REDUCING THE TUBERCULOSIS BURDEN IN MIGRANT POPULATIONS THROUGH LATENT TUBERCULOSIS INFECTION INTERVENTIONS: A SERIES OF COST-EFFECTIVENESS ANALYSES

by

JONATHON CAMPBELL

BSc, University of Toronto, 2012

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Pharmaceutical Sciences)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

February 2018

ABSTRACT

BACKGROUND: In many low tuberculosis (TB) incidence countries, TB rates have stagnated. In these countries, TB disproportionately affects migrant populations due to reactivation of latent TB infection (LTBI) acquired prior to immigration. Treatment of LTBI can significantly reduce risk of TB. The objective of this thesis is to determine the performance of common LTBI diagnostic tests in migrant populations and evaluate the cost-effectiveness of LTBI screening and treatment at various stages of the migration process and in migrants with chronic diseases, such as chronic kidney disease (CKD), that increase risk of TB.

METHODS: A literature search determined the sensitivity of LTBI diagnostic tests: the tuberculin skin test (TST) and interferon-gamma release assay (IGRA). A meta-analysis was completed to determine the proportion of migrants testing positive with TST and IGRA from countries of various TB incidences. Discrete event simulation models evaluated the cost-effectiveness of LTBI screening and treatment in migrants: immediately post-immigration, prior to immigration, and at time of late stage CKD diagnosis or dialysis initiation. Incremental cost-effectiveness ratios (ICERs) were calculated for quality-adjusted life years.

RESULTS: Sensitivities of 88.9% and 78.2% were found for the IGRA and TST, respectively. Fewer migrants test positive with an IGRA compared with a TST. Immediately after immigration, no LTBI screening was cost-effective when applied universally to all migrants (ICERs >$138,484), but can reduce the TB burden in migrants >20%. IGRA screening pre-immigration and rifampin treatment post-arrival can reduce the TB burden by >40% and results in ICERs <$49,035 compared to no screening in migrants from countries with a TB incidence ≥30 per 100,000. Likewise, in migrants from countries with a TB incidence ≥30 per 100,000, IGRA screening and isoniazid treatment at time of dialysis initiation was dominant and in migrants ≥60 years of age at late stage CKD diagnosis resulted in ICERs <$47,554.

CONCLUSIONS: In order to sustainably reduce the migrant TB burden in low incidence countries, LTBI screening should be performed with an IGRA. LTBI screening should be targeted to migrants from countries with a TB incidence ≥30 per 100,000 pre-immigration or at high-risk of TB post-arrival, such as dialysis patients.

LAY SUMMARY

Tuberculosis (TB) is an airborne infectious disease that most often exists as dormant or latent TB infection (LTBI) but can progress to active, infectious TB disease. Offering LTBI screening and treatment can reduce the risk progression. Diagnosis of LTBI can be performed using a tuberculin skin test (TST) or the interferon-gamma release assay (IGRA), the latter being better at identifying LTBI in certain groups. This thesis describes an evaluation of methods to screen and treat LTBI in migrant populations, where, in countries like Canada, migrants are disproportionately affected. Through these analyses I have identified that offering IGRA screening and subsequent treatment to migrants from countries with a high TB burden prior to immigration or to those who are at high-risk of progressing to active disease post-arrival is cost-effective. These results can help shape healthcare policy to reduce the TB burden in migrants moving forward.

PREFACE

This thesis was conducted at the University of British Columbia (UBC) with support from clinicians and researchers at the British Columbia Centre for Disease Control. The UBC Behavioral Research Ethics Board under application numbers H12-02807, H14-00914, H16-00265, and H13-03216, approved all research. I would like to acknowledge the contributions of these collaborators here.

Chapter 2 has been published and peer-reviewed in the journal *Molecular Diagnosis and Therapy* in the year 2015 (Campbell JR, Krot J, Elwood K, Cook V, Marra F. A systematic review on TST and IGRA tests used for diagnosis of LTBI in immigrants. *Mol Diagn Ther* 2015;19(1):9-24). This chapter is entirely based on this publication, with changes for continuity and coherence in the thesis. For this chapter, I was involved in conceptualization and interpretation of the data, I performed the literature search and extraction, completed the analysis, wrote the initial drafts, and completed the final submitted work. Jane Krot performed the literature search and extraction with me in tandem to ensure accuracy. Victoria Cook and Kevin Elwood provided expert opinion throughout and were involved in the editing and review process. Fawziah Marra (Lalji) was involved in conceptualization and results interpretation, and was the main author responsible for editing and reviewing.

Chapter 3 has been published and peer-reviewed in the journal *Molecular Diagnosis and Therapy* in the year 2015 (Campbell JR, Chen W, Johnston J, Cook V, Elwood K, Krot J, Marra F. Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis. *Mol Diagn Ther* 2015;19(2):107-17). This chapter is entirely based on this publication, with changes for continuity and coherence in the thesis. For this chapter, I was involved in conceptualization and interpretation of the data, I performed the literature search and extraction, performed data analysis, wrote the initial drafts, and completed the final submitted work. Wenjia Chen provided expert statistical opinion throughout and created Figures 3-3 and 3-4. James Johnston, Victoria Cook, and Kevin Elwood were involved in conceptualization and topic direction, provided expert opinion throughout, and were involved in the editing process. Jane Krot performed the literature search and extraction with me in tandem to ensure accuracy. Fawziah Marra (Lalji) was involved in conceptualization, topic direction, results interpretation, and was the main author responsible for editing and reviewing.

Chapter 4 has been published (Campbell JR, Johnston JC, Sadatsafavi M, Cook VJ, Elwood RK, Marra F. Cost-Effectiveness of Post-Landing Latent Tuberculosis Infection Control Strategies in New Migrants to Canada.

PLoS ONE 2017;12(10):e0186778). This chapter is entirely based on this manuscript, with changes for continuity and coherence in the thesis. For this chapter, I was involved in conceptualization and data interpretation, I performed the literature search to source model parameters, I developed the model and its scenarios, performed the data analysis, wrote the initial drafts, and completed the final submitted work. James Johnston was involved in conceptualization, provided expert opinion on the model and its parameters, and was involved in the editing and review process. Mohsen Sadatsafavi provided expert modeling opinion and provided insight into figure development; he was involved in the editing and review process. Victoria Cook and Kevin Elwood provided expert opinion on parameter selection and were involved in the editing and review process. Fawziah Marra (Lalji) was involved in conceptualization, provided input into scenarios analyzed, aided in data interpretation, and was the main author involved in the editing and review process. I would like to acknowledge the staff at the British Columbia Centre for Disease Control for providing data on latent tuberculosis infection costs (personal communication) and Anik Patel for his advice during model development.

Chapter 5 is under peer-review (Campbell JR, Johnston JC, Cook VJ, Sadatsafavi M, Elwood RK, Marra F. Pre-Immigration Latent Tuberculosis Infection Screening Strategies in New Migrants to Low-Incidence Countries: A Cost-Effectiveness Analysis). This chapter is entirely based on this manuscript with changes for continuity and coherence in the thesis. For this chapter, I was involved in conceptualization and data interpretation, performed the literature search to source model parameters, I developed the model and its scenarios, performed the data analysis, wrote the initial drafts, and completed the final submitted work. James Johnston and Victoria Cook provided input on scenarios and were involved in conceptualization; they provided expert opinion and were involved in the editing and review process. Mohsen Sadatsafavi provided expert modeling opinion and was involved in the review and editing process. Kevin Elwood provided expert opinion and was involved in the review and editing process. Fawziah Marra (Lalji) was involved in conceptualization, provided input into the scenarios analyzed, aided in data interpretation and presentation, and was the main author involved in the editing and review process. I would like to acknowledge the staff at the British Columbia Centre for Disease Control for providing data on latent tuberculosis infection costs (personal communication).

Chapter 6 is based on manuscript(s) currently under preparation for submission; changes have been made for continuity and coherence in this thesis. Data for this chapter was provided by Immigration, Refugees, and Citizenship Canada, Population Data BC, and the Patient Records and Outcome Management Information System

(Project Reference 14-106). For this chapter I was involved in the conceptualization of the study, was responsible for epidemiological analysis of data, constructing a discrete event simulation model, performing data analysis of results, constructing figures, writing the initial drafts, and completing the final submitted work. James Johnston was involved in the conceptualization and scope of the research, provided expert opinion on tuberculosis and chronic kidney disease, aided in data interpretation, and participated in the manuscript editing process. Victoria Cook provided expert tuberculosis opinion, aided in data interpretation, provided discussion points, and participated in the manuscript editing process. Lisa Ronald was responsible for cleaning the data used for epidemiological analysis, providing expert tuberculosis and epidemiologic opinion, and participated in the manuscript editing process. Mohsen Sadatsafavi provided expert cost-effectiveness and epidemiologic opinion and participated in the manuscript editing process. Robert Balshaw provided expert methodological input and participated in the manuscript editing process. Kamila Romanowski provided expert chronic kidney disease and tuberculosis opinion, provided intellectual content, and participated in the manuscript editing process. Adeera Levin was involved in study conceptualization and facilitated renal data acquisition. Fawziah Marra (Lalji) was involved in conceptualization, provided input into the analyses performed, participated in data interpretation, provided discussion points, and was the main author involved in the editing process. I would like to acknowledge the staff at the British Columbia Centre for Disease Control for providing data on latent tuberculosis infection costs (personal communication), the British Columbia Renal Agency for supplying data from the Patient Records and Outcome Management Information System, and Wenjia Chen for her advice during survival analysis.

The data stewards of Population Data BC facilitated a data linkage used to inform portions of this thesis. All inferences, opinions, and conclusions drawn in this thesis are my own, and do not reflect the opinions or policies of the Data Steward(s).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AIDS	Acquired Immune-Deficiency Syndrome
BC	British Columbia
BCCDC	British Columbia Centre for Disease Control
BCG	Bacillus Calmette-Guérin
CAD	Canadian Dollar
CADTH	Canadian Agency for Drug Technologies and Health
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CKD	Chronic Kidney Disease
CXR	Chest X-Ray
DALY	Disability-Adjusted Life Year
DDI	Drug-Drug Interaction
DES	Discrete Event Simulation
DM	Diabetes Mellitus
DOT	Directly Observed Treatment
DOTS	Directly Observed Therapy Short-Course
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked Immune-Spot Assay
EQ-5D	EuroQuol Five Dimensions Questionnaire
ESRD	End-Stage Renal Disease
EVPI	Expected Value of Perfect Information
HIV	Human Immunodeficiency Virus
HUI3	Health Utilities Index Mark 3
ICER	Incremental Cost-Effectiveness Ratio
IFN-γ	Interferon-Gamma
IGRA	Interferon-Gamma Release Assay
IME	Immigration Medical Exam
INH	Isoniazid
IRCC	Immigration, Refugees, and Citizenship Canada
LTBI	Latent Tuberculosis Infection
MLE	Maximum Likelihood Estimation
MTB	*Mycobacterium tuberculosis*
NICE	National Institute for Health and Care Excellence

Abbreviation	Definition
NMB	Net Monetary Benefit
NTM	Non-Tuberculous Mycobacteria
OR	Odds Ratio
PAF	Population Attributable Fraction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMIS	Patient Records and Outcome Management Information System
PSA	Probabilistic Sensitivity Analysis
PY	Person Years
QALY	Quality-Adjusted Life Year
QFT	QuantiFERON
QFT-G	QuantiFERON-Gold
QFT-GIT	QuantiFERON-Gold In Tube
RCT	Randomized Controlled Trial
RIF	Rifampin
SEQ	Sequential Screening
SF-6D	Short Form Descriptive System
SG	Standard Gamble
SHR	Sub-distribution hazard ratio
SIGN	Scottish Intercollegiate Guidelines Network
TB	Tuberculosis
TNF-α	Tumour Necrosis Factor Alpha
TST	Tuberculin Skin Test
TTE	Time-to-Event
TTO	Time Trade Off
USD	United States Dollar
WHO	World Health Organization
WTP	Willingness-to-Pay

GLOSSARY

Term	Definition
Active Tuberculosis	The symptomatic, infectious state of tuberculosis infection, generally characterized by a prolonged cough
Cascade of Care	The many steps required for a patient to go from being identified for screening to adequately completing treatment
Discount Rate	Takes into account our preference for immediate returns over future returns
Discrete Event Simulation	A type of microsimulation where time moves forward at discrete intervals and where interactions can be modeled simultaneously allowing for flexibility and efficiency in complex models
Dominant	When an intervention has lower costs and higher benefits than the base case intervention; this intervention should be implemented
Dominated	When an intervention has higher costs and lower benefits than the base case intervention; this intervention should not be implemented
Extended Dominance	When an intervention has higher costs and higher benefits than the base case, but another intervention has a lower incremental cost-effectiveness ratio; this intervention should not be implemented
High Tuberculosis Incidence Country	A country that has an estimated annual tuberculosis incidence ≥100 and <200 per 100,000 population
Immune-Suppressed	A health state whereby an individuals immune system is impaired either due to illness or medication
Incremental Cost-Effectiveness Ratio	Calculated via the additional costs of an intervention divided by the additional benefits of an intervention.
Late Stage Chronic Kidney Disease	Stage 4 or stage 5 chronic kidney disease (i.e. estimated glomerular filtration rate <30 ml/min per 1.73m^2) not requiring dialysis
Latent Tuberculosis Infection	The asymptomatic state of tuberculosis infection, where an individual has adequately contained the bacteria and is not infectious
Low Tuberculosis Incidence Country	A country that has an estimated annual tuberculosis incidence <30 per 100,000 population
Migrant	A person that now resides in a country different from their country of birth. Used synonymously in this thesis with terms such as “foreign-born” and “immigrant.”
Moderate Tuberculosis Incidence Country	A country that has an estimated annual tuberculosis incidence ≥30 and <100 per 100,000 population

