between each race, age and gender group. Several permutations of the model were tested and evaluated based on the Akaike Information Criterion (AIC) and Bayesian Information Criteria (BIC), the significance of main effects, and the extent to which the adjusted weighted frequency of the IGRA hit or missed

the target population total of 244,540,589. When interaction terms were excluded, the adjusted weighted frequency of the sample typically exceeded the target population.

The final model included age, race and gender variables as well as first-order interaction terms. Parameter estimates, p-values and predicted probabilities/weight adjustments for a given predictor (holding others equal to zero) are displayed in Table A.1.

These adjusted sample weights were used to generate our estimates of LTBI prevalence overall and among the foreign born presented in Table 1 of the body of this paper.

Table A.1: Probability of Inclusion in IGRA Sample (N=7080) versus MEC sample aged 6+ (N=7821), using 2-year MEC weights

Parameter	Coefficient Estimate	Coefficient P-Value	Predicted Prob. IGRA Participation [Holding Others=0]	Weight Adjustment [Holding Others=0]
Intercept	2.485	<.0001	0.923	1.083
Female	-0.032	0.922	0.921	1.086
Black	0.422	0.310	0.948	1.055
Asian or Other Race	-0.017	0.969	0.922	1.085
Hispanic: Mexican-American	0.154	0.725	0.933	1.071
Hispanic: Other	-0.136	0.681	0.913	1.095
Age 25 to 44	0.861	0.024	0.966	1.035
Age 45 to 64	0.285	0.437	0.941	1.063
Age 65 Plus	0.793	0.051	0.964	1.038
Black * Age 25 to 44	-1.198	0.005	0.784	1.276
Black * Age 45 to 64	-0.536	0.177	0.875	1.142
Black * Age 65 Plus	-1.423	0.001	0.743	1.346
Asian * Age 25 to 44	-1.136	0.018	0.794	1.259
Asian * Age 45 to 64	-0.276	0.565	0.901	1.110
Asian * Age 65 Plus	-0.957	0.062	0.822	1.217
Hispanic-Mexican * Age 25 to 44	-0.331	0.551	0.896	1.116
Hispanic-Mexican * Age 45 to 64	0.170	0.758	0.934	1.070
Hispanic-Mexican * Age 65 Plus	-1.102	0.072	0.799	1.251
Hispanic-Other * Age 25 to 44	-0.767	0.184	0.848	1.179
Hispanic-Other * Age 45 to 64	0.358	0.546	0.945	1.058
Hispanic-Other * Age 65 Plus	-0.558	0.364	0.873	1.146
Female * Black	0.080	0.787	0.929	1.077
Female * Asian-Other	-0.439	0.214	0.886	1.129
Female * Hispanic-Other	-0.172	0.702	0.910	1.099
Female * Hispanic-Mexican Am.	0.123	0.770	0.931	1.074
Female * Age 25 to 44	0.450	0.231	0.950	1.053
Female * Age 45 to 64	0.439	0.284	0.949	1.054
Female * Age 65 Plus	-0.057	0.893	0.919	1.088

Table A.2: Difference in Weighted Probability of IGRA Subsample by Age, Race, Poverty and Foreign Birth (T-Tests)

Parameter	Difference in P(IGRA)	P-Value	Intercept: P(IGRA|No Characteristic)	P(IGRA|Characteristic)
Female	0.39%	0.6138	94.26%	94.65%
Age 15 to 24	-2.99%	0.0059	94.99%	91.99%
Age 25 to 44	1.74%	0.017	93.89%	95.63%
Age 45 to 64	0.22%	0.8021	94.39%	94.61%
Age 65 Plus	0.01%	0.9887	94.46%	94.47%
Black	-4.17%	<.0001	94.95%	90.79%
Hispanic: Mexican American	0.28%	0.77	94.44%	94.72%
Hispanic: Other	-0.10%	0.9245	94.47%	94.37%
Asian and Other Race	-1.42%	0.1102	94.57%	93.15%
White	2.32%	0.0007	92.94%	95.26%
Foreign Born	-1.34%	0.0822	94.71%	93.37%
Poverty	-3.19%	0.0012	95.31%	92.11%
2-Year MEC Weight (10,000)	0.02%	0.0113	92.61%	(Continuous)
PSU Pseudo-Variable	-0.44%	0.4311	95.13%	(Continuous)
Strata Pseudo-Variable (Rescaled)	-0.17%	0.04	95.47%	(Continuous)

Variance Adjustment for the IGRA Subpopulation Analysis

This analysis is only concerned with persons over age 6. However, rather than merely sub-setting this population, valid variance estimation must take into account the entire sample and the sample size of the created subdomain, since the properties of the subdomain may differ from the overall sample design. In SAS, this variance adjustment was accomplished by specifying that observations with missing responses were *not completely missing at random* (NOMCAR), which ensures that the full structure of the complex, multistage cluster sample is reflected in error estimates [159].

Treatment of Missing Values

Missing values for predictor variables in the LTBI risk factor model were recorded to reflect their likely value. Among the LTBI subsample, there were no missing values for age, race or gender. Missing values for predictor variables were recoded. Two respondents did not know if they were foreign born and one respondent refused. They were reclassified as US born and foreign born, respectively. The 44 participants that did not know whether they lived with someone with TB disease were classified as not being close contacts. Poverty status was unavailable for about 8% of the sample. We performed regression analysis to identify a model to impute missing values with the predicted Income-to-Poverty ratio. Race, age, foreign birth, diabetes, and weight strata and PSU variables were all significant predictors of the poverty to income ratio:

*Income-to-Poverty-Ratio = 1.55418 + 0.42101*black + 1.30727*Asian + 0.15472*Hispanic – 0.20127*FB – 0.36351*Diabetes- 0.16138*SDMVPSU – 0.03407*SDMVSTRArescaled + 0.01707*WTMEC2Yrtenthous;*

Variance and Confidence Interval Computations

Our variance estimates for IGRA positive prevalence were calculated using the Taylor linearization method. The formulas for deriving variance are shown in Equation A.3 and Equation A.4, where $\hat{p}$ is the unweighted sample proportion, $\hat{p}_w$ is the weighted sample proportion, $\hat{p}_{w,SRS}$ is the

equivalent sample proportion for a simple random sample, DEFF is the design effect, n_E is the effective sample size, and f is the sampling fraction (n/N).

$$VAR(\hat{p}_w) = \hat{p}_w \times (1 - \hat{p}_w)/n_E \text{ , where } n_E = n/DEFF \quad \text{Equation A.3}$$

$$DEFF = VAR(\hat{p}_w)/VAR(\hat{p}_{w,SRS}), \text{ where } \hat{p}_{w,SRS} = \frac{(1-f)\times(\hat{p}_w)*(1-\hat{p}_w)}{n-1} \quad \text{Equation A.4}$$

Reported 95% confidence intervals for the proportion of IGRA positive persons overall and by subgroup were calculated using the Wilson Score method, which has been shown to be more accurate than the normal approximation interval, particularly for rare events, and less prone to being overly conservative [110, 160]. The Wilson Score method also avoids the problem of negative lower confidence limits when estimating rare events, which one encounters when applying estimating confidence limits under the normal approximate interval [161]. The Wilson Score confidence interval was defined as:

$$\frac{\left(\hat{p}_w + \frac{1.96^2}{2n_E} \pm 1.96 \times \sqrt{\frac{\hat{p}_w \times (1 - \hat{p}_w)}{n_E} + \frac{1.96^3}{4n_E^2}}\right)}{1 + \frac{1.96^2}{n_E}} \quad \text{Equation A.5}$$

Data Management and Analysis Tools

Data management and analysis were conducted in SAS 9.3 (SAS Institute, Cary, NC). Adjusted LTBI prevalence and 95% confidence intervals were estimated using PROC SURVEYFREQ. PROC SURVEYLOGISTIC was used to identify LTBI risk factors and to adjust for unequal probability of IGRA test participation.

Appendix B: Meta-Analysis Synthesis and Error Estimation Methods

Meta-analyses were used throughout this paper to estimate several parameters: the overall progression rate, the relative risk of progression and /or TB disease associated with each medical risk factor, the relative risk of LTBI associated with smoking and the prevalence of LTBI among injection drug users in the United States. This appendix documents the meta-analysis methods used to compute estimates of the overall TB progression rate and the relative risk of progression by age, foreign birth and each medical risk factor.

Fixed-Effects, Random-Effects and Adjusted Fixed-Effects Meta-Analysis Models

We conducted meta-analysis and produced Forest Plots with a modified version of a Microsoft Excel spreadsheet-based template developed by Neyeloff and colleagues [118]. If there was substantial between-study heterogeneity, a random-effects model was used. If heterogeneity was low, a fixed-effect model was used [121, 118]. Heterogeneity was assessed with Cochran's Q test [122]. The formula for Q is given in Equation B., where *e*s is the point estimate and w is the study weight, equal to the inverse variance, associated with each study. If Q is higher than the critical value for the chi-squared distribution with degrees of freedom k minus 1, where k is the number of studies, heterogeneity is low and a fixed effects model can be used.

$$\mathrm{Q} = \sum (w * es^2) - \frac{[\sum w * es]^2}{\sum w} \qquad \text{Equation B.1}$$

Variations on the fixed and random-effects models were employed when pooling relative risk parameters, as described below. In addition, when synthesizing estimates of the overall progression rate a weight adjustment was required to avoid penalizing studies with relatively lower LTBI prevalence rates or higher case rates, as described below. We therefore employed five meta-analysis models, each of which are presented separately in this section: fixed-model for estimating a normally distributed parameter, fixed-effects model for estimating relative risk, adjusted fixed-effects model for estimating the progression rate, random-effects model for estimating a normally distributed parameter, and a random-effects model for estimating relative risk.

Fixed-Effects Model for Estimating a Normally Distributed Parameter (Unadjusted)

Estimates derived from the unadjusted fixed-effects model were calculated with the following steps:

1. *Identify the point estimates (es_i) and the standard error (se_i) associated with each study*. If the SE was not published we imputed the SE based on the published confidence interval and the normal approximation interval.

2. *Compute unadjusted inverse-variance individual study weights (w)*. The unadjusted individual study weight is equal to the inverse of the variance:$w = \frac{1}{se\text{^}2}$.
3. *Compute the pooled summary estimate* $(\overline{ES})$*.* The summary point estimate is equal to the weighted average of the individual point estimates.
4. *Compute the pooled standard error* $(\overline{SE})$ *and Confidence Intervals of the Summary Estimate.* The variance of the summary estimate is equal the inverse sum of the individual study weights. The formula for the standard error is shown in Equation B.2. The confidence interval constructed around the pooled summary estimate is defined as $\overline{ES} \pm 1.96 * \overline{SE}$.

$$\overline{SE} = \sqrt{\frac{1}{\sum w_i}} \qquad \text{Equation B.2}$$

Fixed-Effects Model for Estimating Relative Risk

The fixed-effects model described above assumes that the outcome of interest is normally distributed. The sampling distribution of relative risks and odds ratios deviates from normality, rendering this method inappropriate. Instead, we construct sampling weights and pooled estimates around the natural log of the relative risk, which has an approximately normal sampling distribution [162]. Following methods described in Cohn and Becker, we identify the pooled RR summary estimate and confidence interval with the following steps [163].

1. Identify the RR point estimate $\widehat{RR}$ and confidence interval from each of the selected studies.
2. Compute the natural log of the RR point estimate $LN(\widehat{RR})$ and derive the standard error, $SE(LN(\widehat{RR}))$. The equation for SE(LN(RR)) is given in Equation 6 in the main text.[61]
3. *Compute inverse-variance individual study weights (w)*. The unadjusted individual study weight is equal to the inverse of the log relative risk variance: $w_i = \frac{1}{SE(LN(RR))\text{^}2}$.
4. *Compute the pooled summary estimate*$(\overline{RR})$*.* The natural log of the pooled RR is equal to the weighted average of the RR natural logs: $LN(\overline{RR}) = \sum(w_i * LN(RR)_I)$. The summary estimate is therefore the exponentiated weighted averaged : $\overline{RR} = EXP(\sum(w_i * LN(RR)_I))$.
5. *Compute the Confidence Intervals of the Summary Estimate.* The standard error of the pooled natural logs,$SE(LN(\overline{RR}))$, is the square root of the inverse sum of weights, as shown in in Equation B.2. The 95% confidence interval around $\overline{RR}$ is given by Equation B.3.

$$95\%\ CI = EXP(LN(\overline{RR}) \pm 1.96 * SE(LN(\overline{RR})) \qquad \text{Equation B.3}$$

[61] The equation for the standard error of the log relative risk assumes the sample sides for the contingency table are known. If the sample sizes are unkown, the SE(LN(RR)) can be imputed based on the published confidence interval for the RR: SE(LN(RR))=(LN(RR)-LN(RR_LOWERCI))/1.96.

Adjusted Fixed-Effects Model for Estimates of the Overall Progression Rate

The summary estimate for the overall progression rate was derived with meta-analysis synthesizing the results of two types of studies: cohort studies, which observed a cohort of LTBI test positive persons over time and derived the progression rate by dividing the number of TB cases arising within the cohort by the LTBI positive person-years observed; and non-cohort dual population studies, which impute the progression rate by dividing total TB cases reported to the CDC by the estimated number of LTBI test positive persons based on a representative sample (typically NHANES). Differences in error estimation associated with these two types of studies complicated the assignment of study weights to each study. This section describes the novel weight-adjustment method developed to allow weight assignment that properly reflected the power of each study.

For cohort studies, the progression rate confidence interval (Ci) is determined with Wilson's method, a variation on the normal approximation interval method for a proportion (see Equation A.5 in Appendix A). The width of the CI is therefore primarily determined by the size of the LTBI positive cohort. For non-cohort dual-population studies, by contrast, the progression rate CI is determined by the upper and lower bounds of the LTBI prevalence estimate, since the cohort of LTBI positive persons is not directly observed (see Equation B.6). Since higher prevalence estimates correspond to lower progression rates, the width progression rate CI for non-cohort studies is primarily driven by the LTBI prevalence estimate, which does not reflect true variance associated with the PR estimate. Thus, a weight adjustment method was required to avoid penalizing studies with smaller prevalence estimates and to facilitate weight assignments on the basis of variance in the estimate.

Our estimate of the overall progression rate was derived from an adjusted fixed-effects model, calculated with the following steps:

1. *Identify the point estimates (es_i) and the unadjusted standard error (se_i) associated with each study*. The unadjusted SE from non-cohort studies of the progression rate (e.g., Shea, Horsburgh, our original estimate) was imputed based on the progression rate point estimate $\left(\widehat{PR}\right)$ and the upper limit of the confidence interval (PR_UpperCI) (Equation B.4), which, in turn, are determined by the LTBI Prevalence point estimate $\left(\widehat{LTBI_Prev}\right)$ and case rate (Equation B.5).[62] As demonstrated in Equation B.6, the size of the unadjusted SE of the progression rate estimate (SE(PR)_Unadjusted) is therefore largely determined by the LTBI point estimate (a lower point estimate corresponds to a larger SE; cutting the LTBI rate in half results in a ~4.5 times increase in the SE) and the case rate (a higher case rate corresponds to a one-to-one increase in the size of the SE).

$$SE(PR)_Unadjusted = \frac{\left(PR_UpperCI - \widehat{PR}\right)}{1.96} \qquad \text{Equation B.4}$$

[62] The upper limit of the progression rate estimate is used because it corresponds to the lower limit of the LTBI prevalence confidence interval, which is the standard error in the context of Wilson's score interval.

$$\widehat{PR},\ PR\ 95\%\ CI = \frac{CaseRate \times \%_Reactivated}{\widehat{LTBI_Prev}}, \frac{CaseRate \times \%_Reactivated}{\widehat{LTBI_Prev} \pm 1.96 * SE(LTBI_Prev)} \quad \text{Equation B.5}$$

$$SE(PR)_Unadjusted = \left(\frac{CaseRate}{\widehat{LTBI_Prev} - 1.96 * SE(LTBI_Prev)} - \frac{CaseRate}{\widehat{LTBI_Prev}}\right) * \frac{\%_Reactivated}{1.96} \quad \text{Equation B.6}$$

2. *Compute unadjusted individual study weights (w)*. The unadjusted individual study weight (w) is equal to the inverse of the variance: $w = \frac{1}{se\text{^}2}$.

3. *Compute adjusted individual study weights (wA).* When synthesizing literature estimates of the progression rate, a weight adjustment was required to avoid penalizing studies with larger estimates of the progression rate due to relatively low LTBI prevalence estimates and/or high case rates. As shown in Equation B.6, the unadjusted weight of evidence for progression rates is more influenced by the case rate and LTBI prevalence point estimate than the LTBI estimate standard error, with higher prevalence estimates corresponding to smaller progression rate standard errors. The consequences of not adjusting are illustrated by comparing the weights associated with the Shea 2014 study (N=7,386) and the Horsburgh 2010 study (N=447). In Shea 2014, overall LTBI prevalence was estimated to be 4.2% (95% CI 3.3-5.2) and the rate of cases due to reactivation was 4.2 per 100,000 persons. This corresponds to a progression rate estimate of 84 (95% CI 71-105, unadjusted SE: 10.5) per 100,000 person years, computed by dividing the rate of reactivated cases by the LTBI prevalence point estimate and lower and upper confidence limits [38]. In Horsburgh 2010, LTBI prevalence was 24.5% (95% CI 21.2-28.1) and the rate of reactivated cases was 22.1, corresponding to a progression rate estimate of 90 (95% CI 77-108, unadjusted SE: 8.9). In unadjusted analysis, the weight of evidence associated with the Horsburgh study would be about 50% larger (0.013 versus 0.009), despite being a much smaller study (N=447 versus N=7,386). The adjusted weight (wA) associated with progression rate estimates was derived as follows:

    a. *Compute adjusted SEs (seA) for progression rate estimates*. The adjusted SE is equal to the standard error associated with the progression rate estimate assuming a uniformly applied, standardized LTBI prevalence point estimate and TB case rate. We chose a uniform case rate of 4.0 and an LTBI prevalence point estimate of 5.4%, the average of the Shea 2014 and our original estimate for ages 15+. The SE formula is shown in Equation B.7. This method allows an apples-to-apples comparison between non-cohort studies and avoids artificially inflating the weight of studies with lower progression rate point estimates.

$$SE_PR_Adjusted = \left(\frac{3.4}{0.05 - 1.96 * \text{LTBI_SE}} - \frac{3.1}{0.05}\right)\frac{1}{1.96} \quad \text{Equation B.7}$$

    b. *Compute adjusted individual study weights (wA)*. The adjusted study weight (wA) is equal to the inverse of the adjusted variance, $wA = \frac{1}{seA\text{^}2}$.

4. *Compute the Synthesized Summary Estimate* $(\overline{es})$*.* The summary point estimate is equal to the adjusted, weighted average of the individual point estimates.
5. *Compute the Pooled Standard Error* $(\overline{SE})$ *and Confidence Intervals of the Summary Estimate.* The variance of the adjusted summary estimate is equal to the inverse of the sum of the unadjusted study weights. The standard error formula is shown above in Equation B.2. Unadjusted weights are used because they reflect the true variance associated with each individual estimate.

Random Effects Model for Estimating a Normally Distributed Parameter

If significant between-study heterogeneity was present, a random-effects model was used. The random effects model assumes that variability is due in part to underlying variability in the parameter we are estimating and thus that the true value of the parameter can vary from study to study. This is achieved by adjusting the weight of each study with a constant, the random-effects variance component (RVEC) that represents the variability in the parameter.

1. Follow steps 1 and 2 for the Fixed-Effects Model for Estimating a Normally Distributed Proportion.
2. *Compute the random-effects variance component (RVEC).* The formula for RVEC is given in Equation B.8, where k is the number of studies and Q is calculated with Equation B.8 [118].

$$RVEC = \frac{Q - (k-1)}{\sum w - \left(\frac{\sum w^2}{\sum w}\right)} \qquad \text{Equation B.8}$$

3. Compute the random-effects individual study weights (w_R). Random-effects study weights are equal to the inverse variance plus the RVEC: $w_R = \frac{1}{(SE^2 + RVEC)}$.
5. *Compute the pooled summary estimate and confidence interval*. The summary estimate is equal to the weighted average using random-effects weights. The variance is equal to the inverse of the sum of weights, as in the fixed-effects model. The confidence interval constructed around the pooled summary estimate is given by $\overline{ES} \pm 1.96 * \overline{SE}$.

Random Effects Model for Estimating Relative Risk

The random effects model for estimating relative risk is the meta-analysis model most frequently used throughout this analysis. It is combines steps 1-3 of the fixed effects model for estimating relative risk and steps 2-3 of the random effects model for estimating a normally distributed proportion. It involves all of the steps of the fixed effects model for estimating relative risk with the inclusion of the RVEC constant defined in steps 3-4 from the random-effects model for estimating a normally distributed parameter.

Error Estimation for Derived Estimates

Derived estimates are those based on the sum, difference, product or ratio of two estimators taken from different samples or models. These derived estimates also require confidence intervals. This section documents how we estimated the standard error of derived estimates and is based on statistical guidance issued in conjunction with the American Community Survey [164].

Ratio of Two Estimators

In non-cohort studies of the TB progression rate (wherein progression is not directly observed), the relative risk of progression is the ratio of two independently estimated progression rates. We cannot directly compute the RR and confidence interval associated with the risk factor for progression because the numerator (progression rate with risk factor) is not a subset of the denominator (progression rate overall or without the risk factor). The standard error for a ratio of two estimators taken from independent samples is given in Equation B.9. In the case of progression rate RRs, we use the unadjusted SEs associated with both progression rate estimates.

$$SE\left(\frac{A}{B}\right) = \frac{1}{B}\sqrt{SE(A)^2 + \left(\frac{A}{B}\right)^2 \times SE(B)^2} \qquad \text{Equation B.9}$$

Product of Two Estimators

When estimating the reactivation rate and confidence interval associated with a risk factor we multiply the baseline reactivation rate estimator by the relative risk estimator. The standard error for a product of two estimators taken from independent samples is given in Equation B.10.

$$SE(A \times B) = \sqrt{A^2 \times SE(B)^2 + B^2 \times SE(A)^2} \qquad \text{Equation B.10}$$

Sum or Difference of Two Estimators

The standard error for a sum or difference of two estimators taken from independent samples is given by the following formula:

$$SE(A \pm B) = \sqrt{SE(A)^2 + SE(B)^2} \qquad \text{Equation B.11}$$

Converting the Relative Risk Reference Group to the General Population

Because the policy context is to compare the efficacy of testing and treating a high-risk foreign born group to a random foreign born individual, our estimates of RR used the overall population as the reference category, rather than the population lacking the characteristic. Most studies publish RRs that compare the risk for a risk factor group to a group lacking the risk factor (RR_RfvsNoRF). In the general population, we imputed the RR versus the population with or without the risk factor (RR_RfvsOverall) with the conversion formula specified in Equation B.12, where *PrevRF* is the population prevalence of the risk factor. Confidence intervals for the relative risk versus the general

population were found by applying this formula to the lower and upper bounds of the confidence interval for the relative risk versus the population lacking the risk factor.

$$\text{RR_RfvsOverall} = \frac{\text{RR_RfvsNoRF}}{(\text{RR_RfvsNoRF} * PrevRF) + (1 - PrevRF)} \quad \text{Equation B.12}$$

Converting Odds Ratios to Relative Risks

For characteristics with prevalence less than 10%, we assumed that relative risks were equivalent to published odds ratios [123, 78]. For all other parameters, published odds ratios (OR) were converted to relative risks (RR) using Equation B.13, where PrevRef is the prevalence of the characteristic in the reference group.

$$\text{RR} = \frac{\text{OR}}{(1\text{-}PrevRef) + (OR * PrevRef)} \quad \text{Equation B.13}$$

Appendix C: Relative Risk of Progression by Risk Factor: Meta-Analyses and Other Methodological Considerations

1.1. Human Immunodeficiency Virus

Relative Risk of LTBI Associated with HIV Infection

We assume that HIV infected individuals face an equal risk of infection with LTBI as the general population, as there is insufficient evidence to suggest that prevalence is significantly higher among the group [36, 165]. There were 17 and 18 HIV positive subjects with LTBI test results available in 1999-2000 and 2011-2012, respectively. As shown in Table C.1, a significant association between HIV infection and LTBI was not found in 2011-2012 or in a combined analysis of both waves.

Table C.1: Relative Risk of LTBI among HIV Positive subjects on NHANES 1999-2000 and 2011-2012

	2011-2012		Combined 1999-2000 & 2011-2012	
Risk Factor & Model	**Weighted RR (95% CI)**	**Count LTBI+/Sample**	**Weighted RR (95% CI)**	**Count LTBI+/Sample**
HIV Positive, Unadjusted	1.5 (0.4-5.6)	2/18	0.7 (0.2-2.7)	2/35
HIV Positive, Age Adjusted Weighted	1.3 (0.3-5)	2/18	0.6 (0.1-2.5)	2/35
HIV Positive, Age and Birthplace Adjusted	1.7 (0.4-7.2)	2/18	0.8 (0.2-3.8)	2/35

Relative Risk of TB and Progression

HIV infection impairs cell-mediate immunity, the host's defense against the activation of LTBI. There is broad consensus that HIV infection is a risk factor for progression but literature estimates of the extent to which the risk if elevated vary widely. Our meta-analysis of the RR of progression associated with HIV infection therefore used the random-effects model presented in Appendix B.

Seven studies were selected for our meta-analysis, including two studies that controlled for LTBI status. Because the rate of LTBI is assumed to equal that among the general population, we incorporated studies that did not control for LTBI status and set the RR of progression equal to the RR of disease. Some studies have found that HIV co-infection may increase the risk of disease due to recent transmission, which would suggest that the RR of reactivated disease is lower than the RR of disease. However, we assume the percentage of cases due to reactivation is approximately equal based on the results published by Shea et al. Shea found that 10% of genotyped patients with reactivated TB and 14.1% of non-genotyped patients with reactivated TB were HIV-infected during 2006-2008, which parallels the percent of total cases that were HIV infected during that period

based on CDC reporting on the cases with HIV status available [38, 37].[63] Moreover, the case-control study conducted by Patel and colleagues did not find that HIV positive patients face a statistically significant risk of clustering (RR: 1.12, 95% CI 0.76-1.65).

Selected studies are shown in Table C.2. Our summary estimate of the RR is 17.9 (95% CI, 13.1-18.3) versus the HIV uninfected population and 16.9 (95% CI, 12.5-17.2) versus the general population. A forest plot of the 7 studies is shown in Figure C.1.

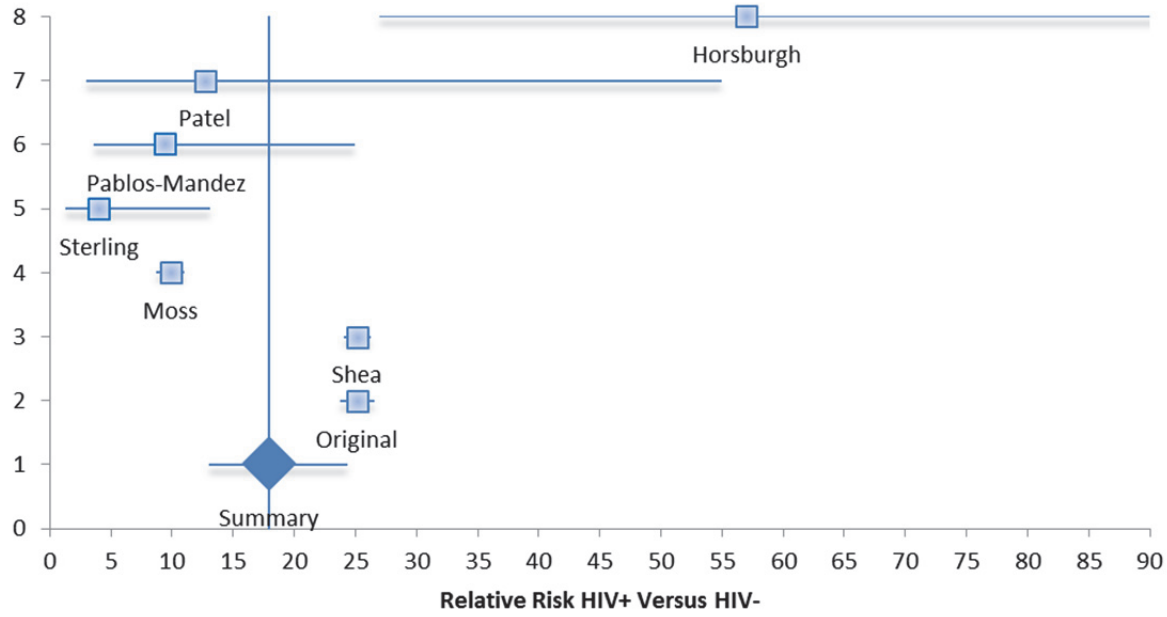
Table C.2: Relative Risk of Progression Associated with HIV Infection: A Random-Effects Meta-Analysis

Source	Methods/Notes	Study Weight: Random-Effects	RR of Progression
Original: CDC 12-13	Presented in the main text. See Table 7	9.263	25.2 (23.8-26.6) ¥
Shea 2014 [38]	2,198 reactivated cases among HIV+ (imputed) versus 16,589 reactivated cases among HIV- IN 2006-2008	9.290	25.2 (24.1-26.3) ¥
Moss 2000 [166]	Prospective cohort of 2,774 homeless in SF. 25 cases, 10 HIV+. Controlled for TST+	8.970	9.9 (8.7-11)
Sterling 2011 [94]	20 cases of TB among 7731 subject receiving LTBI therapy in randomized trial. OR Adjusting for other significant factors	2.150	4.1 (1.3 – 13.2)
Pablos-Mandez 1997 [6]	Case-control study of 5290 discharges with TB, and 37,366 control subjects. Stratified by age	2.839	9.5 (3.6-25)
Patel 2007 [105]	Case-control: 390 cases of TB in Boston matched to LTBI+ controls. Multivariate OR analysis. Controlled for LTBI.	1.540	12.7 (3-55)
Horsburgh 2010 [36]	TST survey and analysis of TB surveillance in Palm Beach County (72 cases). Progression rate of 2300 for HIV+	3.961	57 (27-120)
Selwyn 1989 [167]	Among injection drug users. PR if HIV+ was 7900. No cases developed in HIV.	Excluded – no background inc.	109.7 (59.1-160.4) ς
Summary Estimate, RR of Progression: HIV Positive versus HIV Negative			**17.9 (13.1-18.3)**
Summary Estimate, RR of Progression: HIV Positive versus General Population			**16.9 (12.5-17.2)**

¥ RR of disease. Assuming LTBI rates and the likelihood of reactivated diseases versus disease due to recent transmission does not vary. Shea SE calculated with same method as the original estimate.
± RR as presented in Horsburgh 2011 [168].
ς Assuming the rate of reactivation among HIV negative was equal to the baseline rate computed for this study.

[63] Between 2006-2008 there were 24,661 cases with HIV status available. Among them, 2,565 were HIV positive, yielding a rate of HIV infection among TB cases of 10.4%.

Figure C.1: Forest Plot of Results of 7 Studies Examining the Association between HIV Infection and TB Progression



1.2. Diabetes Mellitus

Relative Risk of LTBI among Diabetics

The epidemiological dynamics governing the relationship between DM and TB are incompletely understood [78, 3]. It is often asserted that DM influences TB risk solely through higher progression rates, owing to a lack of convincing evidence that DM is an independent risk factor for infection [6]. LTBI prevalence is higher among diabetics, as shown in our univariate analysis of NHANES and other published studies [169, 170]. However, DM and LTBI share a common set of risk factors (age, poverty, race) and at least one study has found that the influence of DM is removed when adjusting for those variables [171]. Hernandez and colleagues showed that, among patients with DM, the risk of infection is not associated with the progression of DM [86].

In our analysis of NHANES, however, DM was a significant risk factor for LTBI in adjusted and unadjusted analysis in 2011-2012 (Adjusted RR: 1.6, 95% CI 1-2.5) and in a combined analysis of both waves (Adjusted RR: 1.6, 95% CI 1.1-2.2). Results are shown in Table C.2. It is likely the case that DM is not a true independent predictor of LTBI but is instead a proxy for other socioeconomic factors (e.g., poverty) that predispose an individual to exposure. However, estimates of the RR of disease associated with DM do not control for poverty. Therefore, by dividing the RR of disease by the RR of LTBI we are in effect adjusting our pooled estimate of the RR of progression for poverty and other covariates that increase the risk of both diabetes and TB.

Table C.3: Relative Risk of LTBI among Diabetes on NHANES 1999-2000 and 2011-2012

	2011-2012		Combined 1999-2000 & 2011-2012	
Risk Factor & Model	**RR (95% CI)**	**Count LTBI+/Sample**	**RR (95% CI)**	**Count LTBI+/Sample**
Diagnosed DM, Unadjusted	2.2 (1.5-3.3)	96/630	2.1 (1.6-2.8)	139/999
Diagnosed DM, Age Adjusted	1.7 (1.1-2.6)	96/630	1.7 (1.2-2.3)	139/999
Diagnosed DM, Age and Birthplace Adjusted	1.6 (1-2.5)	96/630	1.6 (1.1-2.2)	139/999

Relative Risk of TB and Progression

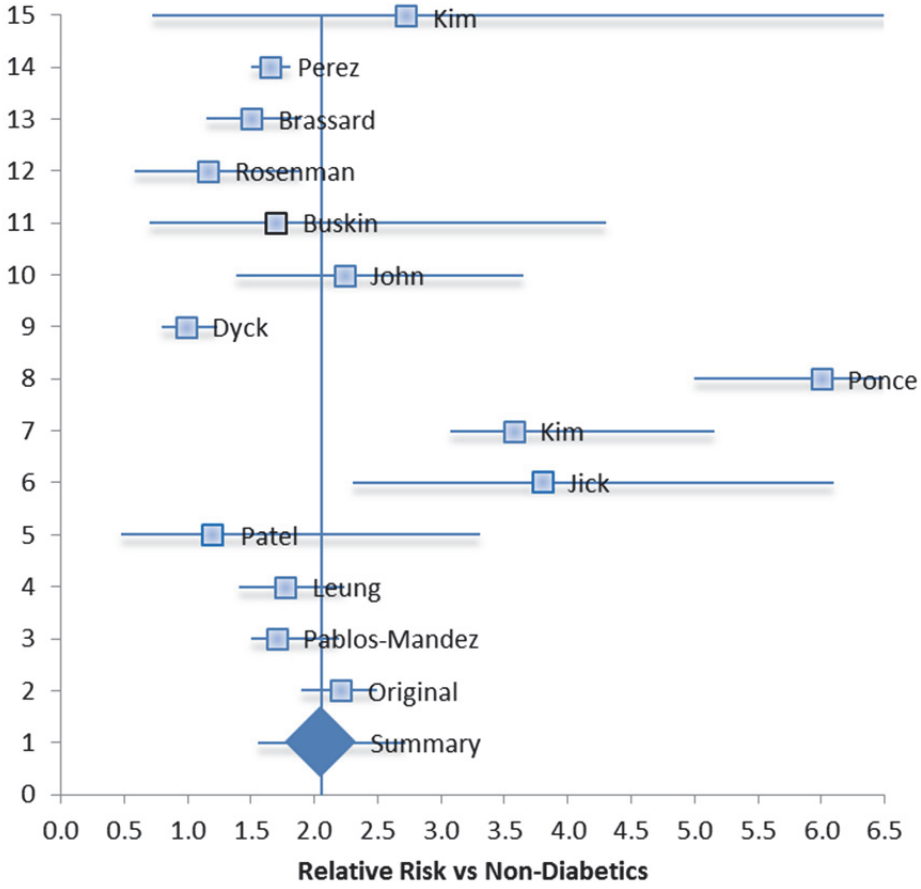
Fourteen studies were included in our meta-analysis of the relative risk of TB disease associated among diabetics. None of the fourteen studies controlled for LTBI test positive status. We therefore estimated the RR of disease and derived the RR of progression using our previously presented estimate of the RR of LTBI. We use a random-effects model due to significant between study heterogeneity. As indicated in Table C.4, several of the RR estimates were drawn from a meta-analysis published by Jeon and Murray that calculated the RRs by deriving data on background TB incidence for the study population [172].

The selected studies and our weighted estimates are shown in Table C.4. Our summary estimate of the RR of TB disease among diabetics is 2.06 (95% CI 1.56 – 2.72) relative to non-diabetics and 1.92 (95% CI 1.5-2.43) relative to the general population. Adjusting for the RR of LTBI, this suggests a statistically insignificant RR of progression of 1.26 (95% CI, 0.79 – 1.7) versus the general population. A forest plot of the 14 studies is shown in Figure C.2. There are two primary limitations to this meta-analysis. First, it does not differentiate the RR associated with insulin-dependent or uncontrolled DM. Other studies have shown that the extent to which DM may influence progression risk if determined by the severity of DM [6]. Second, some of the studies included in the meta-analysis of the RR of disease adjust for some of the factors that predict exposure risk (primarily age and race). For these studies, dividing the RR of disease by the RR of LTBI may under-estimate the RR of progression by over-adjusting for exposure risks. A better method may adjust on a study by study basis rather than adjusting the summary estimate.

Table C.4: Relative Risk of Progression Associated with Diabetes Mellitus: A Meta-Analysis

Source	Methods/Notes	Study Weight: Random-Effects	RR of Disease
Original: CDC, 2012-2013	Presented in the main text. See Table 7. Adjusts for foreign birth.	4.3	2.2 (1.9-2.5)
Pablos-Mandez 1997 [6]	Case-control study of 5290 discharges with TB, and 37,366 control. Adjusts for age, medical risk factors, poor education, foreign birth	4.3	1.7 (1.5-2.2)
Leung 2008 [173]	Cohort study. 42,659 patients aged 65+ in Hong Kong. 477 cases analyzed. Adjusts for age and sex.	4.1	1.8 (1.4-2.2)
Patel 2007 [105]	Case-control: 390 cases of TB in Boston matched to LTBI+ controls. Univariate analysis	2.2	1.2 (0.5-3.3)
Jick 2006 [174]	Case-control study of TB cases in UK in 1990-2001. 497 cases and 1966 controls. OR adjusted for immunosuppressives, smoking, BMI, pulmonary disease.	3.4	3.8 (2.3-6.1)
Kim 1995 [175] ±	Cohort study. 5105 TB cases in South Korea. Adjusts for age.	4.3	3.6 (3.1-5.2)
Ponce de Leon 2004 [176] ±	TB Cohort with separate DM survey. 581 TB cases in Veracruz Mexico from 1995-2003. Adjusts for age	4.2	6 (5-7.2)
Dyck 2007 [177] ±	TB Cohort with separate DM survey. 1118 cases in Canada. Adjusts for age, sex, race.	4.1	1 (0.8-1.2)
John 2001 [178]±	Cohort study. 166 TB cases in renal transplant patients in India 1983-2003. Adjusts for age and other medical conditions	3.4	2.2 (1.4-3.7)
Buskin 1994 [179]	Case-control. 151 cases / 545 controls. King County. Adjusts for Age.	2.3	1.7 (0.7-4.3)
Rosenman 1996 [180]±	Case-control. 148 cases / 290 controls. New Jersey. Adjusts for age, sex, race.	2.8	1.2 (0.6-1.9)
Brassard 2006 [181] ±	Retrospective Cohort. 112,300 patients with RA in U.S. 1998-2003. 386 TB. Cases. Adjusts for age, sex, immunosuppressive regimens, other medical risk factors	4.0	1.5 (1.2-1.9)
Perez 2006 [182] ±	Case-control. 3847 cases / 66,714 controls. Texas/Mexico border. Adjusts for age, sex, other medical risk factors	4.3	1.7 (1.5-1.8)
Kim 2008 [183]	Retrospective Cohort: RRs among the 1809 cases with cancer versus 1809 controls without cancer. 11 cases of TB among cancer patients. Not age adjusted	1.5	2.7 (0.7-10.3)
Relative Risk Summary Estimates: Random-Effects Model		**Vs No DM**	**Vs All**
RR of Disease = RR of Progression without adjusting for LTBI RR		2.06 (1.56-2.72)	1.92 (1.5-2.43)
RR of Progression, Adjusting for LTBI RR		1.29 (0.78-1.8)	1.26 (0.79-1.7)
±As calculated in Jeon et al [172]			

Figure C.2: Forest Plot of Results of 14 Studies Examining the Association between Diabetes and TB Disease



1.3. End State Renal Disease

Relative Risk of LTBI

Assessing the relative risk of LTBI in ESRD or hemodialysis patients is difficult due to small sample sizes on NHANES, a limited literature base, and high anergy rates to TST among the hemodialysis population [184]. Two out of 12 and two out of 19 subjects with ESRD tested LTBI positive 1999-2000 and 2011-2012, respectively.