Term	Definition
Quadrant I	When an intervention has higher costs and higher benefits than the base case (i.e. a tradeoff exists); a decision is to implement should be based on the incremental cost-effectiveness ratio
Quadrant II	When an intervention has lower costs and higher benefits than the base case (i.e. dominant); this intervention should be implemented
Quadrant III	When an intervention has lower costs and lower benefits than the base case (i.e. a tradeoff exists); a decision to implement this intervention must be carefully made based on the policy makers goals
Quadrant IV	When an intervention has higher costs and lower benefits than the base case (i.e. dominated); this intervention should not be implemented
Quality-Adjusted Life Year	An outcome measure that combines both the duration and quality of life lived
Reactivation of Latent Tuberculosis Infection	The process whereby an individual progresses from latent tuberculosis infection to symptomatic and possibly infectious active tuberculosis
Strict Dominance	When an intervention has higher costs and higher benefits than the base case, but another intervention has lower costs and higher benefits; this intervention should not be implemented
Tradeoff	In the context of healthcare decisions, when a sacrifice must be made to obtain a benefit (e.g. increase costs to increase population health)
Very High Tuberculosis Incidence Country	A country that has an estimated annual tuberculosis incidence ≥200 per 100,000 population
Willingness-to-Pay Threshold	In the context of a healthcare system, it is the most they are willing to pay for a specific outcome (e.g. per quality-adjusted life year)

ACKNOWLEDGMENTS

This thesis would not have been completed without the guidance, support, mentorship, and friendship of several individuals. I would like to thank Dr. Fawziah Lalji for her guidance and mentorship throughout my graduate career. Her ambitious research lab, focused on skill development and productivity, fostered my development as an academic. She provided me with both encouragement and tough love when I needed it most, which continues to push me to always improve and has helped make me who I am today. I would like to acknowledge the mentorship of Dr. James Johnston throughout my Ph.D. He was a constant source of insight into my research and always provided me with opportunities to improve my skillset and further my research career. I would like to thank Dr. Mohsen Sadatsafavi for his methodological insight into economic analysis and his constant encouragement throughout my graduate career. I would like to thank Dr. Victoria Cook for her unique and insightful thoughts into this thesis, which encouraged me to think about tuberculosis from different perspectives. I would also like to thank Dr. Kevin Elwood who provided excellent clinical opinion and support throughout. Dr. Wenjia Chen offered continuous statistical support and was a pleasure to collaborate with. Dr. Lisa Ronald worked very hard to provide me with data to complete this thesis for which I am very grateful. Dr. Mohamed Wehbe, Jacob Gordon, Ankur Midha, Jason Asnis, and Dr. Anik Patel gave continuous motivation and support during my Ph.D. To all other colleagues, for there are too many to name, I would like to personally thank you for your support throughout my graduate career. I finally would like to thank University of British Columbia for their financial support during my Ph.D. and the British Columbia Centre for Disease Control for their generous financial support throughout.

DEDICATION

This work is dedicated to my loving parents, Kevin and Liz Campbell, for their unwavering love and support, my two brothers, Christopher and Duncan Campbell, who were always there when I needed them, my grandmother, Marilyn Neilly, for always keeping me humble and focused, my wonderful partner, Leviana Coccia, for her unbelievable love, companionship, and encouragement through the graduate school process that appeared to be without an end, and to the members of my family who are no longer with us, John and Geneva Campbell and Bert Neilly, I hope I have made you all proud.

CHAPTER 1. INTRODUCTION

1.1 Research Statement

This research aims to address the growing proportion of active tuberculosis (TB) cases occurring in foreign-born populations in countries with a low TB incidence (<30 incident cases per 100,000 population per year), such as Canada. In the past, activities to eliminate TB have primarily been targeted to halting active transmission of disease from individuals infected [1,2]. These efforts have been effective at reducing the TB burden. In Canada, this, as well as the advent of effective therapy, caused TB incidence to decline by approximately 95% from 1946-2000 (annual decline of 4.6%), however the annual decline from 2000-2010 has lessened considerably to only 2.2% [3]. During this time there has been a significant shift in the demographics of people with TB. In 1970 only 10% of annual TB cases occurred in foreign-born persons, in 2015 it had risen to >70% [3,4]. While active transmission is the main driver of TB in Canadian-born populations, reactivation of long standing TB infection, called latent TB infection (LTBI), drives TB incidence in migrant populations living in low TB incidence countries [4]. Current TB prevention strategies in low-incidence countries are not geared to fulsomely address LTBI and subsequent reactivation in migrants and as a result TB disproportionately occurs in migrant populations. This thesis provides a comprehensive evaluation of LTBI diagnostic tests and their use at various stages of the migration process to determine what type of LTBI screening and treatment in migrant populations can be cost-effective. **Figure 1-1** showcases the migration pathway many migrants undergo and the opportunities for LTBI screening throughout. Each major step in the pathway is addressed in this thesis with the overarching goal of guiding policy makers' decisions of which migrant populations to screen for LTBI, how to screen and treat for LTBI, and when to screen for LTBI.

Chapter 2 and 3 of this thesis address the performance of commonly used LTBI diagnostic tests, the tuberculin skin test (TST) and interferon-gamma release assay (IGRA), in the foreign-born. Chapter 4 investigates the cost-effectiveness of post-immigration LTBI screening in new migrants using data from Canada. Pre-immigration LTBI screening in potential immigrants and its cost-effectiveness is examined in the context of low TB incidence countries in Chapter 5. The final research chapter, Chapter 6, uses administrative data from British Columbia to determine if the optimal timing of LTBI screening in foreign-born persons diagnosed with Stage 4 or worse chronic kidney disease (CKD) is at CKD diagnosis or at initiation of dialysis.

To aid the reader in understanding the contextual basis for this research, further description of TB, LTBI, migration, and economic analysis is necessary. The remaining sections of this introduction give special focus to the distinction between TB and LTBI and methods of screening and treating for both; the epidemiology of TB worldwide and in Canada and the difficulty of foreign-born tuberculosis; LTBI management; the underlying medical co-morbidities that drive TB and; the general approach to economic evaluation in relation LTBI. The introductory chapter is concluded with a research rationale.

1.2 Tuberculosis Infection

TB is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) and in 2016 was the cause of death in over 1.7 million people worldwide [5,6]. The organism is acquired through droplet transmission from an individual with active TB, invariably of the respiratory tract [7]. Upon exposure to an active case, infection is dependent on several factors, including, but not limited to, infectiousness of the active case, time spent in proximity to the active case, virulence properties of the MTB strain, and the immune status of the person exposed [8–10]. In those infected, approximately 5% fail to mount a sufficient immune response, and within two-years progress to active disease; for classification purposes, this rapid process is termed primary progression (active transmission) [3,11]. The remaining individuals are able to mount a suitable immune response, which encapsulates the bacteria in a granuloma, however TB bacteria may not be fully eliminated and continue to replicate [12]. Individuals in this state are said to have dormant or latent TB infection. For the majority of people, their immune system is able to contain TB bacteria for the remainder of their lives and active disease never occurs, however for approximately 5-10%, there will be eventual uncontrolled bacterial replication and subsequent active disease; this process is known as reactivation TB [3,7,12,13]. The progression through the spectrum of TB infection is graphically displayed in **Figure 1-2**.

The majority of active TB is pulmonary, however virtually any part of the body can be infected with TB, and in people with extrapulmonary TB, the diagnosis can be more difficult [14,15]. Typically, symptoms such as cough and fever lasting longer than 3 weeks are a signal that someone may have active TB. A detailed symptom screen and medical evaluation can elicit further information about recent exposure to known cases or distant exposure in years past [14]. When TB is suspected, a chest x-ray (CXR) is performed to identify abnormalities. Clinicians can also opt to take sputum samples to perform triplicate measures of acid-fast smear and mycobacterial

culture to determine the presence of TB. While triplicate measurements of acid-fast smear only has a sensitivity of 80% it is quicker than the higher sensitivity test of sputum culture (>95%), which can take 6-8 weeks for clinicians to receive the results due to the slow growing nature of the microorganism [16]. Upon active TB diagnosis, patients are treated for two-months with four effective drugs, most often isoniazid, rifampin, ethambutol, and pyrazinamide. After the "intensive phase" of treatment and completion of 60 doses of each drug, patients are given four more months of treatment or 120 doses in a "continuation phase" with at least two effective drugs, typically isoniazid and rifampin in drug-sensitive cases [17]. In a proportion of patients, however, this will not be adequate to achieve the gold standard measure of treatment success of culture conversion, and the continuation phase can be extended three more months [18]. The outcomes for TB in high-income countries like Canada are very good, with over 90% achieving a favorable outcome by the end of treatment and rates of relapse over the following five-years being very low [3].

LTBI is different from active TB in that it does not present with any symptoms. Persons with LTBI are not infectious and there is no current gold-standard test to confirm the diagnosis [3,7,12]. There are currently two types of diagnostic tests used to aid in the diagnosis of LTBI and both are contingent on the body having previously developed an immune response to TB antigens [19–21]. As a result, in individuals with impaired immunity, LTBI diagnostic test sensitivity generally suffers due to anergy [22]. In addition, the tests are sub-optimal for identifying infection due to unacceptable rates of false-positives in certain populations and generally poor sensitivity, even in immunocompetent individuals [20,23,24]. Furthermore, the tests do not demonstrate any ability to predict if and when reactivation will occur [25]. Nevertheless, these tests are key tools to help identify those with LTBI.

The most commonly used screening test for LTBI is the tuberculin skin test (TST) developed over 100 years ago. The TST uses a non-specific mixture of antigens in the purified protein derivative. This complicates result interpretation in individuals who have received the TB vaccine, Bacillus Calmette-Guérin (BCG), in the past or have been infected with non-tuberculous mycobacteria (NTM), as there is cross-reactivity with the antigens present in the TST [26]. Because of this, those with BCG or NTM may have a false positive TST [27,28]. A TST is performed via intradermal injection of purified protein derivative in the forearm; 48-72 hours later the induration size is measured in millimeters. The size of the induration is generally proportional to the immune response generated by the body as a result of the antigens injected. Various cut-points exist to define a positive test (e.g. ≥5mm, ≥10mm, or ≥15mm) depending on risk of infection, risk of developing TB, NTM prevalence, and BCG vaccination status [3,29,30].

Regardless of cut-point used, however, TST performance is reliant on the skill of the clinician placing and reading the test, as well as the patient's willingness to return to have the test read [29,31–33]. Previously performed meta-analyses evaluating TST performance at cut-off value for a positive result of ≥10mm, found that in populations with active TB the TST had a pooled sensitivity of 76%. In populations at very low risk of TB infection, it had pooled specificity of 60% and 97% among those vaccinated and not vaccinated with BCG, respectively [24,34].

Newer LTBI diagnostic test are the IGRAs, which use much more specific antigens to test for immune sensitivity to MTB and therefore are not affected by BCG vaccination and many common NTM [35]. IGRAs are made to detect TB either by using an enzyme-linked immunosorbent assay (ELISA) or an enzyme-linked immune-spot assay (ELISPOT) and are based on interferon-gamma (IFN-γ) production in response to antigen stimulation. In ELISA, after blood is drawn, it is incubated in mitogen tubes. The tube is centrifuged and the plasma is removed. The IFN-γ produced is then measured via ELISA using a standard curve [36]. In ELISPOT, after blood collection, T-cells are counted and placed in four ELISPOT wells coated to capture IFN-γ. Antigens are added to each well and if the T-cells react with these antigens, IFN-γ is produced and captured. The plate is washed and a secondary antibody is added to bind the captured IFN-γ; a substrate is added to bind this antibody and create spots that can be counted [37,38]. In both ELISA and ELISPOT, indeterminate results are infrequent, but do occur due to faulty controls, impaired immunity, or operator and laboratory factors [35]. In the previously mentioned meta-analyses, the pooled sensitivity of ELISA and ELISPOT based assays was 81%, while the pooled specificity was 96% [24,34].

The decision of which LTBI diagnostic test to use is more complicated than simply assessing test validity. The long history of the TST has allowed extensive characterization of responses, which helps clinicians estimate the future risk of TB when coupled with demographic factors; similar IGRA-based data is scarce [39]. Furthermore, the ease of use and portability of the TST allows for its widespread use in the field and in remote locations, oftentimes where LTBI testing is most needed. However, since this test requires a return visit to yield a result, populations with a high probability of not returning are poor candidates for TST screening; this limits TST use in many high-risk populations, such as the homeless and injection drug users, who may be quite nomadic in their movement [40,41]. Being a newer test, the IGRA has not been as well characterized as the TST and the relatively sharp cut-points for test positivity are a cause of concern in patients who test just above or below the threshold [42]. Serial IGRA testing can lead to unexplained reversions (positive to negative) and conversions (negative to positive). It is this inter-patient variability that hinders IGRA interpretation [43–48]. Additionally, to perform an IGRA, adequate lab space

within a reasonable distance is required to receive results. The increased direct costs associated with the IGRA, therefore make the TST the preferred test in many higher TB incidence, low-middle income countries, despite widespread BCG vaccination use [49]. The advantages and disadvantages of each test must be carefully weighed in specific scenarios and populations [3].

Individuals who test TST or IGRA positive are further scrutinized to come to a diagnosis, which may include examination of medical history, recent TB exposure, CXR, and further testing to rule out active TB [19]. In individuals treated for LTBI, there is no data to suggest that treatment increases risk of drug-resistance in those developing active disease [3]. A decision to treat someone for LTBI requires a careful consideration of the risks and benefits of various treatment regimens. If it is determined an individual is likely to have LTBI and the benefit of treatment outweighs the risk (e.g. adverse drug reaction), they may receive any of the two main LTBI treatment regimens currently in use in Canada [3]. The first regimen is nine-months of daily isoniazid, a thoroughly studied drug that has little risk of drug-drug interaction (DDI), but has an age-dependent risk of isoniazid-induced hepatotoxicity that can be fatal [50]. In a five-year trial, it was determined that 12-months of daily isoniazid lead to a risk reduction in future reactivation of 93% [51]. Post hoc analysis determined equivalency of a nine-month regimen with this regimen, which resulted in the shorter duration being adopted [52]. However, completion of nine-months isoniazid therapy is variable but generally poor in practice, approximately 60% [53,54]. The second regimen is four-months of daily rifampin, a newer regimen that has much better completion in general practice compared to isoniazid [53,54]. Rifampin is generally well tolerated, with low rates of adverse events comparatively, however DDI risk is high in certain subsets of patients, including those on dialysis (due to drug treatment for often occurring co-morbid conditions) and those being treated with anti-retroviral therapy for human immunodeficiency virus (HIV) [50,55,56]. Rifampin efficacy is uncertain, as no randomized controlled trial (RCT) has been published on 4 months of therapy that was designed to assess efficacy in comparison with nine-months of isoniazid. However, a study performed in silicosis patients treated for 3 months noted a 65% reduction in 5-year risk of reactivation TB [57,58]. A further opinion piece and analysis has suggested a four-month regimen would yield ≥80% reduction in reactivation TB risk [59]. In other low-incidence countries a newer regimen consisting of once weekly administration of isoniazid and rifapentine for three months is in use and has demonstrated success in achieving extremely high completion rates and excellent short-term outcomes [60]. In Canada, this regimen is not routinely

available [3,60]. Accordingly, as this thesis uses the Canadian healthcare system as the setting for most analysis, this rifapentine-based regimen will not be discussed further.