There is some evidence to support the assumption that LTBI rates are elevated in this population. First, ESRD patients share many risk factors with diabetic patients (over 50% of ESRD patients on NHANES 2003-2012 had diagnosed diabetes). Second, a study of LTBI prevalence among a sample of ESRD patients in Taiwan showed a high prevalence of LTBI (34.4% by IGRA and 54% by TST), though the study did not compare these rates to the general population. However, due to the lack of conclusive evidence supporting the hypothesis that LTBI risk is elevated in the ESRD population, we assume prevalence is the same as the general population.

Relative Risk of TB Disease and Progression Associated with ESRD: A Meta-Analysis

We synthesized literature estimates of the RR of TB disease associated with ESRD using a random-effects model. Nine studies were selected, none of which controlled for LTBI test status. Selected studies are shown in Table C.5. We estimate that ESRD confers a risk of TB disease of 11.03 (95% CI 7.1-17.4) versus the general population. If we assume that LTBI rates do not vary, this is equivalent to the RR of progression. If we assume that ESRD patients face a relative risk of LTBI equal to that of diabetics (1.6, 95% CI 1.1-2.2), the RR of progression is 7.02 (95% CI, 4.8-9.2) versus the general population.

Table C.5: Relative Risk of Progression Associated with ESRD: A Meta-Analysis

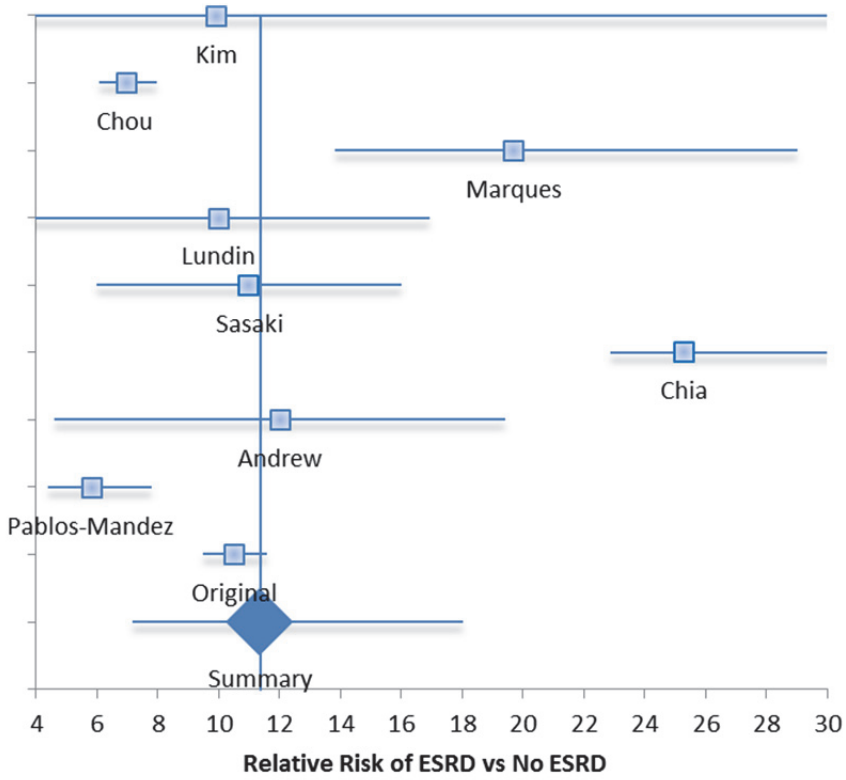
Source	Methods/Notes	Study Weight: Random-Effect	RR of Disease
Original, CDC 2012-2013	Presented in the main text. See Table 7. Adjusts for foreign birth.	2.53	10.5 (9.5-11.6)
Pablos-Mandez 1997 [6]	Case-control. 5290 cases / 37,366 controls. Adjusts for age, medical risk factors, poor education, foreign birth, diabetes. Risk associated with "chronic renal insufficiency"	2.43	5.8 (4.4-7.8) ±
Andrew 1980 [185]	Cross-sectional. 10 TB cases in 172 patients on dialysis observed over 10 years. Incidence was 12 times greater than general pop.	1.58	12 (4.6-19.4) ¥
Chia 1998 [186]	Case-control. 7 cases of TB among 560 patients on dialysis observed for 4 years. Compared to age-matched controls.	2.53	25.3 (22.9-31.5)
Sasaki 1979 [187]	Cross-sectional. T12 TB patients out of 367 patients on hemodialysis from 1967-1976. 6-16 times greater than general population of country. RR estimate is midpoint.	2.05	11 (6-16)
Lundin 1979 [188] ᶜ	Cohort. TB was diagnosed in 8 undergoing maintenance hemodialysis; incidence 10 times that of the general population.	1.33	10 (3.1-16.9)
Marquez 2008 [189]	Cross sectional. 1266 patients receiving dialysis in Brazil. TB observed in 30. Unadjusted.	2.36	19.7 (13.8-29)
Chou 2001 [190]	Cross sectional. Taiwan 1997. All newly diagnosed cases of TB among patients on dialysis. Case rate was 493.4, 6.9 times that of the general population (71.1). SEs imputed from population data.	2.52	6.9 (6.1-8)
Kim 2008 [183]	Retrospective cohort. 11 cases of TB out of 1809 cancer cases	0.63	9.91 (1.17-83.60)
Summary Estimates of Relative Risk – Random Effects Model		**Vs No ESRD**	**Vs General Pop.**
RR of Disease = RR of Progression without Adjusting for LTBI		11.37 (7.2-18.1)	11.13 (7.1-17.4)
RR of Progression, Assuming LTBI RR Equal to DM LTBI RR		7.1 (4.9-9.3)	7.02 (4.8-9.2)

± Derived from RR of progression calculated in Horsburgh 2004. [168]

¥ Confidence interval imputed based on SE for estimated TB rate in ESRD population.

ᶜ Confidence interval imputed. Assuming a background case rate of 14.7 (U.S., 1976) implies a study population of 5,442 person-years and an SE for the case rate among dialysis patients of 52.

Figure C.3: Forest Plot of Results of 9 Studies Examining the Association between Tuberculosis Disease and ESRD



1.4. Immunosuppressive Therapy and Solid Organ Transplantation

Relative Risk of LTBI

We assumed that patients receiving immunosuppressive therapy, including SOT recipients, do not experience elevated rates of LTBI. This assumption may be false. Other studies have assumed that immunosuppressive conditions increase the risk of infection and disease to a similar degree [78]. In the case of transplant recipients, other factors beyond a higher rate of reactivation likely contribute to the observed elevated risk of TB, including donor transmission of LTBI and nosocomial acquisition. Studies have shown that a high proportion of post-transplant TB patients were TST negative pre-transplant [191, 192]. However, this is more likely explained by anergy to TST in patients with end-stage organ failure than by post-transplant acquisition of infection [193]. Regardless, in terms of the estimate of the overall burden associated with the risk group, our simplifying assumption that the RR of disease is attributable only to a greater risk of progression is mathematically equivalent to disaggregating the risks between infection and disease.

Relative Risk of TB Disease and Progression Associated with Immunosuppressive Therapy

In accordance with the statement of the American Thoracic Society and the CDC on TB progression risk factors, we decompose the progression risk associated with immunosuppressive therapy into four classes of immunosuppressive therapy: tumor necrosis factor–alpha (TNF-α) antagonists, systemic corticosteroids equivalent to ≥15 mg of prednisone per day, immune suppression drug therapy following recent solid organ transplantation (SOT), lifelong maintenance immunosuppressive therapy associated with SOT, and other immune suppression therapy not captured by the aforementioned categories [90].[64] This section presents a separate meta-analysis for recent SOT recipients, defined as having had an SOT in the past year, as this category is associated with significantly higher RRs than any of the other immunosuppressive therapy classes due to more intensive immunosuppression during the first year post-transplantation.

TNF-α Antagonists, Long-Term High-Dose Corticosteroids, Post-SOT Maintenance Immunosuppression and Other Immunosuppressive Therapies

Thirteen studies were selected for our meta-analysis of the relative risk of TB disease associated with immunosuppressive therapies, including eight studies addressing TNF-alpha antagonists, five studies addressing long-term high-dose corticosteroids, one study addressing 'other' immunosuppressive therapies (principally, traditional DMARDs), and two studies addressing lifelong immunosuppression following SOT. Risks associated with recent SOT are analyzed in the following section. Long-term high-dose corticosteroids is defined as a dose of 15mg/day of Prednisone or equivalent for 2-4 weeks, as this is the dose that has been shown to suppress tuberculin reactivity, an indicator of immune suppression [194, 195]. Studies have shown that lower or intermittent doses of corticosteroids are not associated with TB risk [196].

Our meta-analysis is presented in Table C.6. As indicated, several of the RR and confidence intervals were not reported in the original publication and were imputed using data on the background incidence among the study population lacking the risk factor. Random-effects models were used for all studies with multiple categories. We found an RR of 4.7 (95% CI, 2.5-5.3) associated TNF-alpha antagonists, 3.3(95% CI 1.8-3.9) associated with long-term high dose steroids, 7.6 (95% CI 3.5-8.3) associated with post-SOT maintenance immunosuppression, and 1.2 (95% CI 1-1.44) associated with traditional DMARDs. Our overall pooled estimate of the relative risk of TB disease for all aforementioned classes of immunosuppressive therapy was 4.7 (95% CI 2.9-5.2). A forest plot of these results is shown in Figure C.4.

A limitation to this analysis is that it does not account for potential interactions between these risk factors. A retrospective cohort study of 112,300 patents with rheumatoid arthritis (RA) found that

[64] In the CDC TB surveillance data collection manual, immunosuppression is indicated if the patient had immunosuppression" due to either a medical condition or medication, such as hematologic or reticuloendothelial malignancies (e.g., leukemia, Hodgkin's lymphoma, carcinoma of the head or neck), or immunosuppressive therapy, such as prolonged use of high-dose adrenocorticosteriods (e.g., prednisone)." (CDC, 2009).

the RR of TB disease associated with disease modifying anti rheumatic drugs (DMARD) was lower among current users of corticosteroids than non-current users (0.7, 95% CI 0.3-1.38) [181].

Table C.6: Risk of TB and Progression Associated with Immunosuppressive Therapy and Long-Term Corticosteroids: A Meta-Analysis

Source	Category	Methodological Notes	RR of Disease & Progression
Original: CDC 12-13	Any, TNF, Post-SOT (Ever)	Cross-sectional. See Table 7. Case rate of 22.1. Does not significantly change when limited to foreign born.	Any: 7.4 (5.5-9.8) TNF: 6.5 (4.1-10.5) SOT Ever: 5.2 (4.9-5.4)
Askling 2005 [197]	TNF-alpha antagonists	Case-control. Sweden 1999-2000. Compared incidence of TB in 3 RA cohorts and 2 general population cohorts. Unclear if adjusted.	2.0 (1.2 – 3.4)
Keane 2001 [198]	TNF-alpha antagonists	Cross-sectional. U.S. 1998-2001. All reported TB cases after infliximab through FDA Med Watch: 70 case. ~121,000 on infliximab per year. Rate of 24.4 in Infliximab group versus 6.2 (0.6-34) in untreated RA group. RR and. SE imputed	3.9 (2.7-5.9)
Wallis 2004 [199]	TNF-alpha antagonists	Cross-sectional. U.S. 1998-2002. Granulomatous infectious associated with infliximab or Etanercept. 138 cases. Average case rate of 47.5. Higher infliximab. RR and CI imputed.	4.45 (3.71-5.19)[x]
Wolfe 2004 [200]	TNF-alpha antagonists	Case-Control. USA 1998-1999. Incidence was 6.2 (2-34) in 10,782 RA patients prior to infliximab. Case rate was 52.5 (14-134) in 6,460 RA patients treated with infliximab. RR imputed	8.47 (2.31-21.68)[x]
Gomez-Reino 2003 [201]	TNF-alpha antagonists	Cross-sectional. Spain 2000-2001. 1,357 patients treated with infliximab. 17 cases of TB. Incidence was 1503 (avg) versus background rate of 21. Incidence in RA patients not exposed to TNF blockers was 95. Avg RR vs non-infliximab RA patients.	15.8 (12.85-19.7)
Carmona 2005 [202]	TNF-alpha antagonists	Cross-sectional. Spain 2002-2003. Comparing RA patients on TNF blockers to RA patients not exposed to TNF blockers. 4,780 patient-years of exposure to TNF blockers/ 788 controls patients. 27 cases among treatment group.	6.2 (2.6-16.9)
Brassard 2006 [181]	DMARDS (Traditional, Biologics), Corticosteroids [y]	Retrospective Cohort. 112,300 patients with RA in U.S. 1998-2003. 386 TB. Cases. Adjusts for age, sex, immunosuppressive regimens, other medical risk factors. Overall rate of 219. Corticosteroid defined as > 30 days. Risk of TB declines if on steroids and DMARDS (RR: 0.7, 95% CI 0.3-1.38) vs DMART only	Biological: 1.5 (1.1-1.9) Traditional: 1.2(1.0-1.5) Steroids: 1.7 (1.3-2.2)
Jick 2006 [174]	Long Term High-Dose Steroids	Case-control; 497 TB Cases, 1,966 controls matched on age, sex. Dosage cutoff: >= 15 mg of prednisone equivalents/day.	4.9 (95% CI 2.9-8.3)
Kim 1998 [203]	Long-Term High-Dose Steroids	Retrospective. Korea 1990-1995. 269 rheumatic disease for patients with moderate to high doses of corticosteroids. ~ 4 years of observation. 21 TB cases. Incidence of TB was 2000 per 100,000 PYs. RR imputed based background incidence of TB in Korea from 1990 (164, WHO reported). RR is not age adjusted.	12.2(7.3-17.1) [x]
Cohn 1994 [204]	Long-Term High-Dose Steroids	Meta-analysis on corticosteroid use and peptic ulcers. 6602 patients (3335 on steroids and 3267 controls). 5 cases of TB all occurring in steroid group. Crude OR	1.3 (0.2-2.7)
Pal 2002 [205]	Long-Term High-Dose Steroids	Case Control. India. 143 patients on corticosteroids and 141 matched control. TB developed in 7 cases and no controls. Background incidence of 100.	2.04 (1.81-2.30)
Chen 2006 [206]	Ever Received SOT (5 years post-op): Renal	Retrospective. Taiwan 1983-2003. 756 renal transplant recipients. 29 patients had TB (+ 2 recurrent). Mean post-Tx period of 58 months. Incidence of 767 imputed assuming 5 years post-op period. RR derived from background incidence of 71.1 (Taiwan in 1997) [190].	11.4 (9.3-13.6)
Summary Estimates, RR of Disease vs General Population			
TNF-α antagonists, Random Effects (8 Studies)			**4.66 (2.45-5.3)**
Long=Term High-Dose Steroids vs General Population, Random Effects (5 Studies)			**3.33 (1.81-3.94)**
Post-SOT Maintenance Immunosuppression, Random Effects (2 Studies)			**7.56 (3.49-8.33)**
'Other' Immunosuppressive Therapies/ Traditional DMARDs, Fixed Effects (1 Study))			**1.2 (1-1.44)**
Any Immunosuppression (excluding Recent SOT), Random Effects (13 Studies)			**4.74 (2.87-5.22)**

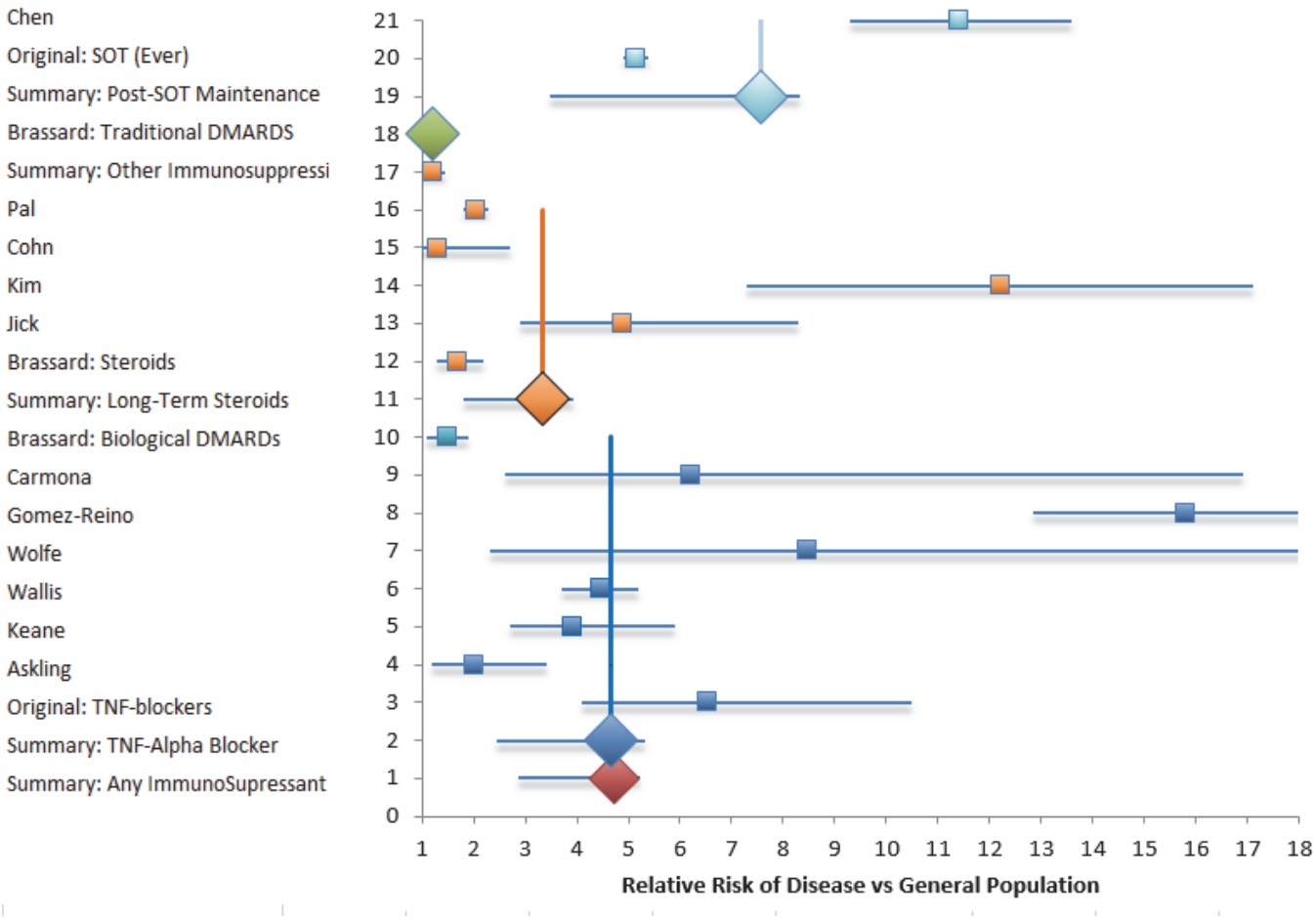
[y] DMARDS = Disease Modifying Antirheumatic Drugs. Biological DMARDS were included in the TNF-a antagonist pooled estimate because the main medications were Infliximab and Etanercept. The biological DMARD RR was used for the 'any immunosuppressive' pooled RR estimate.

[x] RR and CI imputed

[c] CI imputed

A limitation to this analysis is that it does not account for potential interactions between these risk factors. A retrospective cohort study of 112,300 patents with rheumatoid arthritis (RA) found that the RR of TB disease associated with disease modifying anti rheumatic drugs (DMARD) was lower among current users of corticosteroids than non-current users (0.7, 95% CI 0.3-1.38) [181].

Figure C.4: Forest Plot of Studies Examining the Association between Immunosuppressive Therapies and Tuberculosis Disease



Recent Solid Organ Transplant

The relative risk of TB disease associated with SOT is frequently cited as 20-74 [207]. The risk of TB associated with SOT is highest during the first year after transplantation, presumably due to greater levels of immunosuppressive therapy. Singh and Patterson found that approximately two-thirds of TB cases associated with SOT occurred during the first year after transplant [192]. A review by Munoz and colleagues found a median time to tuberculosis onset of 9 months in 61-63% of patients [207].

Four studies were examined for our meta-analysis of the association between recent SOT and TB disease including two studies exclusively addressing heart transplants, one study addressing renal

transplants and one study addressing lung, renal, kidney and heart transplants. Selected studies are shown in Table C.7.

Confidence intervals were not reported for three out of four studies and were imputed based on apparent sample sizes. Using a fixed-effects model we estimate that persons that received an SOT within the past year face a relative risk of TB disease of 34 (95% CI 27.3-42.3). We present a pooled estimate of all organs. However, it is likely that the risk varies significantly by organ. A prospective cohort study in Spain found an RR of 73 for lung transplants versus a weighted average of 27 [191]. A forest plot of these 4 studies is shown in Figure C.5.

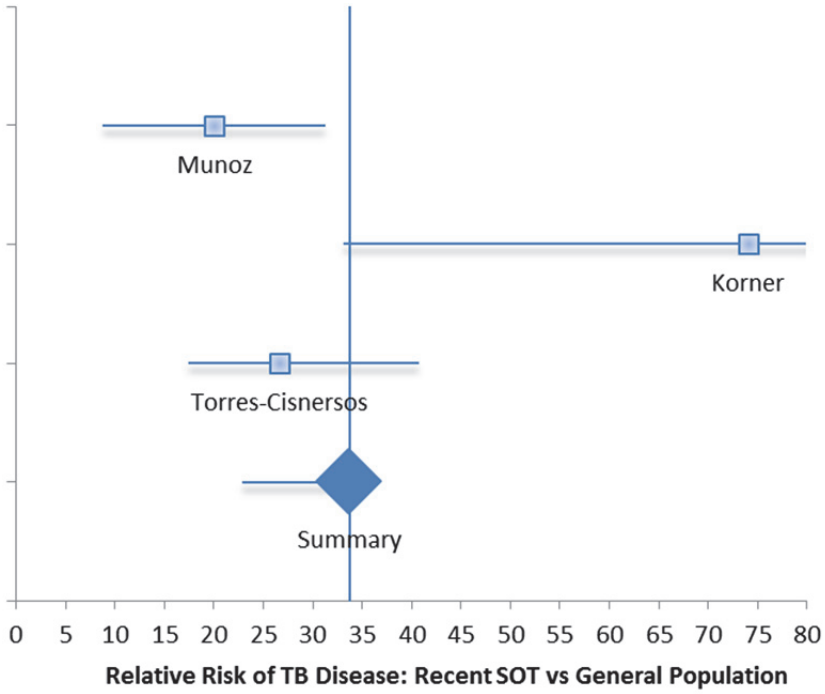
Table C.7: Risk of TB Disease Associated with Recent Solid Organ Transplantation: A Meta-Analysis

Source	Category	Methodological Notes	RR of Disease & Progression
Torres-Cisneros 2008 [191]	Recent SOT (Last Year): All	Prospective cohort. Spain 2003-2006. 4,388 SOT recipients.21 TB cases reported in median follow-up of 360 days. Global incidence was 512 (317-783). Background incidence of 18.9 Lung transplants had highest at 2072. 95% of cases occurred within 1st year post-op.	All SOT: 27 (17-41) Lung: 73 (28-194) Renal:30 (15-59) Kidney: 19(9-40) Heart: 14 (2-97)
Korner 1997 [208]	Recent SOT (Mean 15 months): Heart	Retrospective cohort. Germany 1989-1996. 716 heart transplant recipients. Followed for median 3.5 years. 7 cases of TB. TB developed in 2.5 to 41 months post-op (mean: 15). Incidence of 798 relative to a background incidence of 17.5 in Germany in 1993. CI for RR imputed based on presumed SE for incidence.*	45 (12-79) [c]
Munoz 1995 [209]	Recent SOT (Mean 3 months): Heart	Cohort. All heart transplant recipients in Madrid, Spain 1989-1993. TB diagnosed in 3/144 patients plus 9 more found in literature; incidence of 1350. Background incidence of 67. Mean time to develop TB was 76 days (range 55-102). CI imputed assuming person-year denominator of 339 (12/0.0135)	20 (9-37) [c]
Lichtenstein 1983 [210]	Recent SOT (Most within 1 year): Renal	Retrospective cohort and meta-analysis. U.S. 1980s. 47 cases reviewed. 65% of cases within first year. Minimal TB rate among renal transplant recipients is 480-530 vs background incidence of 13.1. RR CI imputed assuming a sample size of 9307 (47/0.0051)	36.6 (28-50) [c]
Summary Estimate, RR of Disease & Progression, Recent SOT Recipients, Random Effects			**31.9 (25.3-40.3)**

[c] CI imputed

*Progression rate was re-calculated. The study reports a progression rate of 1300 and an RR of 74, which is not consistent with the data. There were 7 cases within a mean person-time of 14.7 months.

Figure C.5: Forest Plot of Studies Examining the Association between Recent Solid Organ Transplantation and Tuberculosis Disease



1.5. Malnutrition / Low Bodyweight

Malnutrition increases the risk of TB disease by decreasing cell-mediated immunity, the principal means by which the host keeps TB latent [211]. Because malnutrition is a difficult risk factor to directly observe in a clinical setting, it is decomposed into observable characteristics linked to malnutrition: low bodyweight and surgeries associated with malabsorption and weight loss such as Gastrectomy and Jujeno-Ilial bypass surgery.

Relative Risk of LTBI Associated with Low Bodyweight

We assume the prevalence of LTBI among the underweight population is equal to that among the general population. Low bodyweight is not significantly associated with LTBI status on NHANES 2011-2012 or ON NHANES 1999-2000 and 2011-2012 combined (see Table C.8).

Table C.8: Association between LTBI and Low Bodyweight on NHANES

	2011-2012		Combined 1999-2000 & 2011-2012	
Risk Factor & Model	**RR (95% CI)**	**Count LTBI+/Sample**	**RR (95% CI)**	**Count LTBI+/Sample**
Low Bodyweight: Crude RR	1 (0.5-1.9)	12/159	0.6 (0.3-1.2)	18/295
Low Bodyweight: Age Adjusted	1.3 (0.6-2.8)	12/159	0.8 (0.4-1.6)	18/295
Low Bodyweight: Age and Birthplace Adjusted	1.3 (0.6-3)	12/159	0.9 (0.4-1.8)	18/295

Relative Risk of TB Disease and Progression among Underweight Persons (BMI < 18.5)

Six studies were selected for our examination of the relative risk of TB progression associated with low bodyweight including three studies that controlled for LTBI test status. Because the prevalence of LTBI is assumed to equal that among the general population, the RR of progression was equal to the RR of disease. The definition of underweight and normal weight varied by study. We selected the RR estimates that were closest to those comparing persons with a body mass index (BMI) under 18.5 kg/m² to those with a mean BMI of approximately 24-26.[65]

Selected studies are shown in Table C.9. A random-effects model was used to compute summary estimates. Our summary estimate of the RR of progression among persons with a BMI less than 18.5 is 3.3 (95% CI 2.5-4.37) versus the population with a BMI of approximately 25 and 3.13 (95% CI 2.41-4.05) versus the general population. A forest plot of the six studies is shown in Figure C.6.

This meta-analysis suffers from several limitations. To ease interpretation, we present the risk as binary. However, evidence suggests there is a log-linear relationship between BMI and tuberculosis incidence [125]. The Sterling trial, for example, found an adjusted relative risk of progression of 0.81 (95% CI 0.73-0.90) per one unit increase in BMI [94]. Moreover, selected studies are old (most performed more than 50 years ago) or in countries outside of the United States where BMI is correlated with malnutrition.

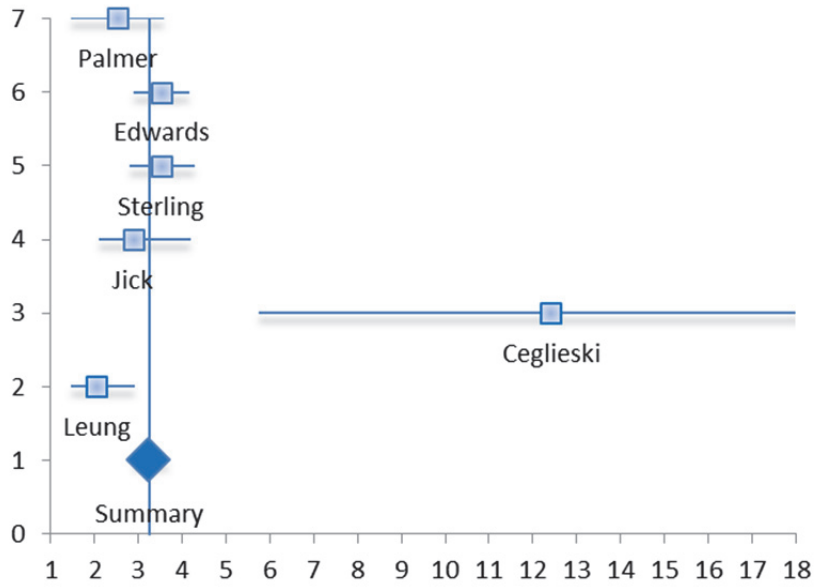
[65] The average BMI among persons over age 15 was 26.6 on NHANES 2011-2012.

Table C.9: Relative Risk of TB Disease Associated with Low Bodyweight: A Meta-Analysis

Source	Methods/Notes	Weight: Random-Effect	RR of Disease & Progression
Palmer 1957 [212]	Cohort. 23,541 TST reactors GE 10mm; 68754 total subjects age 17-21. Controls for LTBI+; < 19.1 versus median (23.7) BMI	6.23	2.53 (1.5-3.6)
Edwards 1971 [213]	Cohort. 823,199 age 17-21, 4 years follow up. Controlled for LTBI+; < 19.6 versus > 23.9 BMI	10.62	3.52 (2.9-4.2)
Sterling 2011 [94] ±	Cohort. 20 cases of TB among 7731 subject receiving LTBI therapy in randomized trial. OR Adjusting for other significant factors. RR 18.5 vs 24.5 (imputed)	10.20	3.54 (2.8-4.3)
Jick 2006 [174]	Case-control study of TB cases in UK. 497 cases and 1966 controls. OR adjusted for immunosuppressives, smoking, pulmonary disease. RR for BMI < 20	9.02	2.9 (2.1-4.2)
Cegielski 2012 [214]	Cross-sectional. 13,419 subjects, 10 years of follow up, Did not control for LTBI; BMI of 18.5 versus 18.5-25	4.19	12.43 (5.8-27)
Leung 2007 [215]	Cohort. 42,116 age ≥ 65; 5 years follow up. Did not control for LTBI+; < 18.5 versus 25-29.9 BMI	8.73	2.06 (1.5-2.9)
Summary Estimate, RR of Progression for BMI < 18.5 Versus Mean (~25)			**3.3 (2.5-4.37)**
Summary Estimate, RR of Progression for < 18.5 Versus General Population			**3.13 (2.41-4.05)**

± Sterling published the RR for a 1 unit BMI increase: 0.81 (0.73-0.9). The RR for 18.5 versus 24.5 was imputed.

Figure C.6: Forest Plot of Results of 6 Studies Examining the Association between Low Body Mass Index and Tuberculosis



1.6. Cancer

The statement issued by the CDC and American Thoracic Society identified "leukemia, lymphoma and cancers of the head, neck or lung" as risk factors for progression to TB disease [3]. Hematological malignancies (HM) – lymphomas, leukemias, and related cancers - have received particular attention and have been shown to increase the risk of TB progression through immune suppression due to either the tumor itself or the therapeutic regime [183]. Our meta-analysis of the risks associated with select malignancies is presented in Table C.11. Because the relative risk associated with HM has been found to be higher than other cancers, we distinguish between HM and solid organ malignancies (SOM). Precise definitions are provided in Appendix D.

Relative Risk of LTBI

We assume there to be no significant association between the risk of LTBI and hematological cancers due to insufficient evidence. Among the 21 subjects with HM across NHANES 1999-2000 and 2011-2012 only 1 had a positive LTBI reaction. In unadjusted analysis, there is a significant positive association between LTBI and solid organ cancers on both NHANES 2011-2012 and a combined analysis of both waves. The significance of the relationship is removed when adjusting for age. Adjusting for foreign birth strengthens the association (as discussed elsewhere, foreign birth is negative associated with SOM and positively associated with LTBI), producing an RR of 1.8 (95% CI, 0.9-3.8). However, because the confidence interval includes the null we cannot reject the hypothesis that LTBI prevalence among solid organ cancer patients is equivalent to the general population.

Table C.10: Association between LTBI and Solid Organ Cancers on NHANES 1999-2000 and 2011-2012

	2011-2012		Combined 1999-2000 & 2011-2012	
Risk Factor & Model	**RR (95% CI)**	**Count LTBI+/Sample**	**RR (95% CI)**	**Count LTBI+/Sample**
Solid Organ Cancer: Crude RR	2.7 (1.3-5.7)*	20/103	1.9 (1-3.6)*	25/182
Solid Organ Cancer: Age Adjusted	1.9 (0.9-4.3)	20/103	1.5 (0.8-2.9)	25/182
Solid Organ Cancer:: Age and Birthplace Adjusted	2.2 (0.9-5.4)	20/103	1.8 (0.9-3.8)	25/182

Relative Risk of TB and Progression

Eight studies were selected for our meta-analysis of the association between malignancies and TB progression, including two studies on solid organ malignancies, one study on hematological malignancies and six studies covering both categories. None of these studies controlled for LTBI test status. If the study did not explicitly report RRs, RRs were derived by obtaining data on average background incidence for the study population and years. Relative risks were calculated for solid organ malignancies (SOM), hematological malignancies (HM) and for either cancer ("all").

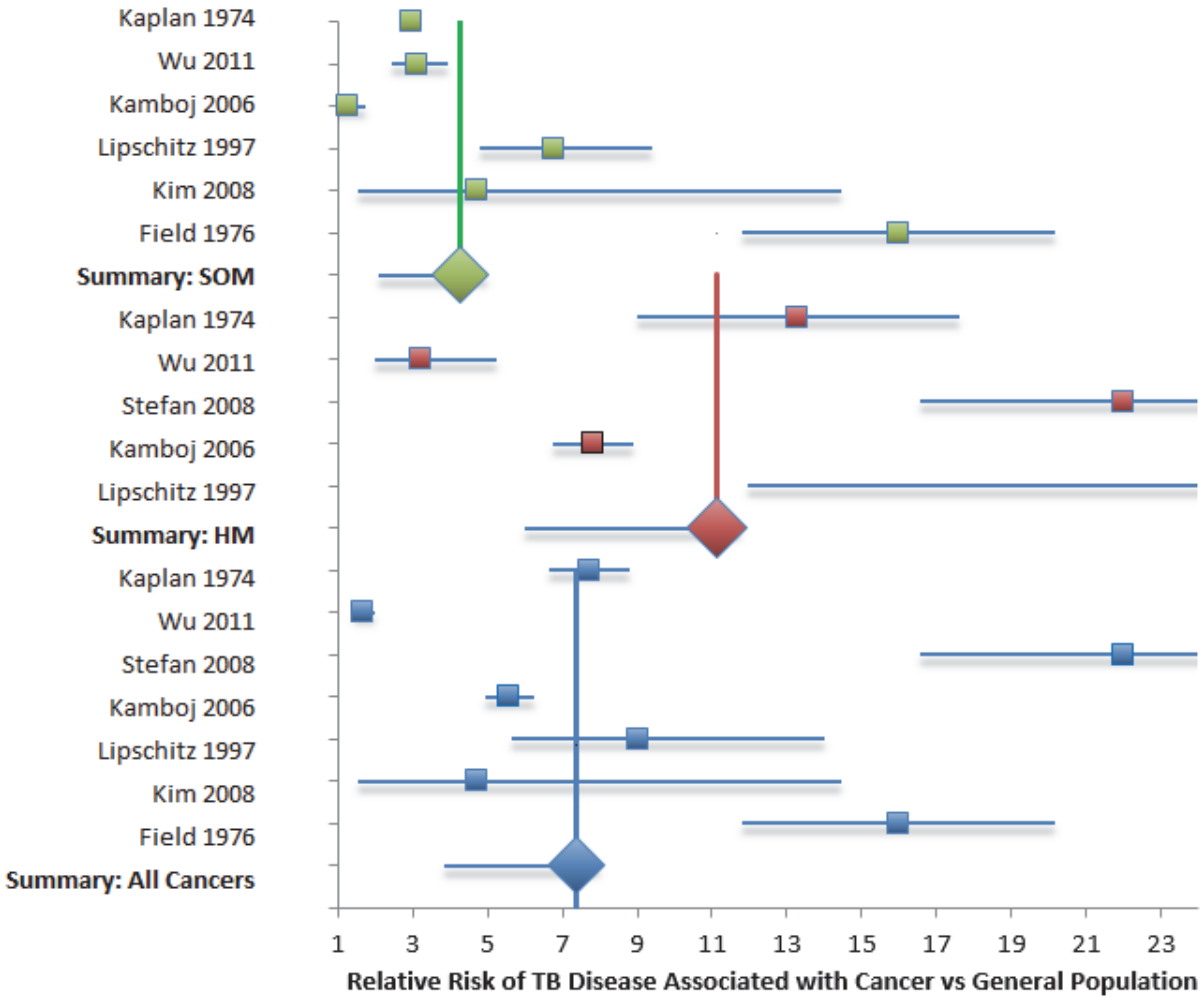
Selected studies are shown in Table C.11. A random effects model was used to compute summary estimates for each cancer type. Our summary estimate of the RR of progression and disease was

8.68 (95% CI 5.7-11.6) for all TB-related cancers, 10.23 (95% CI 6.4-14.2) for hematological cancers and 5.13 (95% RR 3-37) for solid organ cancers. A forest plot by cancer type is shown in Figure C.7.