As should be evident, the pathogenesis of TB infection can vary widely patient-to-patient and with current technology it is impossible to predict who will progress to active disease with any certainty. Interventions exist to significantly reduce risk of progression from LTBI to active disease, however their implementation is erratic and inadequate in most cases. As such, a significant proportion of TB in low-incidence countries originates from reactivation of undiagnosed and untreated LTBI, perpetuating the cycle of transmission.

1.3 Tuberculosis Epidemiology

1.3.1 World Overview

TB has long been a devastating disease worldwide. The most recent report from 2017 was no exception, with TB being one of the top 10 causes of death worldwide and the leading cause of death due to a single infectious agent, surpassing HIV/AIDS in this respect [61]. In 2016, 1.7 million people lost their lives to TB and 10.4 million incident cases of TB occurred, for a worldwide incidence of 140 cases per 100,000 population (**Figure 1-3**) [6]. Furthermore, it is estimated that one quarter of the world population (approximately 1.7 billion people) currently have LTBI [62]. This reservoir of TB infection has the potential to perpetuate the TB epidemic for the coming century unless it is addressed adequately; using conservative estimates of lifetime risk of reactivation (cumulatively 5%), reactivation TB due to LTBI causes approximately 2 million active TB cases annually.

The highest TB burden regions in the world exist in Africa, South-East Asia, the Eastern Mediterranean, and the Western Pacific, with the epidemic driven, in part, by HIV co-infection, drug resistant TB, poverty, poor nutrition, inadequate access to diagnostics and treatments, and lack of clinician suspicion of TB [5,63,64]. Furthermore, active transmission of TB is common due to the lack of resources available for case finding and contact tracing, the stigma associated with TB, and low level of suspicion of TB by clinicians [63,65,66]. In the Americas and Europe, TB incidence is relatively low and largely affects marginalized populations, such as the homeless, injection drug users, some Aboriginal populations, and migrants [67–70]. The largest contributor in the majority of these countries are migrants, which make up >40% of all TB cases in 88% of low-incidence countries included in a recent survey [4]. The major driver of TB in migrants is reactivation TB due to long-standing LTBI

[71–73]; in many jurisdictions, routine LTBI screening in migrants is not performed and where it is performed, the programs perform sub-optimally [4,53].

TB elimination worldwide requires an adequate response to TB in both the highest and lowest incidence countries aimed at the epidemiologic drivers of TB. World Health Organization (WHO) strategies such as the End TB Strategy [74] and the Framework Towards Tuberculosis Elimination in Low-Incidence Countries [70] are designed to impact reduction in TB incidence rates from the current average decline of 1.5% per year to >10% per year by 2035. Tailoring these strategies to the epidemiologic characteristics of TB in local settings will be one of many necessary steps to reach these targets.

1.3.2 Canadian Overview

After peaking in the mid 1940's with 104 cases of TB per 100,000 population [3], TB incidence in Canada declined rapidly over the ensuing three decades to 16 cases of TB per 100,000 population in the mid 1970's (annual decline of 6%) [3]. Improved understanding of the disease, the advent of streptomycin, isoniazid, and other anti-tuberculosis drugs, and, spurred by an explosion in the gross domestic product per capita, better nutrition and living conditions, improved public health infrastructure, and a significant reduction in the number of TB contacts per case, contributed to this decline [3,75]. Improved case management allowed adequate contact tracing and case isolation aimed to prevent ongoing, active transmission of TB [75]. Indeed, with the rapid decline seen to the mid 1970's, it appeared only a matter of time before TB in Canada was a thing of the past.

Over the ensuing four decades, the decline in TB rates slowed substantially and by 2015 the TB rate in Canada was 4.7 cases per 100,000 population (annual decline of 3%) [3]. Many factors were responsible for the halving of this decline, including the HIV epidemic [76], lack of funding from governmental bodies [66], and a failure to address the socioeconomic drivers of TB in certain populations [64]. Most importantly, however, may be the changing epidemiology of TB. Like many other low-incidence countries, TB disproportionately affects certain marginalized populations [76]. In 2015, over 90% of TB cases occurred in just 25% of the Canadian population [77]. The foreign-born accounted for 71% of TB cases (14.8 cases per 100,000 population; 21% of the Canadian population) and Canadian-born Aboriginals accounted for 20% of TB cases (19.9 cases per 100,000 population; 4% of the Canadian population); the remaining 9% of cases occurred in Canadian-born non-Aboriginals (0.6 cases per 100,000 population; 75% of the Canadian population). The reasons for TB being so prevalent in the two former

populations are complex. The next section will delve into the complexities of foreign-born TB, however for a broad discussion of TB in Canadian-born Aboriginal populations the reader is directed to the following excellent resources [3,78–86].

1.3.2.1 Tuberculosis Epidemiology and Prevention in the Foreign-Born

In the foreign-born, the high proportion of cases is due to increased global migration and changing source locations of new migrants to Canada [3]. In the 1940's, the foreign-born population in Canada was just over 2 million people (20% of the total Canadian population), with >1.9 million originating from Europe and the United States [87]. In 2015 the foreign-born population was 6.7 million people (21% of the total Canadian population), but >4.4 million originate from areas outside Europe and the United States, many with a high incidence of TB [5,6,87]. As a result, while in 1970 only 15% of all TB cases in Canada occurred in the foreign-born, this proportion has nearly quintupled over the subsequent 45 years [3]. While changing migration patterns have driven this dramatic shift in TB burden, the Canadian healthcare system has yet to adapt to the changing TB epidemiology. Canada saw its greatest decline in TB rates by halting active transmission effectively [88], however genotypic studies suggest that active TB in migrant populations in low-incidence countries is driven by reactivation TB due to LTBI acquired prior to migration. Estimates of the proportion of TB cases occurring through this route suggest it may be upwards of 85% [71–73].

Various subgroups make up the term "migrant" or "foreign-born," and TB risk varies between them, however most fall into three major categories: economic class, family class, and humanitarian class [89]. The highest risk category is the humanitarian class, consisting of refugees who have TB rates twice as high as other migrants [3], likely due to poorer health and active transmission associated with crowded conditions [90]. Even though TB screening is done after arrival in Canada for refugee claimants (those applying for refugee status at arrival) these increased rates are consistently seen, suggesting that LTBI screening may be prudent to prevent longitudinal TB cases in this population [3]. Family class migrants are the next highest risk, with TB rates slightly lower than the humanitarian class. The economic class of migrants makes up two-thirds of all new migrants each year and has significantly lower TB rates than family and humanitarian class migrants [3]. Regardless of subgroup, however, TB rates remain significantly elevated when compared to the Canadian-born non-Aboriginal population [77]. Even though steps exist throughout the immigration process to detect TB, at the present no formal LTBI screening is done pre-arrival in migrants to Canada [91].

Currently, all new permanent resident applicants (economic class and family class), temporary visitors staying ≥6 months from countries with a TB incidence ≥30 cases per 100,000 population, and convention refugees (those applying for status prior to arrival, humanitarian class), are required to complete an immigration medical exam (IME) prior to arrival [3]. The IME includes a physical and mental assessment, review of medical records, and laboratory and diagnostic tests, one of which is a CXR that can be used as evidence for further testing to potentially diagnose TB [91]. The intention of the assessment is to identify individuals that: are dangers to public health, are dangers to public safety, or will put excessive demand on health or social services [92].

Individuals diagnosed with TB through CXR or mycobacteriological methods are considered dangers to public health. These individuals are not permitted entry until an adequate course of TB therapy is administered, three consecutive negative sputum smears and cultures are obtained, and they show stability or improvement in their CXR over a period of at least three months. Of over 500,000 IME's performed in 2011, only 0.09% yielded a diagnosis of TB [3].

Individuals who have CXR abnormalities indicative of TB, but who are unable to give sputum, must display stability in CXR over a period of 6 months. Individuals with abnormal CXRs who are able to give sputum but have three consecutive negative smears and cultures, must display CXR stability over a period of 3 months; in these cases individuals are diagnosed with inactive TB [3,89]. All individuals who have received previous TB treatment (including those who received it due to diagnosis during the IME) or who are diagnosed with inactive TB are permitted entry to Canada under the requirement of medical surveillance and must report to provincial or territorial authorities within 30 days of landing; in 2014, only 2.4% of the over 250,000 new permanent residents were flagged for post-landing TB medical surveillance [3,93,94]. Medical surveillance entails reporting to the relevant health authorities for follow-up, which is variable across jurisdictions and may include a subsequent CXR, sputum collection, and/or LTBI screening. The surveillance system is passive, with adherence to surveillance reported to be as low as 60% in Ontario between 2002 and 2011 [94].

With no effort to identify LTBI prior to migration through diagnostic testing with either TST or IGRA, all efforts to identify LTBI are done post-immigration. However with only 2.4% of migrants flagged for post-landing surveillance who could *potentially* receive LTBI screening and notably poor adherence with surveillance, it is plausible that fewer than 1% of new migrants may receive and complete LTBI screening immediately post-immigration. This is specifically important as the highest incidence of TB in new migrants is in the first two-years

post-immigration [3,95,96] and many cases may be prevented if adequate screening guidelines were implemented and executed [96]. No systematic programs exist for LTBI screening in all migrants in the years after arrival and screening most often takes place at a clinician's discretion [3,89,97].

The IME and medical surveillance system was never intended to be a platform for LTBI diagnosis and care and instead intended to detect, among other medical conditions, prevalent TB prior to immigration and flag individuals at high-risk for TB post-arrival for follow-up. In this regard, the current system is quite effective at identifying individuals at immediate increased risk of TB post-arrival, with one-third of all TB cases within two years post-migration in new permanent resident cohorts to Ontario occurring in migrants flagged for medical surveillance [94]. The quandary with this system, however, is that while incidence is highest in the immediate two years post-arrival, the majority of TB cases in foreign-born individuals actually occur greater than two-years after arrival, and the majority appear in those never flagged for post-arrival medical surveillance [3,94]. In response, the most recent TB guidelines in Canada called for post-arrival LTBI screening *to be considered* in certain high-risk migrants after arrival [3], the end result, however, would be over one-third of migrants being considered for screening, a fourteen-fold increase from the current 2.4% flagged for follow-up [97]. The resources required for this undertaking are monumental and require significant communication between federal and provincial/territorial entities. Unsurprisingly, there has been no evidence of uptake of these recommendations.

To compound these shortcomings, when migrants *are* diagnosed with LTBI, other obstacles exist to limit adequate completion of therapy along the steps involved in LTBI care. The complete process of LTBI care, from reporting for screening to completing treatment, is known as the LTBI cascade of care.

1.4 Latent Tuberculosis Infection Cascade of Care

The LTBI cascade of care consists of several steps whereby the patients report for screening and eventually complete LTBI treatment. The initial decision to screen for LTBI must come after careful consideration of the subsequent actions that will take place after the result is garnered; in essence, the decision to screen for LTBI must also come with the decision to treat someone for LTBI if they test positive [3,98]. In light of this, support must be provided to patients diagnosed with LTBI to ensure the completion of treatment. The steps in the cascade of care include identifying persons to screen, performing a diagnostic test(s), receiving the result of the test, performing a medical evaluation to rule out active TB and make a treatment decision, initiating LTBI treatment, and completing

treatment (**Figure 1-4**). With so many steps, gaps in the cascade are expected [53,99]. One of the major shortcomings of domestic LTBI screening programs in low-incidence countries is their inability to ensure that new migrants are screened and treated for LTBI—some estimate fewer than 20% of migrants complete therapy [53,99].

Once the decision to screen has been made, several obstacles to adequate follow-up exist. At the present, approximately 67% of those identified for screening are screened and have their test result read (44% in migrants) [53]. Based on global estimates of TB infection, many potential positive results will be missed. Reasons for this poor follow-up are numerous and largely have to do with socioeconomic and cultural barriers. For many migrants at risk of TB, the native language is not the primary language spoken [100]. Lack of effective communication about what LTBI screening is, the reasons for performing it, and the perceived risk associated with a result (e.g. potential costs) discourages patient engagement [101,102]. Engaging new migrants by providing information in their chosen language and using interpreters to ensure adequate communication may be promising [3,103,104]. In Canadian jurisdictions, many new migrants are not covered by provincial healthcare upon arrival [3]. The added cost of paying to see a doctor can be discouraging [105]; considering making migrants eligible for health insurance immediately after arrival may help mitigate this [3]. MTB disproportionately affects the lowest socioeconomic classes [106,107]. Due to this, usual clinic hours are not an option for many migrants and return visits can be difficult [102]. Extending clinic hours and providing several options for test reading may be solutions [3]. Many migrants vaccinated with BCG do not believe they have LTBI and thus will discount a positive test [3,101]. IGRA-based screening may mitigate this issue. Determining the result of the diagnostic test is the most important step in the cascade as it determines the course of action moving forward. Bridging the earliest gaps in the cascade of care will impact the proportion of individuals who receive LTBI therapy the most and make this a vital area of focus.

With a positive test, it is important to rule out active TB with a CXR and symptom screen before the pros and cons of LTBI treatment are discussed with the patient [3,108]. As this step may involve return visits, approximately 80% of patients complete their medical evaluation. Additional factors associated with this completion may be a low perceived risk of infection (i.e. do not believe the diagnostic test result), discontinuation of financial compensation that may have been provided during screening, busy work schedules, and the need to take time off from employment [105,109]. Upfront patient education at the screening stage may aid in improving the proportion of patients who return for their medical evaluation and perceive LTBI therapy as a valuable investment of their time.