Table C.11: Relative Risk of TB Disease and Progression Associated with Select Malignancies

Source	Cancer Type(s)	Methods/Notes	RR of Disease & of Progression*
Field 1976 [216]	Head, Neck, Lung	Retrospective. 59 TB cases in cancer patients. RR of 16. Rate of 90 with RR of 9. SE imputed assuming background incidence of 18.	SOM: 16 (11.8-20.2)
Kim 2008 [183]	Stomach, liver, lung, colon, breast	Case-control. 'Newly diagnosed' cancers. 1809 cases with cancer / 1809 controls; 11 TB cases	SOM: 4.7 (1.5-14.5)
Libschitz 1997 [217]	HM, SOM	Retrospective. 61,931 Cancer Patients; 56 TB cases. Background incidence of 10. SE was imputed.	All: 9 (5.7-14) HM: 25 (12-48) SOM: 6.8 (4.8-9.4)
Kamboj 2006 [218] ±	Cancer Patients	Retrospective. 290 TB cases among 183,843 Patients at Sloan-Kettering Cancer Center 1980-2004; Recently Diagnosed. Compared to background incidence in NYC.	All Cancers: 5.8 (4.7-6.9) HM: 7.8 (6.8-8.9) SOM: 1.3 (0.9-1.7)
Stefan 2008 [219]	Pediatric acute lymphoblastic leukemia	Retrospective. South Africa. Case Rate of 911.7 from 625 patients. SE imputed.	HM: 22 (16.6-27.4)
Wu 2011 [220]	All Cancers	Case control. Taiwan. 16 487 cancer patients / 65 948 controls matched on age and sex.	All: 1.7 (1.4-2) HM: 3.2 (2-5.2) SOM: 3.1 (2.4-3.9)
Kaplan 1974 [221] ±	All Cancers	201 TB Cases at Sloan Kettering Cancer Center 1950-1971. RRs vs NYC from background incidence on TB rates in NYC from 1950-1970 (51) [222]. RR vs U.S. imputed from average background incidence from 1953-1970 (37) [37]. RRs versus NYC were used for the meta analysis.	All vs NYC: 7.7 (6.6-8.8) All vs US: 12.3 (10.6-14) HM vs NYC: 13.3 (9-17.6) HM vs US: 21.2 (14.3-28.1) SOM vs US: 4.7 (3.6-5.9) SOM vs NYC: 3 (2.2-3.7)
Summary Estimates: All Expressed Versus General Population Using Random-Effects Model			
RR of Progression, All TB-Related Cancers (HM and SOM)) (7 Studies)			**7.36 (3.8-8)**
RR of Progression, Hematological Malignances (5 Studies)			**11.13 (6-11.7)**
RR of Progression, Solid Organ Malignancies (6 Studies)			**4.26 (2.1-5)**
*Assuming RR of LTBI is equal to that among the general population. All RRs ± RRs were derived/ not reported in publication.			

Figure C.7: Forest Plot of Results of 8 Studies Examining the Association between Tuberculosis and Hematological and Solid Organ Cancers



1.7. Cigarette Smoking

Relative Risk of LTBI among Current Smokers

When adjusting for age and birthplace, current cigarette smokers were significantly more likely to test positive for LTBI on both NHANES 2011 (RR: 1.7, 95% CI: 1-2.5) and combined NHANES 1999-2000 and 2011-2012 (RR: 1.7, 95% CI 1.3-2.2). Interestingly, the RR is higher and more significant when expanding the definition of smoking to include those that report only smoking "some days" (RR: 1.8, 95% CI 1.5-2.2 across both waves). These results are similar when conducting unweighted analysis. Results of our univariate and multivariate logistic regressions are shown in Table C.12.

Other studies have examined the relationship between smoking and LTBI and several have found a positive association. We therefore synthesized our estimate of the RR from NHANES with those of other studies with a meta-analysis. A fixed-effects model was used. Selected studies are shown in

Table C.13. Because the study by Lindsay and colleagues used NHANES 1999-2000, we used our original estimate from the 2011-2012 NHANES wave only. The summary estimate of the RR associated with smoking versus the general population was 1.53 (95% CI 1.4-1.7). A forest plot of the four studies is shown in Figure C.8.

Despite our meta-analysis suggesting an elevated risk of LTBI associated with smoking, we assume the risk is equal to that among the general population because there is not a clinical explanation for smoking, or any medical risk factor, increasing the risk of infection if exposed.

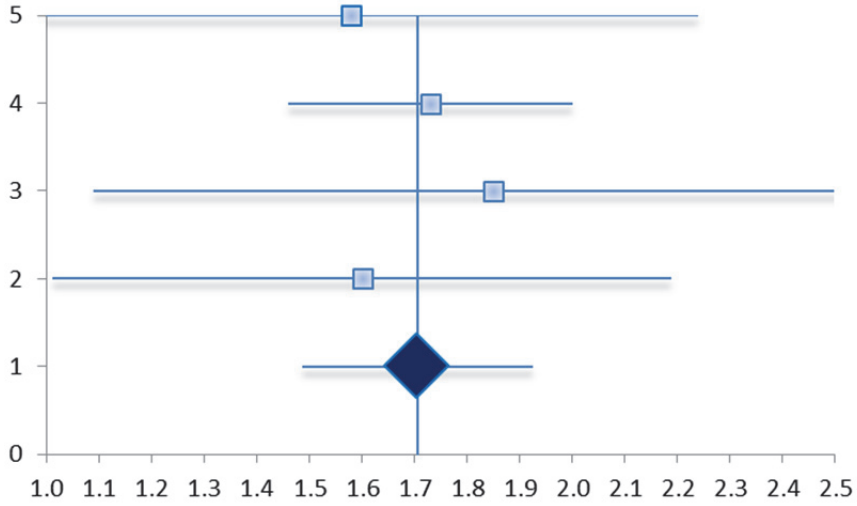
Table C.12: Relative Risk of LTBI Associated with Current Cigarette Smoking on NHANES

	2011-2012		Combined 1999-2000 & 2011-2012	
Risk Factor & Model*	**Weighted RR**	**Unweighted RR**	**Weighted RR**	**Unweighted RR**
Current Smoker, Daily: Crude RR	1.1 (0.7-1.8)	1 (0.7-1.3)	1.2 (0.9-1.6)	1.2 (0.9-1.4)
Current Smoker, Daily: Adjusted	1.6 (1-2.5)*	1.6 (1.1-2.2)*	1.7 (1.3-2.2)*	1.7 (1.4-2.1)*
Current Smoker, >= Some Days, Adjusted	1.7 (1.2-2.4)*	1.6 (1.2-2.1)*	1.8 (1.4-2.2)*	1.8 (1.5-2.1)*
*Adjusted for age and birthplace. In 2011-2012, 82/815 daily smokers were LTBI+ and 102/989 at-least-some-day-smoker were LTBI+. In both waves, 159/1475 daily smokes were LTBI+ and 194/1785 at-least-some-day smokers were LTBI+.				

Table C.13: Relative Risk of LTBI Associated with Cigarette Smoking: A Meta-Analysis

Study	**Smoking Measure/ Notes**	**Study Weight**	**RR vs Not Smoking (95% CI)**
Original: NHANES/CDC	Adult Current Daily / NHANES 11-12, IGRA, RR vs Not Smoking	18	1.6 (1-12.5)
Lindsay 2014 [223]	Adult Active Smoker + Cotinine >= 10 ng/ML / NHANES 99-00 cotinine subset, unadjusted OR, TST	14	1.85 (1.1-3.1
Bates 2007 [224]	Ever Smoker >= 1/day / Meta-Analysis, exclusive of other studies analyzed	133	1.73 (1.46-2.04)
Shin 2013 [225]	Current Smoker Regular / Salivary cotinine levels among injection drug users	13	1.58 (0.92-2.69)
Summary Estimate, RR Versus Not Smoking: Fixed Effects			**1.71 (1.48-1.98)**
Summary Estimate, RR Versus All: Fixed Effects			**1.53 (1.37-1.71)**

Figure C.8: Forest Plot of Results of 4 Studies Examining the Association LTBI and Cigarette Smoking



1: Summary; 2: Original; 3: Lindsay; 4: Bates; 5: Shin. RRs vs Not Smoking Shown

Relative Risk of TB Disease and Progression Associated with Cigarette Smoking

Seven studies were selected for our meta-analysis of the association between smoking and TB disease, including one meta-analysis that synthesized estimates from a set of studies excluded from the present analysis. As discussed in Appendix D, different measures use different measures of smoking, both in terms of current vs. past smoking and smoking frequency or exposure. We define smoking as current, regular smoking.

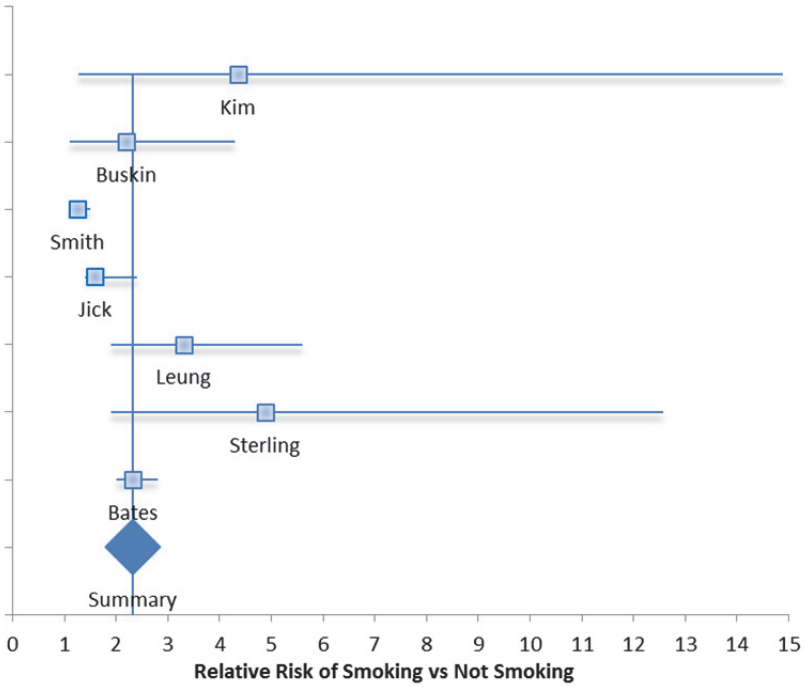
Selected studies are shown in Table C.14. Summary estimates were calculated with a random-effects model. If we assume that LTBI rates vary according to the results described above, our analysis finds that smokers face a positive but statistically insignificant risk of progression (RR: 1.19, 95% CI 0.89-1.45) versus the general population. If we assume that LTBI prevalence is equal to that among the general population, smokers face a statistically significant risk of progression of 1.75 (95% CI 1.42-2.04) versus the general population). A forest plot of the estimates of the RR of disease from these seven studies is shown in Figure C.9.

Table C.14: Relative Risk of Progression Associated with Cigarette Smoking: Literature and Original Estimates

Source	Methods/Notes	Study Weight	RR of Disease (95% CI)
Bates 2007 [224]	Meta-Analysis, exclusive of other studies in table Ag adjusted. Current or Past Smoking Most studies adjust for age, sex, some for alcohol use	9.4	2.33 (2-2.8)
Sterling 2011 [94]	Prospective Cohort; Current Smoker' not explicitly defined, 3,986 TST+ subjects/ 2,146 smokers	3.0	4.89 (1.90-12.58)
Leung 2007 [226]	Prospective cohort; smoking defined as ≥ 1/day. 435 Silicotic Patients. Current Smoking	5.6	3.3 (1.9-5.6)
Jick 2006 [174]	Case-control. UK 1990-2001. 497 cases and 1966 controls. Adjusts for DM, immunosuppression, BMI, pulmonary disease. Current smoker	9.5	Current: 1.6 (1.4-2.4) Past:0.8 (0.5-1.1)
Smith 2015 [227]	Nested Case Control. Northern California 1996-2010. 2,380 cases. Adjusts for age, birthplace.	9.5	Ever: 1.35 (1.2-1.5) Current: 1.26 (1.1-1.5) Past: 1.43 (1.2-1.7)
Buskin 1994 [179]	Case-control; at least 1 per day – from <5 per day; 151 Cases; 545 controls. Adjusts for other significant risk factors. Current Smoking	4.4	2.2 (1.1-4.3)
Kim 2008 [183]	Retrospective cohort. Does not control for age/fb; 11 Cases / 1809 cases with cancer. Current or Past Smoking	2.0	4.35 (1.27 – 14.89)
Summary Estimates of Current Smoking RR, Random Effects Model		**Vs Not Smoking**	**Vs General Population**
RR of Disease = RR of Progression Assuming LTBI Does not Vary		**2.11 (1.57-2.41)**	**1.79 (1.43-1.96)**
RR of Progression Assuming LTBI RR Derived in Table C.13		**1.23 (0.87-1.59)**	**1.19 (0.89-1.45)**

± Relative risk of progression as calculated in Horsburgh 2011 [168]

Figure C.9: Forest Plot of Results of 7 Studies Examining the Association between TB Disease and Smoking



1.8. Alcohol Abuse

Relative Risk of LTBI Associated with Alcohol Abuse

Neither current alcohol abuse nor a history of alcohol abuse was significantly associated with a positive LTBI test result on either NHANES survey with an LTBI test result. Results for persons aged 20 and older are shown in Table C.15.

Table C.15: Relative Risk of LTBI Associated with Alcohol Abuse among Persons aged 20+ on NHANES

	2011-2012		Combined 1999-2000 & 2011-2012	
Risk Factor & Model*	**Weighted RR**	**LTBI+/Sample**	**Weighted RR**	**LTBI+/Sample**
Alcohol Abuse, Ever: Crude RR	0.9 (0.7-1.2)	54/610	1.1 (0.9-1.4)	124/1184
Alcohol Abuse, Ever: Adjusted	1 (0.7-1.4)	54/610	1.2 (0.9-1.6)	124/1184
Alcohol Abuse, Current: Crude RR	0.7 (0.3-1.6)	16/270	0.8 (0.5-1.4)	36/437
Alcohol Abuse, Current: Adjusted	0.9 (0.4-2)	16/270	1 (0.6-1.7)	36/437

*Adjustments for age and birthplace.

Relative Risk of TB Disease and Progression Associated with Alcohol Abuse

A comprehensive meta-analysis of the association between alcohol abuse and tuberculosis was conducted by Lonnroth and colleagues in 2008. Since that publication was released only one published study, the Sterling 2011 trial, has addressed the association between alcohol and TB. We synthesize the estimates of both results with a fixed-effects model, yielding an RR of progression of 3.14 (95% CI 2.08-4.74) versus non-abusers and 2.8 (95% CI, 1.95-3.8) versus the general population. It is worth noting that the Lonnroth review may be defining alcohol abuse more narrowly than our population prevalence estimate (defined in Appendix D). The review found there to be a significant risk among people who drink more than 40g of alcohol per day or have an alcohol use disorder but did not find a significant association between moderate alcohol consumption and TB [228].

Table C.16: Relative Risk of TB Disease and Progression Associated with Alcohol Abuse: Literature and Original Estimates

Source	Methods/Notes	Study Weight	RR of Disease & Progression
Lonnroth 2008 [229]	Meta-analysis of 3 cohort and 15 case-control studies. Random Effects. Summary estimate did not significantly change when restricting to studies that controlled for smoking, age, HIV, sex. Alcohol abuse defined as > 40g per day or has use disorder.	19.7	2.94 (1.89–4.59
Sterling 2011 [94]	Cohort. 20 cases of TB among 7731 subject receiving LTBI therapy in randomized trial. "History of Alcohol Abuse." Crude OR.	3.1	4.8 (1.6-14.8)
Pablos-Mandez 1997	Case-control – hospital discharge. 5290 cases / 37,366 controls. Adjusts for age, medical risk factors, poor education, foreign birth, diabetes. "Alcohol related conditions."	Excluded due to alcohol abuse definition	10.4 (8.3-13)
Summary Estimate, RR of Progression: Alcohol Abuse vs No Alcohol Abuse (Fixed Effects)			**3.14 (2.08-4.74)**
Summary Estimate, RR of Progression: Alcohol Abuse vs General Population (Fixed Effects)			**2.8 (1.95-3.8)**

1.9. Injection Drug Use

Relative Risk of LTBI Associated with Injection Drug Use

The total number of current of historical injection drug users on NHANES 1999-2000 and 2011-2012 was too small to detect a statistically significant association between injection drug use and LTBI prevalence. Age and birthplace adjusted RRs are shown in Table C.17. Currently injecting is positively but not significantly associated with LTBI status in both waves.

However, other studies have found a high a prevalence of LTBI among injection drug users. We conducted a meta-analysis of four observational studies conducted in the United States and Canada and compared the weighted summary estimate to the background prevalence of LTBI test positive status among persons aged 20 in the United States.[66] Based on our weighted analysis of NHANES 2011-2012 presented in the body of this paper, we estimate that 6% (95% CI 5.1-7.1) of the population aged 20 and older is LTBI positive.

Our meta-analysis of LTBI prevalence among injection drug users is presented in Table C.17. Our random effects model estimates an LTBI prevalence of 18.32% (95% CI 13.45-23.18) among injection drug users, which corresponds to an RR of 3.06 (95% CI 2.11-4) versus the general population aged 20 and older.

Table C.17: Adjusted RRs of LTBI Associated with Injection Drug Use on NHANES

	2011-2012		Combined 1999-2000 & 2011-2012	
Risk Factor & Model	**Weighted RR**	**LTBI+/Sample**	**Weighted RR**	**LTBI+/Sample**
Injection Drug User, Current: Adjusted	4.4 (0.4-54.1)	2/10	3.6 (0.6-23.8)	3/18
Injection Drug User, Ever: Adjusted	1.4 (0.4-4.9)	9/70	1.6 (0.7-3.8)	16/121

[66] One study, Brassard 2004, was conducted in Montreal, Canada. We assume that LTBI prevalence in Montreal is comparable to LTBI prevalence in the United States due to similar case rates (4.7 in 2012 in Canada).

Table C.18: Prevalence of LTBI among Injection Drug Users in the United States and Canada, Evidence from 4 Observational Studies

Source	Methods/Notes	Study Weight	LTBI Prevalence among IDUs
Riley 2002 [230]	296 TST results read among IDUs in Baltimore, 1998-1999.Background incidence of 4.2% (Bennett 2008)	0.05	16.1 (12.5-22.4)
Grimes 2007 [231]	119 drug users (crack cocaine with 21% IDUs) in Houston tested with TST and IGRA. Prevalence slightly higher among IDUs	0.03	27.7 (19.3 – 37.5) ±
Solomon 2000 [232]	566 injection drug users in New York City tested with TST from 1995-1996.	0.06	14.0 (11.4–17.1) ±
Brassard 2004 [233]	262 injection drug users in Montreal tested with TST	0.02	22.4 (17.7–28.5)
Summary Estimate, LTBI Prevalence among IDUs, Random-Effects			**18.32 (13.45-23.18)**
Summary Estimate, RR of LTBI for IDUs Versus General Population ɣ			**3.06 (2.11-4)**

*Assumed. Average LTBI prevalence for persons aged 15 and older on NHANES. IDUs: Injection Drug Users

± As reported in Horsburgh 2011.

ɣ Assuming a background prevalence of 6% (95% CI 5.1-71) the IGRA positive prevalence among persons aged 20+ on NHANES.

Relative Risk of TB Disease and Progression Associated with Injection Drug Abuse

Three studies were selected for our examination of the association between injection drug use and TB progression. All of the studies controlled for LTBI test positive status. Two of the studies failed to find a significant association, owing in part to a small numbers of observed TB cases among injection drug users. The largest study (Selwyn et al.) prospectively measured progression among 111 TST positive injection drug users over two years, 49 of whom were HIV positive. TB disease developed in 7 HIV positive injection drug users and no HIV negative injection drug users. These results suggested a very high rate of progression among HIV positive injection drug users (approximately 7900 per 100,000) but relative risk estimates were not published. We imputed the RR by comparing the progression rate Selwyn found among HIV+ injection drug users to the background progression rate among HIV+ non-users identified in Table C.2 of the present analysis.