Upon completion of a medical evaluation, clinicians can decide to recommend treatment or not, and if recommended, a patient will have to decide whether to start treatment; approximately 80% of patients who complete their medical evaluation are recommended treatment (63% in migrants) and 94% initiate treatment [53]. Apart from treatment contraindications, several other factors go into the decision to treat. The decision to start treatment—in the absence of severe adverse effects from LTBI therapy—is a commitment to complete treatment so determining if this is feasible is crucial. Some subpopulations, such as the homeless, injection drug users, and persons with mental health issues are at risk for dropout from therapy. Directly observed treatment (DOT) regimens exist in some jurisdictions for LTBI in populations at high-risk of dropout, however these are quite resource intensive [110–114]. In the context of migrants, perceived risk of deportation or loss of immigration status may play a significant role in seeking care and accepting treatment; patient education may work to alleviate this [115]. In addition, lack of clinician knowledge about the risk of LTBI and the necessity of adequately treating LTBI to eliminate TB may impede recommendation and initiation of therapy [116,117]; improving education would aid in increasing the proportion of patients beginning treatment. When taken as a whole, improving patient/provider education and outreach to marginalized populations can significantly impact the number of patients beginning LTBI treatment.

While significant dropout has been seen at previous steps in the cascade of care, the highest rate of dropout is seen after a patient decides to initiate therapy. On average, just over 60% of patients complete LTBI therapy once they begin [53], however this number can vary widely between programs [54]. Typically, isoniazid therapy is prescribed for a prolonged period of time, around nine-months, which is a key reason for the high rate of incompletion in many instances [118]. Further to this, adverse events leading to treatment cessation occur in approximately 6% of patients [119–123]. Use of four-month rifampin therapy can be more attractive to patients who may not complete a nine-month regimen [53] and adverse events leading to treatment cessation are significantly lower with this therapy at approximately 3% [119–123]. However, similar factors seen at other steps of the cascade play a role in treatment discontinuation, including social factors and health system issues, which can be attenuated with improved accessibility, patient engagement, and patient/provider education [113,114,118,124–127].

Gaps in the cascade of care play a crucial role in reducing the impact of domestic LTBI screening and treatment programs. Filling gaps at each step can significantly impact the number of patients who complete LTBI therapy. For groups at increased risk of TB reactivation due to medical co-morbidities, closure of these gaps is even more important as these are the groups generally targeted for LTBI therapy and the groups that stand to gain the

most benefit. While several reasons have been given to explain the high rates of dropout at each step, for the most part these factors have not been adequately addressed, but research is presently ongoing.

1.5 Risk Factors for Reactivation Tuberculosis

The premise behind screening (and subsequently treating) LTBI is to reduce longitudinal incidence of TB by preventing reactivation of TB and subsequent transmission. With current imperfect technologies it is cost-prohibitive to perform LTBI screening on a massive scale so targeting is necessary; for LTBI, this targeting is two-fold. Firstly, LTBI screening should only be directed to populations with an elevated prevalence of LTBI (e.g. migrants) so as to maximize the number of true LTBI cases detected. However, LTBI tests cannot distinguish who will progress to active disease so we must also direct LTBI screening to populations with risk factors that increase their probability of reactivation TB. Thus, while it is important for us to recognize that migrants have elevated rates of LTBI, it is also imperative to identify subsets that are at increased risk of reactivation TB, which for the most part, include individuals with medical co-morbidities that impair immune system function. Select co-morbidities are outlined in **Table 1-1**.

By and large the biggest risk factor for reactivation TB is HIV infection and acquired immune deficiency syndrome (AIDS), which increases ones risk of reactivation from 5-10% over their lifetime to 5-10% *per year* (up to 37 times the risk of someone without any risk factor) [3,128–130]. Effective use of anti-retroviral therapy (ART) can mitigate this risk somewhat, however HIV and AIDS are associated with more than 1.2 million TB cases and 400,000 deaths each year globally [5,131,132]. The literature surrounding LTBI screening in this population is well established and in Canada there is routine LTBI testing upon an HIV or AIDS diagnosis as it has been shown to be highly cost-effective [3,133].

Transplantation, CKD, and dialysis are other risk factors that confer a high increase in reactivation risk due to the immune suppression that exists in these individuals [134–139]. LTBI screening is common in British Columbia prior to transplantation and dialysis, however it has not been implemented in the early stages of CKD (i.e. prior to dialysis and possibly transplantation) [140]. Previous analyses have shown a steadily increasing risk of TB as CKD progresses, which coincides with our understanding of uremia-induced immune suppression being the likely culprit of increased rates of TB [138,141]. In transplant patients, the risk of reactivation is >20 times the risk of someone without any risk factor due to the use of immunosuppressing drugs prior to and after transplant [3]. This

risk, however, is likely confounded by other factors associated with needing a transplant, namely increased age, lifestyle (e.g. alcohol consumption), and related co-morbidities (e.g. CKD).

Use of other immunosuppressing drugs, like tumor necrosis factor alpha (TNF-α) inhibitors, other biologics, and glucocorticoids moderately increase risk of TB [142–146], which has led some authorities to recommend screening for LTBI prior to initiation [147], although scarce economic data exist to support this [148,149]. These studies have demonstrated approximately five times the risk of TB reactivation when individuals are on these agents and with increasing use of biologics and other immunosuppressants, the population potentially impacted will continue to grow [150]. The reason for this increased risk is impairment of adaptive and innate immune responses by many biologics and steroids [151]. In this immune state, the body's ability to keep TB bacteria encapsulated in granulomas is compromised.

Another moderate risk factor for TB is diabetes mellitus (DM). The increased risk for TB associated with DM is relatively low when compared to someone without any risk factors at approximately 2-3 times [152–156]. Those with poorly controlled diabetes (i.e. HbA1c levels >7%) are at higher risk, however [157]. In both instances the main drivers of this increased risk is impairment of T lymphocytes, macrophages, and polymorphonuclear cells, although it is unclear if these are innate defects due to diabetes or a result of a hyperglycemic environment [158]. While the increased risk of TB in someone with DM is minor, the increasing prevalence of DM worldwide has increased the population attributable fraction (PAF) of DM to TB [159]. In fact, while malnutrition is recognized as the risk factor (risk increase for TB of approximately 4 times) with the largest PAF [160,161], DM has the next highest PAF in settings with a high DM prevalence [162]. It is estimated that >420 million people worldwide have DM as of 2014 for a worldwide prevalence of approximately 6%, making the PAF of DM between five and ten percent [163]. WHO guidelines have concluded that even with high rates of DM, the low prevalence of LTBI does not justify LTBI screening, suggesting that further targeting LTBI screening in DM patients with other conditions that increase the risk of TB or to populations with a higher prevalence of LTBI is necessary [164].

Apart from co-morbid conditions, other risk factors for TB exist. Heavy alcohol consumption (defined as 3 or more drinks per day) and cigarette smoking (greater than 1 pack per day), increase ones risk for TB 2-4 times when compared to someone with no risk factor [165–167]. Many confounding factors may play a role in the increased risk seen with alcohol and cigarettes including social patterns associated with their use, co-morbid

conditions associated with extended use, and their effect on the immune system [168,169]. The exact impact each of these confounders may have on overall risk has yet to be elicited, however.

Utilizing the data surrounding these co-morbid conditions and their effect on TB risk to target screening in migrant populations will be essential to reducing the TB burden. Comprehensive economic evaluation can help determine subgroups that would present good value for LTBI screening and help prioritize implementation amongst them.

1.6 Economic Evaluation

In healthcare, economic evaluation is generally used to determine the value an intervention provides, in a specifically defined subgroup, compared to current practice or another intervention (e.g. the value a new TB therapy provides in HIV patients; the value water fluoridation provides in Canada; the value yearly flu vaccination provides in healthcare workers) [170]. When evaluating the value of these interventions, the incremental value (i.e. the difference in value between this new intervention and current practice and/or other interventions) is interpreted in relation to the incremental cost (i.e. the difference in costs between this new intervention and standard of care and/or other interventions) to arrive at an overall value measure. One such measure is the incremental cost-effectiveness ratio (ICER) [171]. The ICER is calculated as the incremental cost divided by the incremental value of an intervention via: $\text{ICER} = \frac{\text{Cost}_{\text{intervention}} - \text{Cost}_{\text{standard of care}}}{\text{Value}_{\text{intervention}} - \text{Value}_{\text{standard of care}}}$. The ICER is used to guide policy makers' decisions on interventions by giving an easily interpretable value of the increased costs and benefits of a proposed intervention. A policy maker can take the cost per benefit reported and make decisions based on their willingness-to-pay (WTP) for such a benefit [171]. For example, a policy maker may be only willing to spend $10,000 to prevent one case of influenza—the ICER provides a value that can instantly be compared. If the ICER is equal to or less than a policy maker's WTP, then an intervention is generally considered cost-effective, while an ICER greater than a policy maker's WTP is generally considered not cost-effective. An alternate measure of the absolute value of an intervention is the net monetary benefit (NMB), which is calculated via: $\text{NMB} = (\text{Benefit} \times \text{WTP}) - \text{Cost}$. Comparing interventions based on their overall NMB can be a useful way to prioritize interventions for policy makers based on their WTP threshold: the larger the NMB, the more value that intervention provides to society.

One way to define value is the decrease (or increase) in a key clinical outcome provided by the intervention (e.g. fewer TB deaths, fewer cavities, fewer influenza infections, increased years of survival). The second way is to

define value based upon utility, which is a measure of an individual's health status, where 1 represents a perfectly healthy state and 0 represents death [172]. This second method is preferred in many instances as this is a standardized measurement of benefit. The most common utility measure is the quality-adjusted life year (QALY) that not only takes into account the increased duration of life an intervention provides (which may be none in some cases), but also the quality of life in each of those years of life [173]. In the previous examples given, on a population level, fewer TB deaths, fewer cavities, fewer influenza infections, and increased survival all affect utility and the benefit instantly becomes comparable amongst them.

Utility is elicited largely through two methods: standard gamble (SG) and time trade off (TTO). The SG procedure involves gauging participant's willingness to risk death in exchange for being free of a particular health state, [174] while the TTO procedure involves gauging a participant's willingness to exchange years of life to be free of a particular health state [175]. Other methods can be used, such as the visual analogue scale, but these are two main methods to measure utility. As these processes can be time intensive, standardized questionnaires have been developed to estimate utility values. Example questionnaires are the 6-item short form descriptive system (SF-6D) derived from the 36-item Short Form Survey [176], the Health Utilities Index Mark 3 (HUI-3) [177] and the EuroQuol five dimensions questionnaire (EQ-5D) [178]. Each of these questionnaires behaves differently and has been calibrated based on preference weights obtained from specific populations using either the SG (SF-6D, HUI3) or TTO (EQ-5D). In some cases, these questionnaires are not specific enough to adequately capture the quality of life experienced by patients in certain disease states [179,180]. In these instances, it is possible to map a disease specific questionnaire to scores from one the three aforementioned questionnaires so as to allow generalizability of results [181,182]. Unfortunately, there is no currently validated disease specific questionnaire for TB at this time. Regardless, selection of which method to use is dependent on context; a calibrated questionnaire in Canada will not perform equally well in Vietnam, and vice-versa [183].

Further considerations must be given when deciding how to develop an economic model to compare value or benefit, namely the perspective that will be taken and the discount rate used. Perspective refers to how costs and benefits will be accounted for [184]. In many instances, the costs of interventions originate from the healthcare system so it is common to take a healthcare system perspective when accounting for costs incurred. In other situations, researchers can be interested in the cost to society as a whole and decide to take a societal perspective when accounting for costs, which will not only consider costs to the healthcare system, but also to society in the

form of transportation costs, and productivity loss (e.g. absenteeism, and/or presenteeism) [185]. Once a perspective is decided, an appropriate discount rate for future costs and benefits should be selected. Use of a discount rate is common practice as it represents our preference for immediate benefits over future benefits [186,187]. Further factors influencing our decision to discount include: the risk that expected future benefit is never realized due to accidental death or large scale disaster and to account for inflation (i.e. incomes increase over time resulting in the marginal value of a benefit decreasing) [188]. The U.S. panel has decided a discount rate of 3% for costs and benefits is appropriate, citing available data on economic growth and corresponding estimates of the real consumption rate of interest [189]. Alternatively, the Canadian Agency for Drug Technologies and Health (CADTH) in previous years suggested a 5% discount rate, citing society's time preference, but has since updated their recommendations to a 1.5% discount rate, informed by provincial bond rates that have given near uniform returns over time (i.e. a similar measure used by the U.S. panel) [190]. High discounting rates may mitigate the benefit seen with preventative interventions (e.g. vaccines, prophylactic therapy) that may not be seen with interventions providing immediate benefit (e.g. asthma medications, antibiotics).

The decision on which type of economic model to use is dependent on several factors, including the types of questions that need to be answered, the population being modeled, wealth of available data, and logistics [171]. For longitudinal economic models in healthcare, two main model types are used: aggregate level models and individual level models. Aggregate models are often advantageous as they simulate a population on a collective scale assuming population homogeneity (e.g. decision tree, most Markov models), which are adequate for many situations [171]. However when more granularity is needed, individual-based (microsimulation) models are preferred. These models simulate individual people and can more robustly account for much of the heterogeneity in risk factors, disease course, and outcomes, compared with aggregate models. However, these models may be time consuming to develop and model calculations are limited by computational power and long run times (e.g. discrete event simulation, individual sampling model) [171]. It has been common practice in TB research to use Markov models when questions require models to be answered. These models assume that future states only depend on the current state (e.g. are memory-less) and that populations are homogeneous, simplifying assumptions that aid in model development and understanding [191,192]. In practice, the homogeneity assumption may be violated. To account for this, models may be run multiple times using several different sets of parameters to represent many subpopulations. Use of an individual level model, such as a discrete event simulation (DES) model, may be more

appropriate in many cases to delve into how different subpopulations may respond to an intervention [193]. In DES, time moves forward at discrete intervals and simulated patients have the ability to "remember" previous events, allowing simulated patient pathways to better reflect reality [193]. These models are streamlined by creating sets of equations to calculate transition probabilities based on population covariates that can be sampled for each individual entity created.

Regardless of model type chosen, uncertainty in parameters will exist and has to be evaluated. Two ways to evaluate this uncertainty is through univariate (one-way) sensitivity analysis and probabilistic sensitivity analysis (PSA) [194]. In univariate sensitivity analysis, each parameter is varied one at a time, normally to a high or low value different from its point estimate used in the model, and the results are compared to the results of the deterministic model. This form of sensitivity analysis can help identify parameters that may have a significant impact on the overall conclusion of the analysis. Researchers can use this information to further investigate parameters to remove uncertainty [195]. In PSA, all parameters are varied at once, sampled from a probabilistic distribution that has been pre-specified. In PSA, both first-order uncertainty (variability in outcomes of identical patients) and second-order uncertainty (uncertainty around parameter estimates) are accounted for via specification of an outer sample size (i.e. second-order uncertainty; the number of times a parameter is sampled from its probabilistic distribution) and an inner sample size (i.e. first-order uncertainty; the number of patients simulated for each outer sample) [196]. PSA is the most useful type of sensitivity analysis as it accounts for thousands of different parameter combinations.