Our meta-analysis is shown in Table C.19. A fixed effects model was used. We found a RR of progression of 3.79 (95% CI 1.42-10.14) versus non-users and 3.76 (95% CI, 1.42-9.81) versus the general population.

Table C.19: Relative Risk of Progression Associated with Injection Drug Use: Literature and Original Estimates

Source	Methods/Notes	Study Weight	RR of Progression (95% CI)*
Selwyn 1989 [167]	Prospective Cohort. New York City 1980s. Controlled for LTBI+. 520 IDUs. 49/217 HIV+ IDUs were TST+. 62/303 HIV- IDUs were TST+. TB Developed in 7 TST+ HIV+ (progression rate of 7900) and 0 HIV-. RR imputed comparing HIV+ IDU progression rate to progression rate among all HIV found in Table C.2.	2.50	6.5 (1.9-11.2) ±
Sterling 2011 [94]	Prospective Cohort; 3,986 TST+ subjects. 20 cases of TB. 285 TST+ subjects with history of injection drug use.	0.94	1.29 (95% CI: 0.17–9.59)
Patel 2007 [105]	Case-control: 390 cases of TB in Boston matched to LTBI+ controls. Univariate analysis. IDU defined as injecting within	0.54	2.0 (0.14 – 57)

	the past 12 months. 6 TB cases among IDUs.		
Summary Estimate, RR of Progression among IDUs vs Non-Users, Fixed Effects			**3.79 (1.42-10.14)**
Summary Estate, RR of Progression among IDUs vs General Population, Fixed Effects			**3.76 (1.42-9.81)**
± Imputed, as described. IDUs: Injection Drug Users			

Appendix D: Medical Risk Factor Prevalence, Definitions and Associated Life Expectancy

To produce reliable estimates of the burden posed by risk factor sub groups, the definition of the sub group or risk factor had to be consistent across four data sources: NHANES, the CDC surveillance dataset, literature estimates of relative risk and the estimated size of the foreign born population by subgroup.

We derived prevalence estimates for the US and foreign born population aged 15 and above from five waves of NHANES spanning a 10 year period from 2003-2012, supplemented with published statistics from secondary sources. Prevalence for the overall population was estimated as follows. For risk factors with relative high prevalence that may have grown over the past decade, such as diabetes mellitus, the estimate was taken from the 2011-2012 NHANES and validated with an external source. For risk factors with relatively low prevalence lacking a reliable external source, such as immunosuppressant therapy and hematological malignancies, we estimated prevalence with five waves of NHANES surveys. For risk factors with relatively low prevalence with a more reliable external source, such as the U.S Renal Data System or CDC HIV Surveillance, we used figured published by the external source.

Prevalence among the foreign born was estimated by multiplying the overall prevalence by the relative risk of having the risk factor associated with foreign birth by 13.1%, the percent of the US population that is foreign born.[67] For each risk factor, the relative risk associated with foreign birth was estimated with bivariate logistic regression of the difference in prevalence by nativity across fives waves of NHANES (2003 – 2012). If the 95% confidence interval of the odds ratio estimate included the null, prevalence among the foreign born was assumed to be the same as the general population. Specific methods associated with each risk factor are described in the following subsections.

Because the RR of foreign birth is applied to the prevalence among the general population, our estimates of the RR assume the general population as the reference category (RR_FBvsOverall) rather than the US born population (RR_FBvsUSB). This required converting the RRs produced by logistic regression using Equation D.1.

$$\text{RR_FBvsOverall} = \frac{\text{RR_FBvsUSB}}{(\text{RR_FBvsUSB} * 0.131) * (1 - 0.131)} \qquad \text{Equation D.1}$$

This appendix also documents the methods for deriving adjusted life expectancies (LE) associated with each medical risk factor for TB disease progression. For most risk factors, LE adjustments were found by applying the standardized mortality ratio (SMR) associated with the risk factor to the

[67] In 2013 the resident population of the United States was estimated to be 316,128,839 (Census Bureau, 2013). The foreign born population was estimated to be 41,366,734 (CPS, 2014)

annual probability of death at each prevalent age, under the simplifying assumptions that the SMR is constant across ages and equal to the relative risk of death at each prevalent age of the risk factor. If an estimate of the SMR was not available within the published literature, other methods were used, such as subtracting the average years of life lost. Discounted LE by risk group was found by applying the "mixed DEALE" method described in section 6.3 to the undiscounted risk-adjusted LE. Detailed methods for estimating each of the risk-group specific LEs are described within the corresponding sub-section.

1.1. Immunosuppressive Therapy, including Solid Organ Transplant Recipients

Use of Immunosuppressive Therapy Overall and On NHANES

In accordance with the statement of the American Thoracic Society and the CDC on TB progression risk factors, we decompose the progression risk associated with immunosuppressive therapy into four classes of immunosuppressive therapy: tumor necrosis factor–alpha (TNF-α) antagonists, systemic corticosteroids equivalent to ≥15 mg of prednisone per day, immune suppression drug therapy following recent solid organ transplantation (SOT), lifelong maintenance immunosuppressive therapy associated with SOT, and other immune suppression therapy not captured by the aforementioned categories [90].[68] We distinguish between recent SOT recipients, defined as having had an SOT in the past year, and patients that have 'ever received' an SOT because the first year post operation requires more intensive levels of immunosuppressive therapy and is associated with greater relative risks of TB.

We estimated the prevalence of the four broad categories of immunosuppressive therapy by analyzing the Prescription Medication subsection of four waves of NHANES surveys spanning an 8-year period: 2005-2006, 2007-2008, 2009-2010 and 2011-2012. Several waves of survey data were analyzed to account for low raw user counts on any given wave (the total number of users of any immunosuppressive therapy category ranged between 57 and 95). Table D.1 identifies the prescription medications on NHANES that were used to code respondents within each of the four categories of immunosuppressive therapy.

The CDC and American Thoracic Society have stated that ≥15 mg of prednisone or an equivalent corticosteroid dosage administered for more than one month increases the risk of progression to TB disease. Long-term corticosteroid use was indicated only if the respondent had been taking the steroid for more than 30 days. NHANES does not provide data on medication dose. We derived the overall prevalence of high-dose, long-term corticosteroid use by multiplying our weighted estimate

[68] In the CDC TB surveillance data collection manual, immunosuppression is indicated if the patient had immunosuppression" due to either a medical condition or medication, such as hematologic or reticuloendothelial malignancies (e.g., leukemia, Hodgkin's lymphoma, carcinoma of the head or neck), or immunosuppressive therapy, such as prolonged use of high-dose adrenocorticosteriods (e.g., prednisone)." (CDC, 2009).

of the prevalence of total long-term steroid use by 25%, our estimate of the prevalence of higher-dose therapy among corticosteroid recipients receiving high doses [131].[69]

Table D.1: Immunosuppressive Medications on NHANES by Immunosuppressive Therapy Progression Risk Category

Immunosuppression Category	Associated Prescription Medications on NHANES
Post-SOT (Ever Received)	Tacrolimus, Mycophenolate Mofetil, Mycophenolic acid, Cyclosporine.
TNF-Alpha Antagonists	Adalimumab, Etanercept, Infliximab
Long-Term Corticosteroids	Prednisolone, Dexamethasone, Oral Hydrocortisone, Methylprednisolone, Prednisone, Fludrocortisone, Cortisone, Triamcinolone, Unspecified Corticosteroids
Other Immunosuppressive Drugs	Methotrexate, Omalizumab, Natalizumab, Leflunomide, Azathioprine*

*Azathioprine may also be used to prevent rejection of a kidney transplant but is typically prescribed in combination with other post-SOT immunosuppressive medications if used for that purpose.

Use prevalence by drug class was estimated with PROC SURVEYFREQ (SAS 9.3) using the 2-year interview weights and pseudo stratum and primary sampling unit (PSU) variables. Weighed use prevalence and raw user counts for five NHANES survey waves between 2003 and 2012 are shown in Table D.2. Use statistics are fairly stable from 2005-2012 but drop off significantly in the 2003-2004 wave, explained perhaps by the increasing availability and affordability of immunosuppressive medications in recent years. We therefore excluded the 2003-2004 wave in our weighted analysis of use prevalence.

[69] In the study by Van Staa and colleagues on oral corticosteroid use in the United Kingdom, 0.9% of the population was taking an oral corticosteroid (any dosage) and 0.3% of the population was receiving higher-dose corticosteroid therapy, defined as ≥ 7.5 mg of prednisolone or equivalent. The study did not publish the proportion of users taking doses ≥ 15mg per day. However, the mean daily dose was 8.1 mg per day (Van Staa et al, 2000). We therefore estimate that more than half of the higher-dose therapy group was taking ≥ 15 mg per day.

Table D.2: Immunosuppressive Therapy on NHANES over Time Among persons Aged 15 and Older: Weighted Use Prevalence and Raw Counts

	2011-2012		2009-2010		2007-2008		2005-2006		2003-2004	
Medication Name or Class: Taken Last Month	**Use Prev (%)**	**Raw Count**	**Use Prev (%)**	**Raw Count**	**Use Prev (%)**	**Raw Count**	**Use Prev (%)**	**Raw Count**	**Use Prev (%)**	**Raw Count**
Any Immunosuppressive	0.682	41	0.956	66	0.726	49	0.810	44	0.583	36
Any Post-SOT Therapy	0.041	2	0.125	7	0.026	4	0.044	1	0.050	2
Any TNF-alpha Antagonist	0.081	2	0.065	4	0.069	3	0.227	8	0.046	2
Corticosteroids > 30 Days	0.722	52	0.604	68	0.655	51	0.958	55	0.725	51
Corticosteroids > 30 Days – High Dose*	0.181	13	0.151	17	0.164	13	0.239	14	0.181	13
Other Immunosuppressant	0.380	24	0.616	38	0.467	29	0.300	21	0.306	19
Tacrolimus	0.068	7	0.138	10	0.126	7	0.003	1	0.028	2
Mycophenolic_Acid	0.125	12	0.120	10	0.107	8	0.097	3	0.085	5
Sirolimus	.	.	.	.	0.002	1	0.003	1	0.007	1
Cyclosporine	0.007	1	0.028	2	0.052	3	0.097	3	0.007	1
Adalimumab	0.087	3	0.051	4	0.037	2	0.106	3	0.005	1
Etanercept	0.068	1	0.198	8	0.059	3	0.174	6	0.129	5
Infliximab	0.013	1	0.077	3	0.034	1	0.035	1	.	.
Prednisolone > 30 Days	0.023	2	.	.	0.025	2	.	.	0.027	2
Dexamethasone > 30 Days	0.104	6	0.009	1	.	.	0.087	3	0.040	2
Hydrocortisone > 30 Days	0.016	2	0.099	7	0.063	6	0.087	3	0.046	3
Methylprednisolone > 30 D	0.073	1	0.024	3	0.006	1	0.062	2	0.064	3
Prednisone > 30 Days	0.599	47	0.612	62	0.530	47	0.600	41	0.582	41
Fludrocortisone > 30 Days	0.042	3	0.043	3	0.008	2	0.036	3	0.043	3
Cortisone > 30 Days	.	.	.	.	0.081	2	0.010	1	0.008	1
Triamcinolone > 30 Days	.	.	0.023	5	0.092	5	0.201	10	0.227	13
Azathioprine	0.051	5	0.036	3	0.112	6	0.095	4	0.057	3
Methotrexate	0.219	13	0.483	31	0.306	21	0.191	14	0.232	16
Omalizumab	.	.	.	.	.	.	0.005	1	.	.
Natalizumab	.	.	0.028	1	0.037	1	.	.	.	.
Leflunomide	0.112	6	0.068	3	0.013	1	0.008	2	0.044	1

*Assuming that 25% of persons taking prolonged corticosteroids are taking doses >= 15mg/day, as described in the text.

Our weighted analysis suggests that 0.794 percent (95% CI 0.59-0.86) of the U.S. civilian population aged 15 and older is taking an immunosuppressive that places them at risk greater for TB progression. Prevalence by immunosuppressive class is shown in Table D.3.

The total population of persons at risk was found by multiplying the target population (244,540,589) by the weighed use prevalence on NHANES 2005-2012 [108]. The population of foreign-born persons receiving immunosuppressive therapy was derived by multiplying these figures by the fraction of the U.S. population that was foreign born in 2012 by the relative risk associated with foreign birth (see Table D.4).[70] Our final estimates of the prevalence of immunosuppressive use by category and by drug are shown in Table D.3.

[70] In 2013 the resident population of the United States was estimated to be 316,128,839 (US Census Bureau, 2013). The foreign born population was estimated to be 41,366,734 (US Census Bureau, 2013).

Table D.3: Estimated Prevalence of Immunosuppressive Therapy Use in the United States among persons Aged 15 and older from NHANES, 2005-2012

Therapy in Last Month	Est. Use Prev Overall (%)	Use Prev 95% CI	Est. Overall Pop Using Drug	Est. FB Pop using Drug	Raw Count on NHANES
Any Immunosuppressive	0.794	(0.59-0.86)	1,940,552	354,927	200
Any Post-SOT (Ever Received)	0.059	(0.03-0.12)	144,523	44,802	14
Any TNF)Alpha Antagonist	0.109	(0.07-0.18)	267,527	82,933	17
Corticosteroids > 30 Days	0.733	(0.61-0.89)	1,792,483	227,825	226
Corticosteroids > 30 Days – High Dose*	0.183	(0.15-0.22)	448,121	56,956	57
Other Immunosuppressant	0.442	(0.34-0.57)	1,080,380	157,411	112
By Drug					
Tacrolimus	0.084	(0.05-0.14)	205,659	63,754	25
Mycophenolic_Acid	0.112	(0.07-0.17)	274,619	85,132	33
Sirolimus	0.001	(0-0.02)	3,424	1,061	2
Cyclosporine	0.045	(0.02-0.1)	110,777	34,341	9
Adalimumab	0.070	(0.04-0.14)	171,667	53,217	12
Etanercept	0.124	(0.08-0.2)	303,964	94,229	18
Infliximab	0.040	(0.02-0.09)	96,838	30,020	6
Prednisolone > 30 Days	0.012	(0-0.03)	29,345	3,730	4
Dexamethasone > 30 Days	0.050	(0.02-0.12)	122,026	15,509	10
Hydrocortisone > 30 Days	0.066	(0.04-0.12)	161,152	20,482	18
Methylprednisolone > 30 Days	0.041	(0.01-0.12)	100,506	12,774	7
Prednisone > 30 Days	0.586	(0.49-0.69)	1,431,785	181,980	197
Fludrocortisone > 30 Days	0.032	(0.02-0.06)	78,742	10,008	11
Cortisone > 30 Days	0.023	(0.01-0.08)	55,022	6,993	3
Triamcinolone > 30 Days	0.078	(0.05-0.13)	190,497	24,212	20
Azathioprine	0.073	(0.04-0.12)	179,004	26,081	18
Methotrexate	0.300	(0.22-0.41)	734,600	107,031	79
Omalizumab	0.001	(0-0.02)	3,179	463	1
Natalizumab	0.016	(0-0.06)	39,860	5,808	2
Leflunomide	0.051	(0.02-0.11)	124,471	18,135	12

*Assuming that 25% of persons taking prolonged corticosteroids are taking doses >= 15mg/day, as described in the text.

These results align reasonably well with sales volume data, which is publically available for the top 100 prescribed medications in the United States. For example, our analysis suggests that 171,667 persons in the United States took Adalimumab, trade name Humira, in the last month. In 2011, Humira sold 2,450,000 units, or about 204,167 units per month [234]. Humira is administered once every two weeks or less frequently for maintenance dosing.

Immunosuppressive Therapy among the Foreign Born

We conducted weighted logistic regressions to determine whether the prevalence of immunosuppression therapy varied among the foreign born. Results are shown in Table D.4. Foreign birth is negatively associated with the prolonged use of corticosteroids (RR: 0.41, 95% CI: 0.26-0.66) and with the use of “other” immunosuppressant therapy (RR: 0.41, 95% CI 0.23-0.9).

Table D.4: Difference in the Weighted Probability of Immunosuppressive Therapy by Nativity, NHANES 2003 – 2012

Risk Factor	Prev: All	Prev: US Born	Prev: FB	RR vs US Born (95% CI)	RR vs All (95% CI)	Overall Raw Count	FB Raw Count
Any Immunosuppressive	1.30%	1.40%	0.78%	0.56 (0.36-0.85)*	0.59 (0.39-0.87)	443	63
Any Post-SOT Therapy	0.06%	0.01%	0.01%	0.9 (0.18-4.59)	0.91 (0.2-3.12)	16	4
Any TNF-Alpha Antagonist	0.10%	0.09%	0.22%	2.71 (0.76-9.71)	2.21 (0.78-4.54)	19	6
Other Immunosuppressant	0.42%	0.46%	0.20%	0.44 (0.23-0.87)*	0.48 (0.25-0.88)	20	131
Corticosteroids > 30 Days	0.73%	0.81%	0.32%	0.4 (0.26-0.61)*	0.43 (0.28-0.65)	277	33

Prevalence of Recent Solid Organ Transplantation

Our estimate of the population of persons having recently received an SOT (within the past year) was taken from the Organ Procurement and Transplantation Network. In 2013 in the United States, 28,954 persons, approximately 0.01% of the population, received a solid organ transplant [130]. We assumed that the likelihood of recently receiving an SOT does not vary by nativity based on the results presented in in Table D.4.

Prevalence of Solid Organ Transplant Survivors ("Ever Received")

Our analysis of NHANES 2005-2012 suggests that 0.06 (95% CI 0.03-0.12) percent of the population age 15 and older is currently taking post-transplantation immunosuppression therapy (see Table D.3). However, this may under-estimate the total number of transplant survivors because the NHANES list of medications is not comprehensive. Moreover, the wide confidence interval limits inference. We estimate the total number of SOT survivors in the United States based on 10-year survivor data provided by the Organ Procurement and Transplantation Network (OPTN), supplemented with estimates from the literature for 20 year survival rates. The weighted average survivor rate at 1, 3, 5, and 10 years was 94%, 88%, 82%, and 64%, respectively [130]. There were 28,954 SOT recipients in 2011, 28,461 in 2009, 28366 in 2007, 24,910 in 2002, 22,013 in 2000, 19,747 in 1997, 19,390 in 1995 and 17,640 in 1993 (1992 data is unavailable) [235, 130]. OPTN does not provide survival data post 10 years. However, a study on liver transplantation found 21% survival (S.E. of ~3.5%) at 20 years [236]. We assume that, for those that survive 20 years post-operation, life expectancy is equal to that among the general population. Incorporating this estimate we project that 252,386 living persons in the United States are non-recent SOT survivors, including 27,214 that received an SOT in the past year. These estimates correspond to a prevalence of non-recent SOT survivors of 0.092% (95% CI 0.090-0.094%).

Life Expectancy Adjustments Associated with Solid Organ Transplantation

The average age of a transplant recipient in 2011 was 48.7. The weighted mean survival rates at 1, 3, 5 and 10 years post-transplant for all solid organ transplants are 94%, 88%, 82%, and 64%, respectively [130]. Based on the study referenced in the prior section we assume that 21% survive to 20 years post-transplant [236]. We assume that the surviving 21% experience mortality rates

similar to those among the general population at age 69. These data suggest that the average (recent) transplant recipient has about 10.8 undiscounted and 8.9 discounted remaining life years and that the mean age of a transplant survivor (non-recent) is 58.8. At 59 years old, the transplant survivor has approximately 8 undiscounted and 6.9 discounted LYs remaining.