A comprehensive reporting of deterministic analysis and sensitivity analysis results (both typographically and visually) completes an economic evaluation. Deterministic results such as population costs and benefits are reported in table-format along with calculated ICER's of new interventions in relation to the base case. Results of univariate sensitivity analysis are generally reported using tornado diagrams [197]. It allows policy makers to quickly identify the most impactful parameters on the results. Results of PSA are reported in several different ways. Cost-effectiveness planes are very useful when a single intervention is compared to another [198]. See example and further explanation in **Figure 1-5.** Policy makers can use this plane to determine how often an intervention falls in a specific quadrant and determine how variable results are. Cost-effectiveness acceptability curves (CEAC) display results of PSA in the form of likelihood of being cost-effective at various WTP thresholds (see example in **Figure 1-6**). This result is particularly important as different jurisdictions can use different thresholds or WTP thresholds may

vary over time; this graph provides ease of interpretation and flexibility [199]. While highly useful when a small number of interventions are compared, CEAC's become convoluted when numerous interventions are used and may not be appropriate. Efficiency frontiers can accommodate many different interventions easily by plotting the benefit gained against the total cost associated with an intervention [200]. A line is then used to connect the least expensive intervention to the next best value intervention in comparison, which creates a "frontier" where policy maker's can decide which intervention to fund at a given budget. The best value intervention on a frontier is determined by the intervention with the largest incremental NMB compared to the base case and is calculated via: Incremental NMB = $NMB_{intervention} - NMB_{standard\ of\ care}$. See example efficiency frontier in **Figure 1-7** for further explanation.

1.6.1 Economic Evaluation of LTBI Screening

Economic evaluations of LTBI screening have almost exclusively used a decision tree structure with Markov nodes and many do not report QALYs as the outcome, instead electing for clinical outcomes such as number of TB cases prevented and number of TB deaths averted [192,201,202]. Moreover, the results of studies can be vastly different due to underlying assumptions and the level of detail modeled. This section serves to provide an overview of the cost-effectiveness literature surrounding LTBI screening in populations with high-risk co-morbidities or the foreign-born.

Several systematic reviews have been completed summarizing most of the model-based LTBI cost-effectiveness literature, yielding the conclusion that more data are needed before recommending LTBI screening in any population except those with HIV [192,201,202]. Nine studies [133,203–210] have created economic models to evaluate LTBI screening in the foreign-born (excludes contact tracing and outbreak investigations), while eleven studies [133,148,149,211–218] evaluated immunocompromised populations (e.g. HIV, TNF-α inhibitors, dialysis). No study has *properly* evaluated screening of immunocompromised migrant populations. As mentioned previously, LTBI screening is most effective in populations with a high prevalence of LTBI and risk factors that increases their risk of reactivation, making this a major gap in the LTBI economic literature.

1.6.1.1 In the Foreign-Born

Khan *et al* [203] completed the earliest cost-effectiveness study in the foreign-born in 2002, detailing LTBI screening and subsequent treatment in 18-year old migrants to the United States from various regions. The results of this study suggest net savings if the most cost-effective (i.e. intervention with the lowest cost per QALY gained or

per TB case averted) regimen was selected for screening. When evaluating the parameters selected however, there was significant overestimation of TST specificity in migrants from regions with a high BCG prevalence (90% specificity estimated vs. 60% specificity reported in the literature [section 1.2 of this thesis]), significant underestimation in costs, and an assumption of rifampin treatment equivalency with isoniazid treatment. Considering these issues significantly underestimate the overall cost of a universal LTBI screening program, the results of this study might not be enough to recommend LTBI screening in new 18-year old migrants.

An analysis of IGRA and TST screening in new migrants from various TB incidences was completed by Oxlade *et al* [204]. The model developed uses reasonable assumptions for costs and test parameters, however it likely overestimates the prevalence of LTBI in new migrants from moderate (60 cases per 100,000 population) and high (120 cases per 100,000 population) countries, which would yield longitudinal TB incidences well above those experienced in countries like Canada. Despite this, the model makes more reasonable assumptions for LTBI prevalence in low (2 cases per 100,000 population) incidence countries. Given a baseline reactivation rate of 1.1 per 1000 person years [219], in the Canadian-born (28.4 million in 2014; 1.7 cases per 100,000 population) [220], this model suggests approximately 410 TB cases—the true incidence in 2014 was approximately 480 TB cases. The study concludes that in the most optimistic scenario the costs per TB case prevented are $430,000, $48,000, and $46,000 (2004 CAD) in migrants from low, moderate, and high incidence regions, respectively. Considering the cost of managing a TB case is approximately $20,000 [221] and the probable overestimation of LTBI prevalence, this question warrants further evaluation beyond this study.

Linas *et al* [133] completed a comprehensive cost-effectiveness analysis of LTBI screening in long-standing migrants (i.e. who have landed >5 years prior) and recent migrants using TST or IGRA. The model used positive TST prevalence, TST sensitivity, and TST specificity to estimate LTBI prevalence in each of these groups. Baseline reactivation rate was estimated to be 0.79 cases per 1000 person years using a previously published formula that was risk adjusted; this rate is significantly lower than estimates (1.1 to 1.9 cases per 1000 person years) published previously by the same group [219]. Further, the model does not consider all aspects of the cascade of care and likely overestimates the number of individuals completing screening and beginning therapy. The results of their model suggest good value in screening recent migrant adults with an IGRA ($35,200 per QALY gained), but diminishing returns on screening long-standing migrants as their age increases due to a reduction in life years to gain due to aging (~$60,000 per QALY gained if age <45 years, >$100,000 per QALY gained if age ≥45 years). While

promising results from a robust model, not considering all aspects of the cascade of care and assuming full adherence with LTBI screening in recent migrants will overestimate value.

The National Institute for Health and Care Excellence (NICE) conducted two economic analyses on screening new migrants from high prevalence countries using input parameters from two different studies [205]. The model assumed a LTBI prevalence of 30%. All listed parameters were reasonably estimated, however reactivation rate and the costs of managing an active TB case were not explicitly reported, which are two of the most important parameters in LTBI economic models. Nevertheless, the model suggests cost-effectiveness using either set of parameters when screening with an IGRA at a WTP of £30,000 per QALY (~$50,000 CAD per QALY). Using the parameters derived from Pai *et al* [34] it was found that sequential screening with TST followed by IGRA was more cost-effective than IGRA alone; under these circumstances, LTBI prevalence had to be higher than 20% for this intervention to be cost-effective at a WTP of £30,000 per QALY. In sensitivity analysis, reactivation rate was varied from 1% per year to 30% per year; using an IGRA was cost-effective at a WTP of £30,000 per QALY when the reactivation rate was at least 5% per year in both analyses.

Pareek and colleagues [206] completed an analysis that evaluated the cost-effectiveness of LTBI screening for new migrants who were 35 years of age or younger according to NICE guidelines (≥16 years of age and symptom of active TB or from a country with TB incidence ≥40 cases per 100,000 population). The model examined use of TST alone, IGRA alone, or sequential screening with an IGRA if TST-positive for screening and only examined combination 3-month isoniazid and rifampin for treatment. Most parameters were reasonable except the proportion of new migrants completing treatment (95% accept, 85% complete). The most cost-effective intervention was screening migrants from countries with TB incidence higher than 250 cases per 100,000 with an IGRA (£21,565 per TB case averted) and not performing entry CXR. Reducing TB incidence to higher than 150 cases per 100,000 yielded an ICER of £31,867, while reducing it to higher than 40 cases per 100,000 resulted in an ICER of £34,754. Due to only analyzing one treatment method (effectiveness of 65%) and estimating very high treatment completion rates, further investigation is necessary.

Pareek *et al* [207] also performed a cost-effectiveness analysis of recent migrants (<5 years after arrival) who were 35 years of age or younger and had an indication for IGRA screening. Model parameters were informed by routinely collected IGRA results of this cohort due to referral from various healthcare services. Most parameters selected were reasonable, however the proportion of migrants accepting and ultimately completing treatment was

likely overestimated (95% accept, 85% complete). The study found that screening migrants 35 years of age or younger from countries with a TB incidence >150 cases per 100,000 yielded a cost per TB case averted of £20,818. Increasing TB incidence to >250 cases per 100,000 yielded a cost per TB case averted of £17,956. Similarly to Oxlade *et al* [204], the choice of key parameters and ICER's very close to the average cost of managing a single TB case means this question warrants further investigation.

Porco *et al* [208] evaluated LTBI screening of new high-risk migrants flagged for post-arrival follow-up due to pre-immigration medical screening (evidence of infection/abnormal CXR, but no active disease). The model used data from California and projected the added QALYs and costs of implementing LTBI screening in this population. The model assumes very low utility for those with TB (0.45) compared with more recent estimates and assumes very high TST performance (99% specificity, 93% sensitivity). They found that implementing LTBI screening in this high-risk group resulted in saving $25,000 (2004 USD) and adding 8 QALYs per 1000 migrants in a 20-year period. Had more realistic utility and diagnostic values been used, it is likely that these results would change drastically. For comparison, Dasgupta and colleagues [222] completed a similar study evaluating post-arrival follow-up of a similar cohort flagged due to CXR abnormalities. The authors used data from a TB clinic in Montreal to evaluate the true yield of a program under routine conditions. The conclusion was that performing LTBI screening came at a cost of $65,126 (1998 CAD) per TB case prevented, drastically different from those seen in the study by Porco *et al*. As a result, further evaluation of post-arrival surveillance programs is required.

Schwartzman and Menzies [209] completed an economic evaluation of TST screening as an alternative to typical pre-immigration CXR screening to detect TB. In this analysis, high LTBI prevalence (50%) and low LTBI prevalence (5%) were evaluated with an assumption that in those testing positive with LTBI, approximately 35% adequately complete therapy, well in line with recent estimates. Yet an area of concern with this analysis is the high sensitivity (99%) and specificity (97.5%) of the TST used in this model that would overestimate the number of LTBI cases detected and underestimate the cost of improperly prescribing preventative therapy. Nonetheless, the study found similar costs per TB case prevented in both high and low LTBI prevalence at $66,759 and $68,799, respectively. This is almost certainly due to the overestimation of TST performance resulting in nearly all cases detected, with few false positives. Due to this, a more up-to-date analysis of pre-immigration LTBI screening in areas of increased LTBI prevalence is required.

Schwartzman and colleagues [210] developed a cost-effectiveness model to evaluate dual implementation of expanded directly observed therapy short-course (DOTS) and pre-immigration LTBI screening using a TST in Mexico. While it was found that funding expansion of DOTS in Mexico was highly cost saving, the addition of LTBI screening was cost-prohibitive, costing $648,379 per TB case averted (2003 USD). The model likely overestimated TST specificity (85% specificity estimated) in Mexico where a booster BCG vaccine was in effect until 1998 and vaccination coverage is excellent, however had reasonable assumptions for costs and other risks such as adverse events. This limitation would only bias the ICER downwards and while it may not provide the most accurate overall result, it is convincing evidence that universal pre-immigration LTBI screening in migrants from a low-incidence country is not cost-effective.

It is evident that the choice of input parameters plays a significant role in the results of these economic analyses. Six studies evaluated post-arrival LTBI screening and even though several of these studies remained optimistic on select key parameters, the results generally do not favor mass foreign-born LTBI screening. In the two studies evaluating pre-immigration LTBI screening [209,210], the results do not favor implementation in low LTBI prevalence settings and serious questions about parameter selection exist in the study evaluating its use in high LTBI prevalence settings. In the single study evaluating post-arrival LTBI screening of migrants with prior evidence of infection [208], the intervention was found to be cost-effective, however real world data from a similar program disputes the results [222]. Considering the heterogeneity in results, a re-evaluation of pre-immigration and post-arrival screening of migrants with up-to-date, realistic information would further inform policy makers of the value of such programs.

1.6.1.2 In Populations with High-Risk Co-Morbidities

Shrestha *et al* [211] completed a cost-effectiveness analysis of treating LTBI with isoniazid therapy with or without prior TST screening in newly diagnosed HIV-infected individuals in Uganda. The model assumed a high LTBI prevalence (34%) but this is not unreasonable for a high prevalence region like Uganda. The model did assume unreasonable TST sensitivity (89%) and specificity (95%) given that anergy is common in HIV populations yielding sensitivity closer to 70% [223] and that there is a universal BCG vaccination schedule in Uganda [224]. Nevertheless, in a situation where no screening took place and all were immediately treated with isoniazid, an additional 30 QALYs were gained per 100 patients over their lifetime. Generalizing this benefit to similar HIV patients, a program could incur incremental costs of approximately $1.5 million at the national level and still be

cost-effective. While this study demonstrates the benefit of treating LTBI in newly infected HIV patients, studies in high-income countries are necessary to definitively recommend it in these settings.

Burgos and colleagues [212] conducted an economic evaluation of screening adults at very high-risk for LTBI and HIV in Mexico with an IGRA. The initial distribution of health states used in the model were LTBI prevalence of 58% and HIV prevalence of 4%; LTBI/HIV co-infection had a prevalence of 2.3%. In individuals with HIV, the probability to progress to active TB was reasonable at 5.4% per year, however no adjustment to IGRA performance in HIV infected individuals was done and the completion rate of preventative therapy was not stated. In this high prevalence population, 380 incremental QALYs were gained through targeted LTBI screening and treatment in a population of 1000 individuals over a 20 year time horizon. These results are similar to those seen by Shrestha and colleagues [211] and similarly require study in high-income countries prior to definitive recommendation.

Azadi and colleagues [213] completed a study evaluating the implementation of a training program intended to increase the frequency of TST followed by preventive therapy in HIV patients in Brazil. Model parameters were derived from the trial completed evaluating this program, as such test sensitivity and specificity were considered irrelevant (TB rate was directly modeled given test results from the data). The model used disability-adjusted life years (DALYs) as its outcome, a measure of disease burden that rather than counting the number of quality-adjusted life years a cohort lives (like the QALY) measures the number of life years *lost* due to disability, disease, or early death [173]. This study, based on a Markov model, found that increasing the frequency of TST use (and in essence administration of isoniazid preventive therapy) averted 1.14 DALYs per 100 patients at a cost of $2594 (2010 USD) per DALY averted. Comparable to the aforementioned studies in HIV patients, how this research will translate to high-income settings is still unclear.

Capocci *et al* [214] analyzed the cost-effectiveness of LTBI screening newly diagnosed HIV patients in a high-income, low-incidence setting in two different scenarios: low frequency of anti-retroviral therapy and high frequency. The study evaluated different CD4 cut-offs to determine whether IGRA screening was warranted and compared it with no IGRA screening. Using real world data, they found that as anti-retroviral therapy use increased, cost-effectiveness of LTBI screening expectedly decreased. At present, where anti-retroviral use is very common, targeting screening according to CD4 use, region of origin, and duration of anti-retroviral use was highly cost-effective at €5399 (2012 value) per TB case prevented, while screening all came at a cost of €11,130 per TB case

prevented. Similarly, the targeted screening approach came at a cost of €9332 per QALY gained and screening all came at a cost of €18,928 per QALY gained. Based on this data, even if targeted screening was not used, universal LTBI screening in HIV patients falls well below accepted WTP thresholds and should be performed.

Kowada [215] evaluated LTBI screening of HIV positive pregnant women from high TB burden countries using TST, IGRA, or a dual strategy where both tests are given and a single positive represented a positive result. While most model parameters selected were reasonable, the model assumed a relatively small increase in reactivation risk due to HIV of 4.5 (literature value is approximately 37). Furthermore, the model only evaluates a scenario where one *must* screen for LTBI and does not evaluate the incremental benefits of such an intervention compared with not screening. Due to this, it is difficult to make any screening recommendations. Nevertheless, the model found that in a population with an LTBI prevalence of 32%, the most cost-effective option was to perform sequential screening. Only 6-month isoniazid therapy was evaluated. While this evaluation is of interest, lack of comparison to a base case hinders its utility greatly.

Swaminath *et al* [148] evaluated screening for LTBI during treatment with prednisone and prior to initiation of TNF-α inhibitors in 35-year-old males with moderate-severe Crohn's disease. The model had a short time horizon (one year) and questionable choices in parameter selection. Firstly, the reactivation rate in individuals with LTBI was assumed to be 19% for those on biologics, however this is over 100 times higher than common estimates of reactivation rates in individuals with longstanding LTBI. Further, it assumes a TST sensitivity of 15.13% and IGRA sensitivity of 76.78%. Studies in HIV patients (highly immunosuppressed) do not show a clear superiority of TST to IGRA and studies in patients on biologic therapy show high levels of concordance between the tests [35,225], suggesting that these parameter estimates may be flawed. The study concluded that screening with IGRA prevented 4.92 TB cases in the first year compared to TST screening with a cost savings of $71,520 (2011 USD).

Laskin and colleagues [149] assessed LTBI screening in 5-year-old males with kidney disease prior to initiation of steroid therapy. The model utilizes a lifetime horizon with an LTBI prevalence estimate of 1.1%. Other selected parameters are reasonably sourced, however the assumption of reactivation risk declining by 10% per decade representing self-healing is dubious and assuming a perfect utility for the healthy state (especially considering the patients have kidney disease) is likely inaccurate. Finally, the model assumes children will always

be on prednisone, which is not necessarily the case with idiopathic nephrotic syndrome. The model concludes that no screening is dominant to targeted or universal TST screening in a population with minimal LTBI prevalence.

Kowada [216] completed an economic evaluation of screening for LTBI using a TST or IGRA prior to initiation of TNF-α inhibitors in 40-year-old rheumatoid arthritis patients. The model parameters selected for test performance were reasonable, however other methodological issues exist. Firstly, the author states a societal perspective was taken but does not provide relevant cost data. Secondly, the baseline prevalence of LTBI (or baseline TST/IGRA positive prevalence) is not stated. Finally, there is no indication of standard of care. The model determines that IGRA screening is dominant to TST screening in this population.

Van der Have *et al* [217] created a model to assess LTBI screening prior to TNF-α inhibitor therapy in a population of 30 to 60 year old patients with Crohn's disease. In the study, conventional LTBI screening of TST and CXR was compared with the same approach plus a confirmatory IGRA in those TST-positive. The model developed assumes a 9% LTBI prevalence based on positive TST prevalence, however when evaluating IGRA screening, it assumes a 15% reduction in LTBI prevalence from the base case (due to discordance with TST), which may impact conclusions. The model found the addition of an IGRA was not cost-effective, at a cost of €64,340 per QALY gained.

Kowada [133] developed a Markov model to determine if LTBI screening during hemodialysis was cost-effective in a cohort of 40-year-old patients. Similar to other studies by this author, model parameters are generally reasonable, but other issues exist that limit generalizability to targeted settings. The author assumes a significantly higher prevalence of LTBI (40%) that what is seen in traditional low-incidence settings, even though the study uses Japanese specific data. Furthermore, there is no comparison to no LTBI screening in this population, inhibiting our ability to draw any conclusions on cost-effectiveness. The model does determine that IGRA screening is dominant, but without a comparison to an absence of LTBI screening, it is impossible to recommend LTBI screening in dialysis patients based on this study.

In addition to their analysis in foreign-born populations, Linas and colleagues further evaluated LTBI screening in populations with medical co-morbidities, including those with: HIV, DM, end-stage renal disease (ESRD), silicosis, and conditions requiring immunosuppressive medications. In addition to criticisms voiced in section 1.6.1.1, the populations examined in this portion of the study have an extremely low prevalence of LTBI. As mentioned in section 1.6.1, LTBI screening is most valuable in populations at high-risk of reactivation in addition to

having a high prevalence of LTBI. While the aim of the paper was to look at LTBI screening specifically in the United States, a significant opportunity was missed to evaluate LTBI screening in these populations at an increased LTBI prevalence. The study concluded that LTBI screening in HIV populations (twice the LTBI prevalence and twenty-times the reactivation rate of other examined populations) is cost-effective ($12,800 per QALY), while the remaining conditions examined were cost-prohibitive, with ICERs >$350,000 per QALY in populations with silicosis, DM, and ESRD and $129,000 per QALY in populations on immunosuppressive medications.

While much is known about HIV and the benefit LTBI screening plays in the population at any LTBI prevalence, knowing whether to screen for LTBI in populations with other co-morbidities is less clear. LTBI screening can provide significant benefit to immunocompromised populations who would have a worse prognosis if TB occurred [226,227], yet the yield (i.e. the number of potential cases prevented) of screening must be high enough to warrant intervention. As of now, it is uncertain what threshold for LTBI prevalence and reactivation risk must be seen for LTBI screening to be cost-effective and how each threshold changes in regards to changes in the other. The evidence supporting current policy recommendations of LTBI screening at co-morbidity diagnosis is weak. Analysis of these co-morbidities in realistic populations at increased LTBI prevalence would provide strong evidence for policy implementation in high-yield populations and lay the foundation for future work.

1.7 Research Rationale

To date, several national healthcare programs have recommended LTBI screening in high prevalence and/or high-risk populations, but the underlying evidence is sparse and implementation is variable. While some existing evidence suggests LTBI screening can prove valuable in certain situations, methodological concerns in these studies and uncertainty about the absolute cost of interventions to a healthcare system give pause. TB elimination in low-incidence countries will never occur unless new and innovative approaches are undertaken. Implementation of these approaches needs to be supported by convincing real world evidence on cost, benefit, and feasibility. This thesis aims to fill several knowledge gaps and provide credible evidence about costs and benefits of LTBI interventions, while dedicating significant discussion to the feasibility of the suggested interventions. Specifically, the main gaps addressed are:

(1) Current estimates of LTBI prevalence in foreign-born populations are based on TST reactivity. Much is known about the risk of TST false positives in this population, but no meta-analyses exist to estimate LTBI

prevalence based on IGRA reactivity using the wealth of IGRA data now available. Chapter 2 and 3 of this thesis provide a comprehensive evaluation of TST and IGRA screening in foreign-born populations with a focus on test positivity stratified by TB incidence in country of origin.

(2) Significant methodological issues and parameter selection in current economic models mars the cost-effectiveness of post-immigration LTBI screening. While in the past it seemed that this could be an effective method of TB prevention, new literature is available to suggest otherwise. Revisiting this topic (Chapter 4) is necessary to more accurately inform policy makers who have made recommendations on outdated literature that are unlikely to be economically feasible [97].

(3) Recent evaluations of pre-immigration LTBI screening as a part of routine medical exams are scarce, yet this remains one of the most attractive options for TB prevention from a practical point of view for immigrant-receiving countries; doing so can potentially more than double the yield of a traditional post-landing LTBI screening program. An evaluation of the costs and benefits of a program is of high interest to many national TB programmes as they continue to re-evaluate TB policy (Chapter 5).

(4) LTBI screening recommendations in several national TB programs suggest screening at the time of diagnosis for select co-morbidities, yet the data supporting these recommendations is weak. Current economic evaluations are focused in low yield populations for which these recommendations were never intended. A growing population of interest is those with CKD. Current policy in British Columbia is to screen at the initiation of dialysis [228], but there is no economic evidence to support this recommendation. A comprehensive evaluation of LTBI screening in late stage CKD where risk of TB is still elevated [138] and LTBI screening at dialysis initiation could help inform the potential morbidity and mortality that could be averted by such programs (Chapter 6).

1.8 Tables

Table 1-1. Select risk factors for reactivation tuberculosis

Risk Factor	Relative Risk*	Prevalence†	Estimated PAF°	Reason(s) for Increased Risk	References
HIV/AIDS	20-37	212	3.9-7.1%	Dysregulation of both innate and adaptive immunity	[3,229–231]
Transplant	20-74	69	1.3-4.8%	Immunosuppressive therapy post-transplantation	[3,232,233]
Dialysis	3.4-25.3	58	0.1-1.4%	Uremia-induced immune-suppression and reduced function of T-cells, B-cells, and neutrophils	[3,141,232,234,235]
Diabetes	2-3.5	9300	8.5-18.9%	Impaired T-lymphocytes, macrophages, and polymorphonuclear cells	[3,158,236]

*Risk of reactivation TB compared to someone with no risk factor
†In Canada per 100,000 persons
°Calculated via: (Prevalence*(Relative Risk – 1))/((Prevalence*(Relative Risk – 1))+1)
PAF: Population Attributable Fraction

1.9 Figures

Figure 1-1. Typical migration pathway for new permanent residents to Canada and potential areas for implementation of routine LTBI screening