Life Expectancy Adjustments Associated with Immunosuppressive Therapy/Rheumatoid Arthritis

We assume that the life expectancy adjustment for persons receiving non-transplant related immunosuppressive therapy is equal to the life expectancy adjustment for Rheumatoid Arthritis (RA) patients. A cohort study following RA patients from 1955 to 1994 found a standardized mortality ratio (SMR) of 1.27 (95% CI 1.13-1.41) for RA patients over the age of 18 [154]. Applying this SMR to the 2010 life tables and assuming that immunosuppressive therapy was initiated at age 45 we find an undiscounted adjusted life expectancy of 30.0 (95% CI 29-31.1) for TNF-alpha antagonist recipients (mean age 50), 222.6 (95% CI 21.7-23.6) for persons receiving 'other' immunosuppressant therapy (mean age 59), and 23.4 (95% CI 22.5-24.4) for persons receiving long-term high-dose corticosteroids and for the average person taking any immunosuppressant (mean age 58).

1.2. Diabetes Mellitus

Diabetes Prevalence Overall

Diabetes Mellitus is defined for the purpose of this analysis as having diagnosed Type I or Type II diabetes mellitus.[71] Table D.5 shows the estimated prevalence of diagnosed diabetes among persons aged 15 and older on five waves of NHANES surveys from 2003 to 2012.

Table D.5: Diagnosed Diabetes Mellitus among persons Aged 15 and Older on Five Waves of NHANES Surveys, 2003 – 2012

Characteristic/Wave	Est. Overall Prevalence (%)	Prevalence 95% CI	Est. Pop With Dx DM	Est. FB Pop with Dx DM	Raw Count on NHANES
Diagnosed Diabetes – 2003 to 2004	7.18	(6-8.56)	17,548,233	2,298,818	552
Diagnosed Diabetes – 2005 to 2006	7.16	(6.26-8.19)	17,513,019	2,294,205	514
Diagnosed Diabetes – 2007 to 2008	8.04	(6.71-9.59)	19,652,260	2,574,446	765
Diagnosed Diabetes – 2009 to 2010	7.83	(6.95-8.89)	19,152,419	2,508,967	731
Diagnosed Diabetes – 2011 to 2012	8.54	(7.46-9.75)	18,994,690	2,488,304	707
Diagnosed Diabetes – All/2003-2012	7.77	(7.29-8.27)	18,582,639	2,434,326	3269

Our analysis suggests that 8.54 (95% CI 7.46-9.75) percent of the U.S. population aged 15 and older had diagnosed diabetes in 2011-2012. Expanding the sample to persons aged 1 and older we find a prevalence of 6.9% 6.9% (95% CI 6.1-7.9). These results were validated by comparing them to

[71] Diabetes mellitus is a risk factor on the CDC TB surveillance dataset if the patient had a "diagnosis of diabetes mellitus (Type I or Type II) either before or at the time of TB diagnosis" (CDC, 2009).

statistics published in the 2014 CDC National Diabetes Statistics Report, based on data from the National Health Interview Survey. The CDC estimates that in 2012 9.3% of the population had diabetes, including 21 million people (6.7%) with diagnosed diabetes and 8.1 million people (2.6%) with undiagnosed diabetes [127].

Diagnosed Diabetes among the Foreign Born

To assess whether the prevalence of DM among the foreign born is significantly different from that among the general population we conducted weighted logistic regression to of the probability of being diagnosed with DM by nativity across five waves of NHANES. As shown in Table D.6 foreign birth is not a significant predictor of diagnosed DM. We therefore estimate that there were 2.777,066 foreign born persons over the age of 15 with diagnosed DM in 2011-2012 based on the total number of persons with diagnosed DM (21,198,979) and the proportion of the overall population that is foreign born (13.1%).

Table D.6: Difference in Diagnosed Diabetes Mellitus by Nativity among Age 15+, NHANES 2003 – 2012

Risk Factor	Prev: All	Prev: US Born	Prev: FB	RR vs US Born (95% CI)	RR vs All (95% CI)	Overall Raw Count	FB Raw Count
Diagnosed Diabetes	7.60%	7.60%	7.65%	1.01 (0.87-1.16)	1.01 (0.89-1.14)	3268	805

Life Expectancy Adjustment

In a case-control study using data from the Framingham Heart Study, Franco et al found that diabetic men and women age 50 and older live on average live 7.5 (95% CI, 5.5-9.2) and 8.2 (95% CI, 6.1-10.4) years less than their non-diabetic equivalents [151]. Assuming that approximately 50% of the diabetic population is male, this represents an average reduction in life expectancy of 7.9 years (95% CI, 6.4-9.3). This estimate is similar to those found in prior studies. Gu et al found a median life expectancy reduction of 8 years for diabetics between the ages of 55 and 64. The average age of a diabetic over the age of 15 was 59 on NHANES 2003-2012.

1.3. End Stage Renal Disease

ESRD Prevalence Overall and on NHANES

End stage renal disease (ERSD) is defined as stage 5 chronic kidney disease (CKD) requiring dialysis or transplantation, consistent with the definition used for CDC TB surveillance.[72] Literature estimates of the relative risk of TB associated with renal disease typically address the population receiving dialysis, as described in the technical appendix documenting the literature review for each

[72] ESRD is indicated as a risk factor on the CDC surveillance dataset if the patient had end-stage renal disease or chronic renal failure at the time of TB diagnosis. The CDC manual defines ESRD as " condition when chronic kidney failure has progressed to the point where kidney function is less than 10% of normal; requires dialysis or transplantation; also known as stage 5 chronic kidney disease." (CDC, 2009)

risk factor [185, 186, 3]. Our estimate of the overall prevalence of persons with ESRD was taken from the United States Renal Data System. On December 31, 2012, 616,618 persons in the United States aged 15 and older has ESRD, correspondent to a prevalence 0.252% [129].[73] The report does not provide data on the proportion of cases occurring within the foreign born.

For the purpose of our univariate analysis of LTBI prevalence on NHANES, a respondent was classified as having ESRD if the respondent indicated that they had been diagnosed with weak or failing kidneys (KIQ022=1) and they had received dialysis in the past 12 months (KIQ025=1). If the patient did not know or refused to answer the question about kidney failure (KIQ022=7, 9) the value was set to missing. These questions were asked during the interview component of NHANES. Only participants aged 20 and older were eligible. ESRD prevalence by NHANES wave is shown in Table D.7.

Table D.7: ESRD Prevalence on five waves of NHANES and Persons aged 20 and older, 2003 – 2012

Characteristic/Wave	Est. Prevalence (%)	Prevalence 95% CI	Est. Overall Pop With ESRD*	Est. FB Pop with ESRD	Raw Count on NHANES
ESRD -- 2003 to 2004	0.074	(0.03-0.2)	164,840	21,594	9
ESRD -- 2005 to 2006	0.157	(0.08-0.31)	352,524	46,181	17
ESRD -- 2007 to 2008	0.241	(0.13-0.45)	539,984	70,738	22
ESRD -- 2009 to 2010	0.220	(0.11-0.44)	493,399	64,635	22
ESRD -- 2011 to 2012	0.222	(0.13-4324)	496,983	65,105	27
ESRD -- All Waves/2003 to 2012	0.188	(0.14-0.25)	420,834	55,129	97

* Target population of persons aged 20 and older on NHANES 2011-2012 was 223,966,890.

ESRD among the Foreign Born

To assess whether the prevalence ERSD among the foreign born is equivalent to that among the general population we conducting weighted logistic regression ESRD prevalence by nativity across five waves of NHANES. As shown in Table D.8, foreign birth is not significantly associated with the probability of having ESRD. We therefore estimate that there are 80,777 foreign born persons with ESRD in the United States based on the total number of persons with ESRD (616,618) and the proportion of the overall population that is foreign born (13.1%).

Table D.8: Difference in ESRD Prevalence by Nativity, NHANES 2003 – 2012

Risk Factor	Prev: All	Prev: US Born	Prev: FB	RR vs US Born (95% CI)	RR vs All (95% CI)	Overall Raw Count	FB Raw Count
ESRD	0.16%	0.19%	0.06%	0.93 (0.56-1.56)	0.94 (0.59-1.46)	97	24

Life Expectancy Adjustment

The mean life expectancy of a 55 year old person on dialysis is 5 years [237, 238]. The mean age of the ESRD prevalence population in the United States was 60 in 2012 [129]. We assume that the life expectancy of a 60 year old on dialysis is 4.5 years.

[73] 620,136 persons of all ages in the United States (excluding territories) had ESRD, including 3,518 aged 0-14.

1.4. Human Immunodeficiency Virus (HIV)

HIV Infection Prevalence Overall and among the Foreign Born

We define HIV infection as diagnosed HIV infection, as this is the observed risk factor in a clinical setting and is consistent with the definition on the CDC TB surveillance report. We estimated the prevalence of HIV infection with CDC HIV Surveillance data. According to the CDC HIV Surveillance, 930,569 persons aged 15 or over were living with diagnosed HIV infection at the end of 2012, or 0.32% of the target population [46].[74] Our weighted analysis of five waves of NHANES surveys from 2003 to 2013 shows that foreign birth is not a significant predictor of HIV infection (see Table D.9).

Table D.9: Difference in HIV Prevalence by Nativity, NHANES 2003 – 2012

Risk Factor	Prev: All	Prev: US Born	Prev: FB	RR vs US Born (95% CI)	RR vs All (95% CI)	Overall Raw Count	FB Raw Count
HIV Infection	0.43%	0.40%	0.52%	1.29 (0.74-2.26)	1.24 (0.76-1.94)	68	16

[74] At the end of 2012, 933,996 persons were infected with HIV, including 2,548 aged 1-12 and 879 aged 13-14. Prevalence for all ages was 0.2938%.

Life Expectancy Adjustment

A study of life expectancy reductions after HIV diagnosis based on National HIV Surveillance data found that, among 40 year olds diagnosed with HIV in 2005, average life expectancy was 18.1 for males and 20.9 for females [150]. If males account for 80% of all HIV diagnoses, the mean life expectancy is 18.7 years. The mean age of a person with diagnosed HIV infection in 2012 was higher than this starting point by 5.5 years (45.5) [46]. However, empirical trends suggest that life expectancy among HIV infected has increased since 2005. A second study by Hernando et al of 5,914 HIV positive subjects found a standardized mortality ratio (SMR) of 5.6 (95% CI 4.9-6.4) among HIV positive subjects compared to the general population in Spain [239]. This SMR yields an estimated 18.5 remaining life years for the average person infected with HIV. Applying a constant SMR of 5.6 to the 2010 life tables and assuming the average person with prevalent HIV infection is 46 years old and was infected at age 30 yields an undiscounted LE of 19 and a discounted LE of 14.

1.5. Cancer

The statement issued by the CDC and American Thoracic Society identified "leukemia, lymphoma and cancers of the head, neck or lung" as risk factors for progression to TB disease [3]. Hematological malignancies (HM) – leukemia, lymphoma, myeloma and myelodysplastic syndromes – – have received particular attention and have been shown to increase the risk of TB progression through immune suppression due to either the tumor itself or the therapeutic regime [183]. Our meta-analysis of the risks associated with select malignancies is presented in Table C.11 in Appendix C. Because the relative risk associated with HM has been found to be higher than other cancers, we distinguish between HM and solid organ malignancy (SOM).

Malignancy Prevalence Overall

We estimated the prevalence of Hematological Malignancies (HM) and Solid Organ Malignancies (SOM) using data from the SEER Cancer review, 1975-2011. In 2011, 427,109 persons in the United States were living with HM first diagnosed within the past 5 years and 1,750,351 were living with SOM first diagnosed within the past five year. Approximately 0.56% of prevalence cancer patients are aged 0-14 [133]. Using the NHANES population basis these data yield prevalence estimates of 0.174% for HM and 0.890% for SOM.

We compared these figures to estimates of prevalence of persons with HM and SOM from NHANES 2003-2012. Respondents were classified as having one of the associated cancers if they were diagnosed with the last five years.[75] This is approximately consistent with the definition of the risk factor in the published literature. As shown in Table C.11, most studies on the risks of TB associated with cancer address the recently diagnosed population. HM included cancers of the blood, lymphoma and leukemia. Solid organ malignancy included breast, liver, stomach, colon, larynx, windpipe and oral cancers.

[7575]The respondent was classified as having cancer within the past 5 years if their current age less their reported age at diagnosis was *less than* 5, excluding some respondents with birthdays shortly following diagnosis.

Prevalence of HM and SOM on five waves of NHANES are shown in Table D.10. Due to small sample sizes and significant wave-to-wave variation in prevalence, our prevalence estimate is based on the weighted average prevalence from 2003-2012. Based on our weighted analysis, 340,890 persons or 0.14 percent (95% CI 0.09-0.21) of the population aged 15 and older were diagnosed with HM within the past five years; 2,131,416, or 0.87 percent (95% CI 0.73-1.05) of the population aged 15 and older, were diagnosed with SOM within the past five years.

Table D.10: Prevalence of Hematological Malignancies and Solid Organ Malignancies among Persons Aged 15 and Above on NHANES 2003 – 2012

Risk Factor/ Year	Est. Prevalence (%)	Est Prevalence 95% CI	Est. Pop with Risk Factor	Est. FB with Risk Factor	Raw Count on NHANES
2003 to 2004					
Ever Diagnosed with HM	0.35	0.08-0.22	865,918	268,435	19
Diagnosed with HM in Past 5 Years	0.14	0.04-0.07	337,955	104,766	11
Ever Diagnosed with SOM	2.06	0.17-1.7	5,035,091	483,872	130
Diagnosed with SOM in Past 5 Years	0.85	0.15-0.51	2,071,014	199,024	54
2005 to 2006					
Ever Diagnosed with HM	0.33	0.15-0.74	808,451	250,620	12
Diagnosed with HM in Past 5 Years	0.14	0.05-0.4	338,689	104,994	6
Ever Diagnosed with SOM	2.31	1.93-2.77	5,652,556	543,211	117
Diagnosed with SOM in Past 5 Years	0.90	0.68-1.21	2,207,223	212,114	48
2007 to 2008					
Ever Diagnosed with HM	0.38	0.21-0.69	930,966	288,599	21
Diagnosed with HM in Past 5 Years	0.07	0.03-0.19	173,624	53,823	7
Ever Diagnosed with SOM	2.51	2.12-2.96	6,137,235	589,788	172
Diagnosed with SOM in Past 5 Years	0.82	0.57-1.16	1,995,207	191,739	64
2009 to 2010					
Ever Diagnosed with HM	0.45	0.25-0.83	1,104,101	342,271	26
Diagnosed with HM in Past 5 Years	0.19	0.08-0.43	461,937	143,201	11
Ever Diagnosed with SOM	2.45	1.96-3.05	5,979,996	574,678	162
Diagnosed with SOM in Past 5 Years	0.87	0.58-1.31	2,135,084	205,182	61
2011 to 2012					
Ever Diagnosed with HM	0.24	0.13-0.46	587,876	182,241	17
Diagnosed with HM in Past 5 Years	0.06	0.02-0.18	150,392	46,622	6
Ever Diagnosed with SOM	1.94	1.61-2.34	4,740,175	455,531	130
Diagnosed with SOM in Past 5 Years	0.58	0.37-0.9	1,408,798	135,386	48
All Waves: 2003 to 2012					
Ever Diagnosed with HM	0.35	0.27-0.46	858,337	266,085	95
Diagnosed with HM in Past 5 Years	0.12	0.08-0.18	291,492	90,363	41
Ever Diagnosed with SOM	2.25	2.08-2.43	5,508,032	529,322	715
Diagnosed with SOM in Past 5 Years	0.80	0.68-0.95	1,957,547	188,120	275

TB Related Cancers among the Foreign Born

We conducted weighted logistic regressions to assess whether the probability of ever being diagnosed with HM or SOM varies significantly by nativity. Relative risk was assessed using the "ever diagnosed" variable to compensate for small sample sizes, since "ever diagnosed" should correspond to the RR of recent diagnosis. Results are shown in Table D.11: Difference in Malignancy Prevalence by Nativity with Logistic Regression, NHANES 2003 – 2012Table D.11. We set the RR for HM equal to 1 because the confidence interval (0.02-1.08) includes the null. Solid Organ

Malignancy diagnosis is significantly negatively associated with foreign birth (RR: 0.31, 95% CI 0.21-0.45).

Table D.11: Difference in Malignancy Prevalence by Nativity with Logistic Regression, NHANES 2003 – 2012

Risk Factor	Prev: All	Prev: US Born	Prev: FB	RR vs US Born (95% CI)	RR vs All (95% CI)	Overall Raw Count	FB Raw Count
HM: Ever Diagnosed	0.35%	0.38%	0.23%	0.61 (0.3-1.24)	0.64 (0.33-1.2)	95	15
SOM: Ever Diagnosed	2.25%	2.54%	0.83%	0.32 (0.24-0.44)*	0.35 (0.27-0.47)	715	80
All: HM or SOM	2.71%	2.91%	1.03%	0.35 (0.26-0.46)*	0.38 (0.29-0.5)	806	94

Life Expectancy Adjustment

According to the SEER Cancer Review, 10-year survival rates during 1988-2010 for Hodgkin Lymphoma, Non-Hodgkins Lymphoma and Leukemia were 80%, 55% and 47% for Hodgkin Lymphoma, Non-Hodgkins Lymphoma and Leukemia, respectively [133]. We estimate that the mean age of an HM patient diagnosed within the past 5 years over the age of 15 is 61.2. Relative to survival rates for the general population at age 61, weighted average HM survival rates translate to an average annual SMR of approximately 5.4 over a 10-year period. We assume that life expectancy for cancer survivals 10 years post diagnosis is equal to life expectancy for the general population. Applying this SMR to the 2010 life tables yield a life expectancy estimate of 15 for the average person living with HM [51].

The same method was used to estimate remaining life years for Solid Organ Malignances (SO). The weighted 10-year life expectancy for a person recently diagnosed with an SOM is 3.2 out of 10 years. We estimate that the mean age of an SOM patient over the age of 15 is 65.3. Relative to survival rates for the general population at age 63, SOM patience experience an SMR of approximately 7.8 over a 10-year period. Applying this SMR to the 2010 life tables yields a life expectancy estimate of 8.8 for the average person living with SOM [51]. The weighted life expectancy for both HM and SOM is 9.9.

1.6. Malnutrition/ Low Bodyweight

Malnutrition increases the risk of TB disease by decreasing cell-mediated immunity, the principal means by which the host keeps TB latent. [211] Because malnutrition is a difficult risk factor to directly observe in a clinical setting, it is decomposed into observable characteristics linked to malnutrition: low bodyweight and surgeries with attendant malabsorption and weight loss such as Gastrectomy and Jujeno-Ilial bypass surgery.

Underweight

Evidence suggests there is a log-linear relationship between body mass index (BMI) and tuberculosis incidence [125]. However, this paper treats bodyweight as a binary risk factor. Individuals are classified as underweight if they have a body mass index (BMI) under 18.5 kg/m^2. This definition

approximately aligns with the four studies we examined in our meta-analysis of the association between low bodyweight and tuberculosis presented in Table C.9 in Appendix C. In Palmer et al., Edwards et al., Cegielski et al. and Leung et al., the upper BMI limit of the underweight category was 19.1, 19.6, 18.5 and 18.5, respectively.

The prevalence of low bodyweight among persons aged 15 and older on five waves of NHANES is shown in Table D.12. Because the prevalence of low bodyweight did not trend up or down over time, our overall prevalence estimate is based on the weighted average of the five waves. We estimate that 5,685,080 persons age 15 and older, or 2.32% of the population (95% CI 2.06-2.63) has a BMI under 18.5. Body measurements, including BMI, were collected during the MEC component of NHANES.