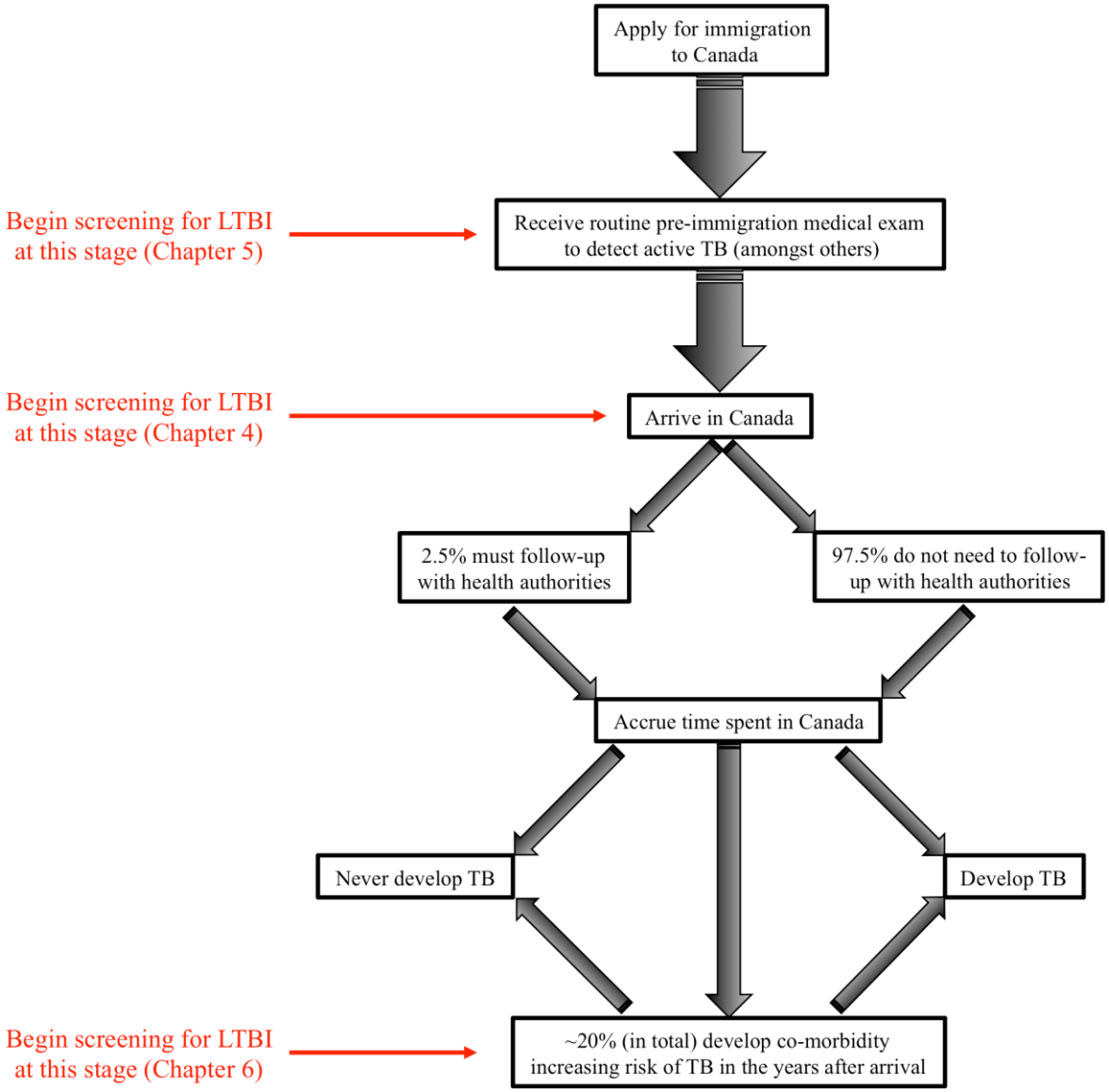


Figure 1-2. Typical pathogenesis of tuberculosis infection

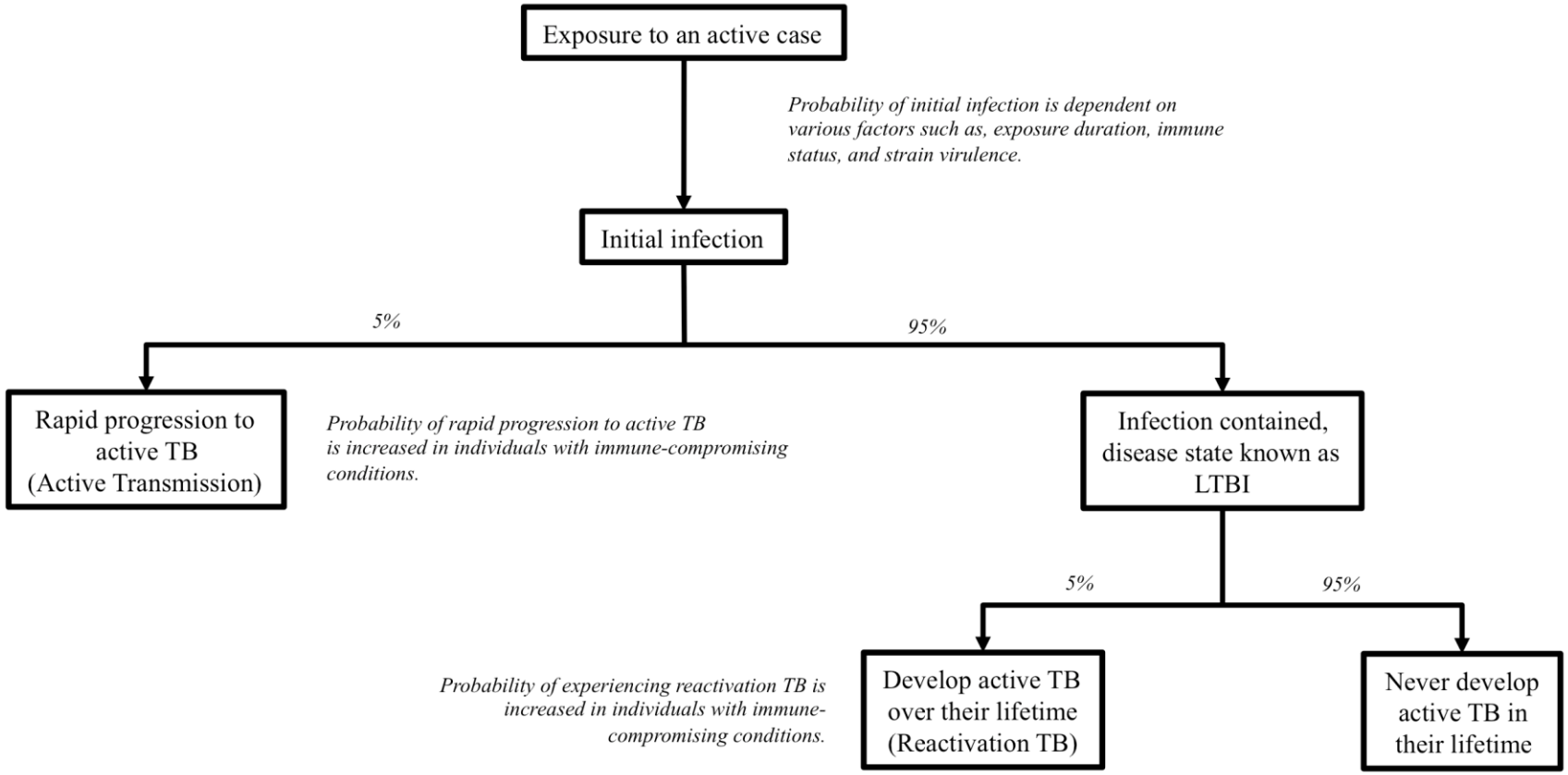
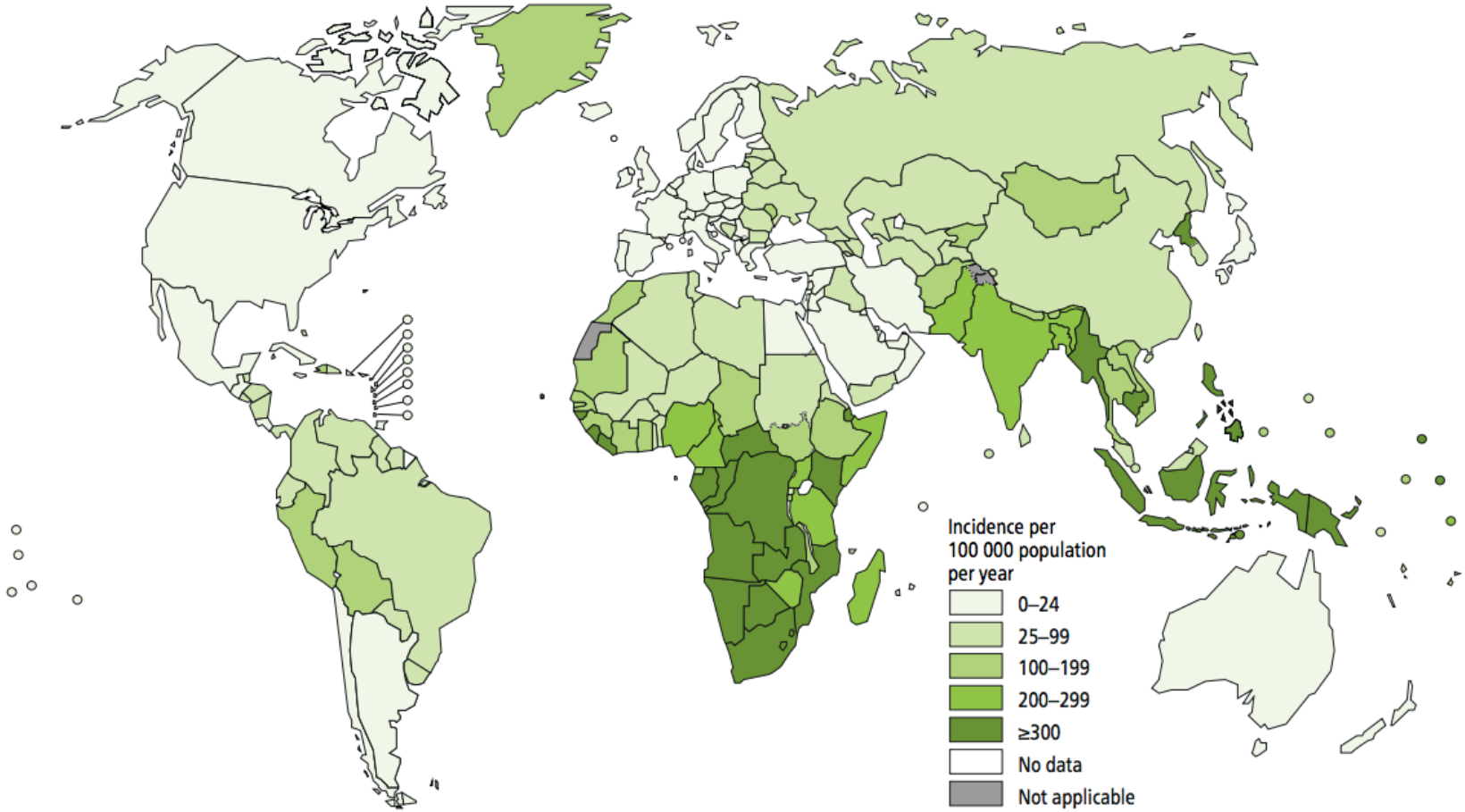


Figure 1-3. Estimated incidence of tuberculosis by country in 2016 [6]. Used with permission.



Reprinted from Global Tuberculosis Report 2017, World Health Organization, Chapter 3: TB Disease Burden, Figure 3-4, Page 31, © World Health Organization 2017.

Figure 1-4. The latent tuberculosis infection cascade of care for a typical patient and the retention of individuals along the cascade [53].

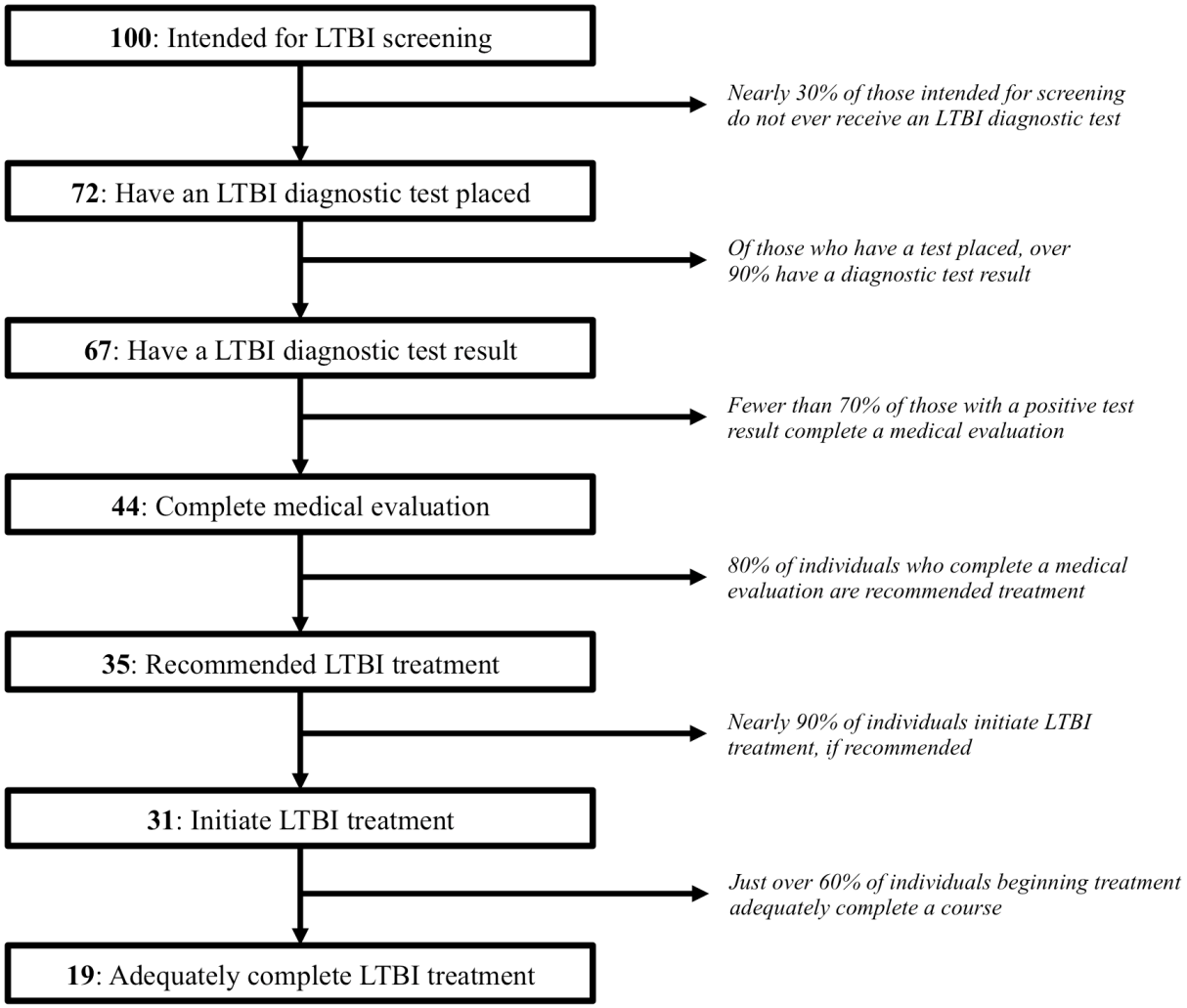


Figure 1-5. An example of a cost-effectiveness plane. Visually one can examine which quadrant the majority of probabilistic runs an intervention falls in (each 'dot' represents one probabilistic run) and use this information to help make a decision about funding and implementation. The plane is broken into four distinct quadrants. In quadrant I, the intervention has an increased benefit and increased cost compared to the base case. In this instance, the policy maker has to make a decision based on their WTP. In quadrant II, the intervention has an increased benefit, but lower cost than the base case; this intervention is called "dominant," meaning it is preferred without any further analysis. In quadrant III, the intervention has a lower cost and decreased benefit compared to the base case. In this instance, policy makers must decide how to proceed, as funding such an intervention would be sacrificing health. An intervention falling in quadrant IV is "dominated;" that is to say, it has higher costs and a decreased benefit compared to the base case and should not be funded.