Table D.12: Prevalence of Low Body Weight among Persons Aged 15+ on 5 Waves of NHANES

Risk Factor / Year	Est. Prevalence (%)	Est. Prevalence 95% CI	Est. Pop. with Risk Factor	Est. FB Population with Risk Factor	Raw Count with Risk Factor
Underweight: 2003-2004	2.23	1.85 - 2.68	5,444,696	713,255	163
Underweight: 2005-2006	2.48	1.89 - 3.25	6,055,559	793,278	178
Underweight: 2007-2008	2.40	1.78 - 3.22	5,863,105	768,067	161
Underweight: 2009-2010	2.20	1.7 - 2.84	5,380,382	704,830	144
Underweight: 2011-2012	2.36	1.85 - 3	5,763,577	755,029	176
Underweight: All Waves	2.33	2.06-2.6	5,701,464	746,892	822

To determine whether the prevalence of low bodyweight was different among the foreign born, we conducted a weighted logistic regression of the association between underweight status and foreign birth across five waves of NHANES from 2003 - 2012. Results are shown in Table D.13. There is insufficient evidence to suggest that foreign birth is associated with low bodyweight.

Table D.13: Difference in Prevalence of Low Bodyweight by Nativity among Persons Aged 15+, NHANES 2003 – 2012

Risk Factor	Prev: All	Prev: US Born	Prev: FB	RR vs US Born (95% CI)	RR vs All (95% CI)	Overall Raw Count	FB Raw Count
Underweight	2.32%	2.37%	2.10%	0.88 (0.66-1.19)	0.9 (0.69-1.16)	645	115

Life Expectancy Adjustment for Low Bodyweight

A recently published meta-analysis of 51 studies examining the relationship between BMI and mortality found that adults with a BMI under 18.5 have a standard mortality ratio of 1.8 [155]. A confidence interval was not found for this estimate. We estimate that the mean age of an underweight person aged 15 and older is 34. Applying the SMR to the 2010 life tables yields an adjusted life expectancy of 40.8 years.

1.7. Cigarette Smoking

Overall Prevalence of Cigarette Smoking

Smoking as a risk factor for TB is defined with several measures within the literature, including "ever smoker", "past smoker", "current smoker" and continuous variables representing exposure or frequency of smoking. This paper focuses on the risks associated with "current smoking" for two reasons. First, it is the most commonly used measure in the studies we examined (see Table C.14 and Table C.12). Second, a recent meta-analysis found that, on average, RRs are lower for ex-smokers than current smokers and that smoking-related TB risks may decline soon after cessation [224].

A respondent was classified as a "current smoker" if they reported smoking over 100 cigarettes in their life and, at the time of the interview, reported smoking every day. This differs somewhat from the CDC definition of a *current smoker*, which includes respondents that smoke "some days" as well as "every day" [228]. We chose the more restrictive definition because most of the studies address a population that smokes more than one cigarette per day. We estimate that 16.4% (95% CI 14-19%) of the population currently smokes at least one cigarette per day.

Table D.14: Current Cigarette Smoking among Persons aged 20 and older on Five Waves of NHANES Surveys, 2003 – 2012

Wave/ Characteristic	Est. Prevalence Overall (%)	Prevalence 95% CI	Est Population*	Est. No of FB Smokers	Raw Count Smokers	Eligible Sample
2003-20014						
At Least Some Days	25.52%	23.22-27.97%	57,161,502	7,488,157	1131/3903	Age 20+, Interview
Every Day	21.29%	19.35-23.6%	47,692,629	6,247,734	934/4100	
2005-2006						
At Least Some Days	24.03%	21.51-26.76%	53,829,994	7,051,729	1089/4973	Age 20+, Interview
Every Day	20.64%	18.1-23.44%	46,223,407	6,055,266	91/4063	
2007-2008						
At Least Some Days	22.82%	20.25-25.62%	51,110,364	6,695,458	1319/4609	Age 20+, Interview
Every Day	19.04%	16.04-22.45%	42,635,905	5,585,304	1105/4823	
2009-2010						
At Least Some Days	20.34%	18.7-22.08%	45,555,537	5,967,775	1346/4872	Age 20+, Interview
Every Day	17.27%	15.54-19.16%	38,679,082	5,066,960	1105/5115	
2011-2012						
At Least Some Days	19.81%	17.62-22.19%	44,360,226	5,811,190	1108/4443	Age 20+, Interview
Every Day	16.40%	14.46-18.53%	36,720,939	4,810,443	912/4639	
All Waves: 2003-2012						
At Least Some Days	22.44%	0.21-0.23%	50,257,946	6,583,791	5993/22800	Age 20+, Interview
Every Day	18.89%	0.18-0.2%	42,309,361	5,542,526	4964/22740	

* Target population of persons aged 20 and older on NHANES 2011-2012 was 223,966,890.

Cigarette Smoking among the Foreign Born

We conducted weighted logistic regression of smoking by nativity across five NHANES waves. Our analysis suggests that the foreign born smoke significantly less than the overall population, whether measured as smoking every day (RR: 0.52, 95% CI 0.46-0.59) or smoking at least some days (RR: 0.64, 95% CI 0.57-0.71). Results are shown in Table D.15.

Table D.15: Difference in Current Cigarette Smoking by Nativity, NHANES 2003 - 2012

Risk Factor	Prev: All	Prev: US Born	Prev: FB	RR vs US Born (95% CI)	RR vs All (95% CI)	Overall Count	FB Raw Count
Smoking at least Some	22.13%	23.84%	15.51%	0.59 (0.53-0.65)	0.62 (0.56-0.68)	5991	997
Smoking Daily	18.89%	20.50%	10.93%	0.48 (0.42-0.55)	0.51 (0.46-0.58)	4962	688

Life Expectancy Adjustment

A study of 216,917 adults in the U.S. National Health Interview survey between 1997 and 2004 found a hazard ratio for overall mortality at 25 to 79 years among current smokers of 3.0 (95% CI, 2.7-3.3) for women and 2.8 (95% CI, 2.4-3.1) for men versus those who had never smoked [156]. Assuming that half of the smoking population is female yields a weighted average of 2.9 (95% CI, 2.7-3.15). We estimate that the mean age of a current smoker is 43 and assume that the average "current smokers" in our model began smoking at age 25 and will quit smoking by age 80. Applying

the hazard ratio to 2010 live tables yields a remaining life years estimate of 28.8 (95% CI, 27.4-30.2), approximately 8 years less than the remaining life years expected for the average American.

1.8. Alcohol Abuse

Overall Prevalence of Alcohol Abuse

The National Household Survey on Drug Use and Health defines heavy drinking as drinking five or more drinks on the same occasion on each of 5 of more days in the past 30 days [240]. In 2013, the survey found that heavy drinking was reported by 6.3 percent of the population aged 12 or older, which was similar to the rate of heavy drinking in 2013 (6.5%) [48]. Heavy drinking was reported by 0.1% of the populated aged 12 and 13 and by 0.7% of the population aged 14. This suggests that approximately 6.63% of the population aged 15 and older engages in heavy alcohol use.[76] We use this estimate for the overall prevalence of heavy drinking because it is more precise and covers a broader range of ages than the NHANES alcohol use questionnaire.

For the purpose of determining the associations between alcohol use and foreign birth and IGRA positivity on NHANES, we defined two variables to represent alcohol use. A respondent was classified as *ever* abusing alcohol if they reported "ever having 4/5 or more drinks per day." A respondent was classified as *currently* abusing alcohol if they reported drinking 4/5 drinks or more on each of 5 or more days per month on average in the past year. The alcohol questionnaire is administered during the mobile examination component of NHANES. Alcohol related data is only available for respondents aged 20 years and older. Prevalence of both alcohol abuse variables on five waves of NHANES is shown in Table D.16.

[76] On NHANES, 12 year olds represent 1.67% of the population aged 12 and older; 13 year olds represent 1.64% and 14 year olds represent 1.84%.

Table D.16: Alcohol Abuse among MEC participants Aged 20+ on Five Waves of NHANES Surveys, 2003 – 2012

Risk Factor/ Wave	Est. Prevalence (%)	Prevalence 95% CI	Est. Pop with Risk Factor	Est FB Pop with Risk Factor	Raw Count on NHANES
2003 to 2004					
Alcohol Abuse Ever	16.09	14.06-18.36	39,357,341	5,155,812	600
Alcohol Abuse Current	6.92	5.49-8.69	16,932,969	2,218,219	187
2005 to 2006					
Alcohol Abuse Ever	16.19	14.59-17.93	39,588,676	5,186,117	618
Alcohol Abuse Current	8.98	7.67-10.5	21,970,994	2,878,200	233
2007 to 2008					
Alcohol Abuse Ever	15.76	13.98-17.72	38,535,929	5,048,207	765
Alcohol Abuse Current	8.20	7.12-9.44	20,064,311	2,628,425	265
2009 to 2010					
Alcohol Abuse Ever	15.96	14.5-17.53	39,021,586	5,111,828	879
Alcohol Abuse Current	7.74	6.65-8.99	18,920,839	2,478,630	325
2011 to 2012					
Alcohol Abuse Ever	15.15	12.81-17.84	37,057,925	4,854,588	655
Alcohol Abuse Current	9.15	7.77-10.75	22,372,040	2,930,737	289
All Waves: 2003 to 2012					
Alcohol Abuse Ever	15.82	15-16.68	39,123,071	5,125,122	3517
Alcohol Abuse Current	8.24	7.67-8.84	19,508,959	2,555,674	1299

Alcohol Abuse among the Foreign Born

Results of the logistic regression of alcohol abuse by foreign birth are shown in Table D.17. Relative to the general population, foreign birth is significantly negatively associated with ever abusing alcohol (RR: 0.75, 95% CI 0.66-0.85) and currently abusing alcohol (RR: 0.80, 0.66-0.96).

Table D.17: Difference in Current Alcohol Abuse by Nativity, NHANES 2003 - 2012

Risk Factor	Prev: All	Prev: US Born	Prev: FB	RR vs US Born (95% CI)	RR vs All (95% CI)	Overall Raw Count	FB Raw Count
Alcohol Abuse Ever	15.82%	16.38%	12.44%	0.73 (0.63-0.84)	0.75 (0.66-0.85)	3517	641
Alcohol Abuse Current	8.24%	8.49%	6.71%	0.78 (0.63-0.96)	0.8 (0.66-0.96)	1299	229

Life Expectancy Adjustment

A 21-year cohort study of 4.1 million Danish adults found an age-standardized mortality ratio (SMR) of 3.64 (95% CI, 346-383) for female alcohol abusers and 3.58 (95% CI, 349-367) for male alcohol abusers versus the general population [157]. Assuming that men are twice as likely to be alcohol abusers yields a weighted average SMR of 3.6 (95% CI, 3.48-3.72). The mean age of a person that currently abuses alcohol is estimated to be 39 and we assume that the average alcohol abuser began abusing alcohol at 25 and will quit abusing alcohol by age 70. We therefore estimate that the adjusted life expectancy of a person currently abusing alcohol to be 30.5 (95% CI 30.2-30.8), approximately 9 years less than the life expectancy for a 42 year old from the general population (39.6).

1.9. Injection Drug Use

Overall Prevalence of Injection Drug Use

Current injection drug users on NHANES were defined as respondents that had used injection drugs within the past 6 months. The prospective cohort study by Selwyn and colleagues assessed TB risk among current users [167]. The Sterling 2011 trial reported risk associated with a "history of injection drug use" and did not find a significant association between a history of drug use and TB progression [94].

Table D.18 shows the prevalence of injection drug use on four waves of NHANES spanning 2005-2012, including both the prevalence of "ever using" injection drugs and the prevalence of current use. NHANES 2003 to 2004 was excluded due to different variable definitions. Data were available for MEC participants aged 18-69. We use the weighted average from 2005-2012 to compensate for small sample sizes. We estimate the 0.37% (95% CI 0.24-0.56%) of the population is currently injecting drugs.

Table D.18: Injection Drug Users among persons aged 18-69 on Four Waves of NHANES Surveys, 2005 – 2012

Wave/ Characteristic	Est. Prevalence Overall (%)	Prevalence 95% CI	Est Overall Population*	Est FB Population	Raw Count Users	Eligible Sample
2005-2006						
Ever Injected	2.41	1.6-3.64	4,932,563	206,773.04	73	Age 20-59, MEC Sample
Current User	0.49	0.29-0.84	1,005,307	42,142.48	15	
2007-2008						
Ever Injected	2.98	2.22-3.98	6,089,861	255,286.99	113	Age 20-69, MEC Sample
Current User	0.41	0.19-0.91	843,510	35,359.95	17	
2009-2010				-		
Ever Injected	1.88	1.37-2.57	3,836,960	160,845.36	89	Age 18+, MEC Sample
Current User	0.17	0.05-0.61	354,442	14,858.20	8	
2011-2012				-		
Ever Injected	2.20	1.31-3.67	4,491,094	188,266.66	82	Age 18-69, MEC Sample
Current User	0.41	0.16-1.05	844,123	35,385.64	11	
All: 2005-2012			-	-		
Ever Injected	2.36	1.96-2.85	4,822,655	202,165.71	357	Age 18-69, MEC Sample
Current User	0.37	0.24-0.56	752,806	31,557.62	51	

*Among MEC participants aged 15 and older, 83.54% were between the ages of 18 and 69

Injection Drug Use among the Foreign Born

As shown in Table D.19, foreign birth is negatively associated with ever using injection drugs (RR: 0.32, 95% CI 0.2-0.51) but does not have a significant association with the current use of injection drugs (RR: 0.49, 95% CI 0.17-1.42). Due to the small number of respondents (51) reporting current use of injection drugs across the four waves, our analysis applies the RR associated with ever using injection drugs to the estimate of both categories of users.

Table D.19: Difference in Injection Drug Use by Nativity, NHANES 2005 - 2012

Risk Factor	Prev: All	Prev: US Born	Prev: FB	RR vs US Born (95% CI)	RR vs All (95% CI)	Overall Raw Count	FB Raw Count
Injection Drugs Ever	2.36%	2.65%	0.86%	0.32 (0.2-0.51)	0.35 (0.22-0.55)	324	24
Injection Drugs Current	0.37%	0.40%	0.20%	0.49 (0.17-1.42)	0.53 (0.19-1.34)	51	8

Life Expectancy Adjustment

A cohort study of 256 injection drug users during 1988-2000 in Baltimore found an adjusted SMR of 5.35 (95% CI, 2.56-9.83) versus the U.S. general population and 2.79 (1.39-4.99) versus the Baltimore general population in 1999-2000 [158]. Given the policy context we use the estimate versus the U.S. general population. We estimate that the mean age of an injection drug user is 37 and assume that the average current injection drug user began using at 25 and that the SMR persists through age 65 to account for the probability of cessation. We therefore estimate an adjusted life expectancy of 32.3 (95% CI, 24.6-39.3).

Appendix E: LTBI Testing and Treatment Parameters

LTBI Treatment Adherence

Three randomized trials have found that a significantly greater proportion of patients randomized to 4H complete treatment relative to those randomized to 9H. A 2004 trial by Menzies et al found that, out of 58 patients randomized to 4R, 53 patients (91%) took 80% of prescribed doses and 50 patients (86%) took more than 90% of prescribed doses, significantly greater proportions than those observe among the patients randomized to the INH regimen [137]. A second trial let by Menzies found a completion rate of 78% among 420 participants randomized to 4R [241]. A trial in Hong-Kong observed 76% completion rates among 161 silicotic patients receiving 4R [139].

Non-randomized retrospective studies have found similar completion rates. Laridzabal et al found that patients on the 4R regiment were significantly more likely to complete therapy than those on the 9H (OR: 5.1, 95% CI 3.3-8.1), with an observed completion rate of 80.5% among the 261 patients taking 4R [136]. A retrospective chart review by Page et al of 1379 patients on 4R and 770 patients on 9H found a completion rate of 75.3% for 4H and 59.9% for 9H [142].[77] In Horsburgh et al, completion rates were higher among patient treated with 4R (69% versus 47% overall), the treatment regimen assumed in this analysis. However, only 91 of the 1,994 subjects initiating treatment were treated with 4-months daily rifampin ("4R"), the treatment regimen assumed in this analysis, while the majority of subjects (1,675) were treated with 9-month daily isoniazid ("9H") [36].

Six studies were selected for our meta-analysis of treatment completion rates for daily 4-month rifampin (4R), including three randomized controlled trials. Selected studies are shown in Table E.1. Using a random effects model, our summary estimate of the 4R treatment completion rate is 77% (95% CI 74%-80%). A forest plot of the results is shown in Figure E.1.

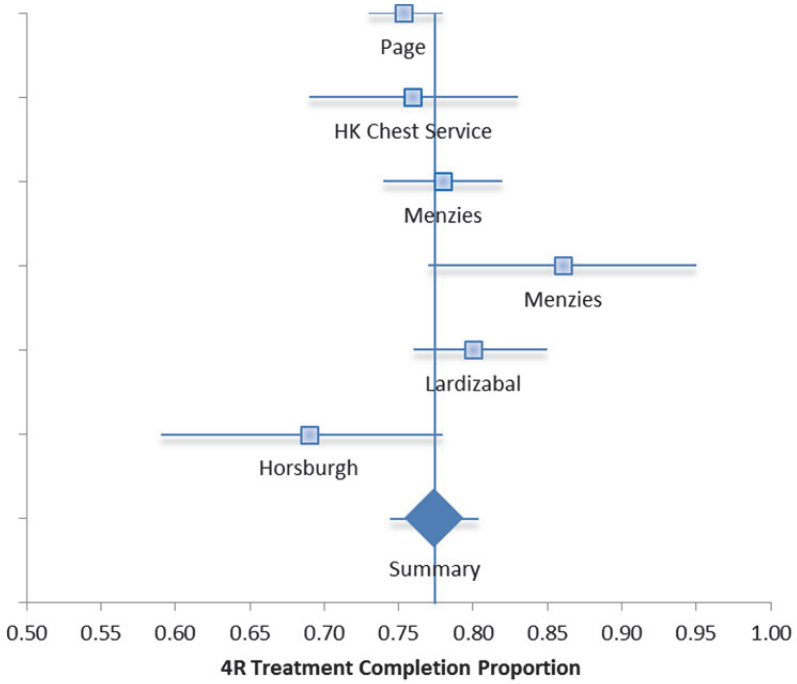
[77] Proportion by time interval among drop outs derived from published completion rates by month.

Table E.1: 4R Treatment Adherence A Random-Effects Meta-Analysis

Source	Methods/Notes	Study Weight: Random-Effects	Treatment Completion (95% CI)
Horsburgh 2010 [36]	Two-stage cluster sample survey at public health clinics across the U.S. and Canada. 91 subjects on 4R.	307	69% (59-78)
Lardizabal 2006 [136]	Retrospective. 261 patients on 4R.	935	80% (76-85)
Menzies 2004 [137] ¥	Randomized trial. 58 patients randomized to 4R.	362	86% (77-95)
Menzies 2008 [241]	Randomized trial. 420 patients randomized to 4R.	935	78% (74-82)
Hong Kong Chest Service 1992 [139]	Randomized trial. 161 patients randomized to 4R.	519	76% (69-83)
Page 2006 [142] ±	Retrospective chart review. 1,379 patients on 4R.	1,265	75% (73-78)
Summary Estimate, 4R Treatment Completion, Random Effects			**77% (74%-80%)**
Summary Estimate, 4R Treatment Completion, Fixed Effects			**77% (75%-79%)**

¥ Completion rate reported for subjects completing at least 90% of prescribed doses.
± Including "clinical completers" that completed at least 80% of prescribed doses over a period greater than 20 weeks. Excluding clinical completers, Page et al found a completion rate of 71.6% for 4R.

Figure E.1: Forest Plot of 6 Studies Examining 4R Treatment Completion Rates



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