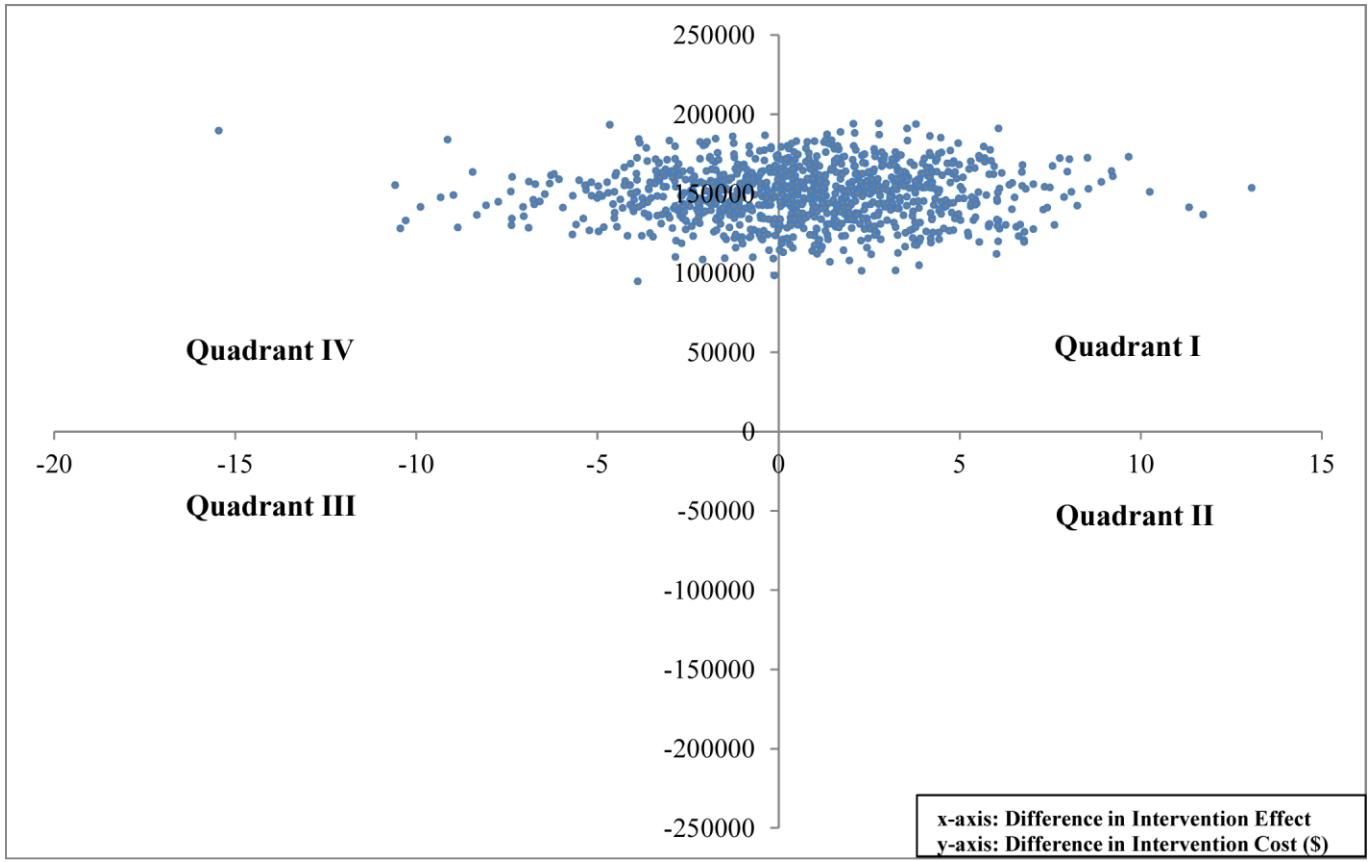


Figure 1-6. An example cost-effectiveness acceptability curve of three interventions. The base case (A) is being considered against two competing interventions (B and C) based on the likelihood that an intervention yields the highest NMB at various WTP thresholds. As WTP increases, the likelihood the base case will provide the highest NMB drops. If a provider has a WTP threshold less than $22,000 the base case is preferred, however past $22,000, intervention B is preferred. In this example, intervention C is never preferred.

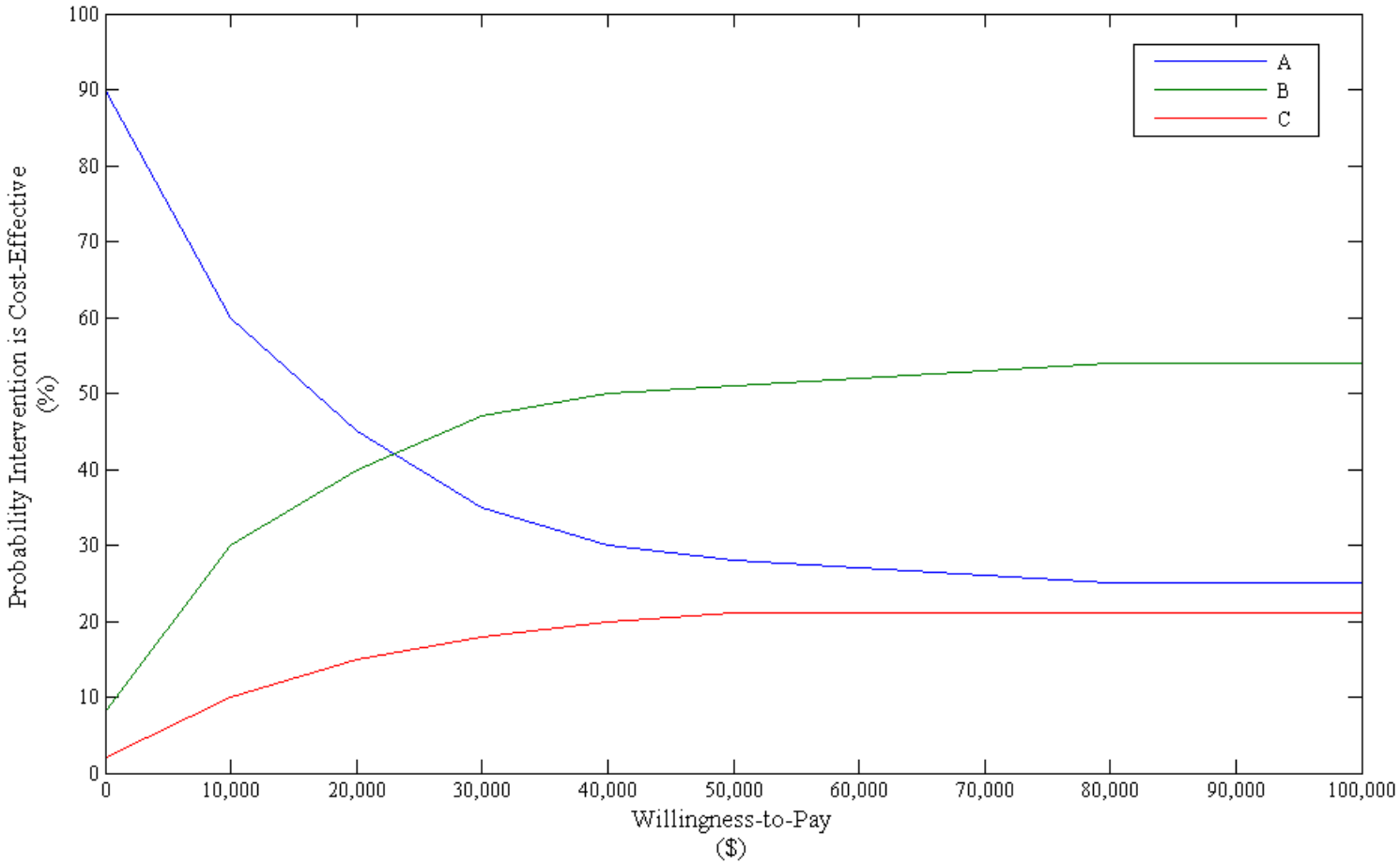
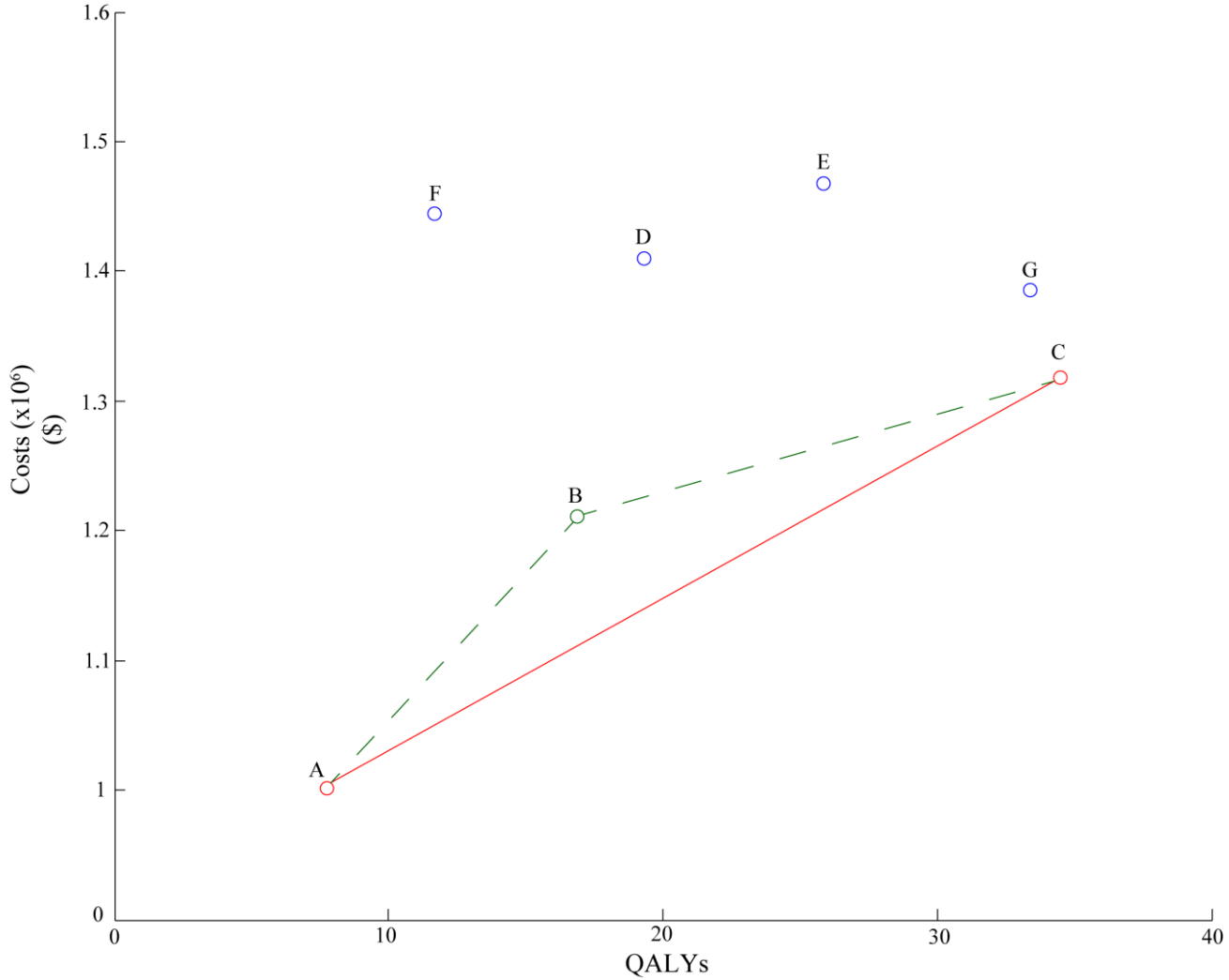


Figure 1-7. An example efficiency frontier for six interventions (B through G) compared to the base case (A). This plot can be interpreted based on slope. The shallowest slope between subsequent interventions will be preferred as this reflects the ICER. From the dotted green line, it is evident that intervention B does not fall on the frontier due to extended dominance by intervention C (i.e. while intervention B is more effective than the base case and less expensive than intervention C, it has a larger ICER than C). It is also easy to determine that interventions D through G are strictly dominated by intervention C, being less effective and more expensive than intervention C.



CHAPTER 2. LATENT TUBERCULOSIS INFECTION DIAGNOSTIC TESTS IN THE FOREIGN-BORN: A SYSTEMATIC REVIEW[1]

2.1 Background

Approximately one-third of the world may be infected with LTBI [5,237]. Worldwide, TB is driven by poverty, poor health infrastructure, and the HIV epidemic. Furthermore, the advent of multiple- and extensively-drug resistant TB strains may hasten TB spread [238,239]. In low incidence countries, increasing migration from high TB incidence regions has slowed declines in TB incidence [240]. Screening for TB disease and LTBI varies country to country. In a recent survey of 31 low-incidence countries, 86% screened immigrants for active TB while 55% screened immigrants for LTBI. Policies, however, on whom to screen and how to screen for LTBI varies widely [241,242]. Presently, many countries are reviewing their TB screening policies and are considering screening for LTBI along with active TB shortly after arrival [3,243].

Approximately 5–10% of those infected with LTBI develop active TB within their lifetime [244]. For new immigrants to low incidence countries, the highest incidence of active TB development is within the first five years of arrival [245]. Current methodology for diagnosing LTBI uses the TST or IGRA in combination with CXR, physical examination, exposure, and medical history to establish an LTBI diagnosis [108]. The TST is an inexpensive and easy to use test, but suffers from low specificity partially due to false positivity related to BCG vaccination [24,246]. There are two commercially available IGRAs, the QuantiFERON-Gold In-Tube® (QFT-GIT) (Cellestis, Valencia, CA, USA) and T-SPOT®.*TB* (Oxford Immunotec, Marlborough, MA, USA), which detect interferon gamma production due to reaction with TB-specific antigens to diagnose LTBI [247,248]. IGRAs are more expensive however they demonstrate higher specificity in BCG-vaccinated individuals [24]. The sensitivity and specificity of these tests for LTBI is still uncertain with no gold standard test available and as a result estimates vary [24]. This leaves large uncertainty around the most cost-effective screening decisions.

There are very few reviews evaluating outcomes associated with screening immigrants, with available reviews examining LTBI screening practices, LTBI testing in narrow immigrant populations, or assessing active TB

[1] Adapted with permission from: Campbell JR, Krot J, Elwood K, Cook V, Marra F. A systematic review on TST and IGRA tests used for diagnosis of LTBI in immigrants. *Mol Diagn Ther* 2015;19(1):9-24.

only [242,249–251]. With screening of new immigrants that arrive to low incidence countries for LTBI emerging as a focus of many new recommendations [3,241] knowledge of prevalence of positive tests and expected outcomes is vital. The objective of this chapter was to conduct a systematic review of studies that evaluated diagnostic tests for LTBI specifically in immigrant populations in terms of recommendation for LTBI treatment, long-term active TB development, and positive test prevalence in various age and TB incidence strata, to inform the use of each diagnostic test.

2.2 Methods

2.2.1 Literature Search Strategy and Study Selection

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [252]. A literature search to identify articles concerned with TST and/or IGRA use in immigrants to low TB incidence countries was conducted in the following databases: MEDLINE (1980 to April 2014); EMBASE (1980 to April 2014); Cochrane Central Register of Controlled Trials (April 2014); Cochrane Database of Systematic Reviews (2005 to April 2014); CAB Direct (1980 to April 2014); CINAHL (1980 to April 2014); Web of Knowledge (1980 to April 2014); and PubMed (1980 to April 2014). References of selected studies were further screened and assessed for entry. The PubMed search strategy used was "tuberculosis" AND ("test*" OR "screen*") AND ("immigra*" OR "refugee*" OR "migra*" OR "foreign born*").

Citations were screened, assessed for eligibility, and included in the systematic review based on the following inclusion criteria: take place in a low-incidence country, as defined by Canadian guidelines (<30 cases per 100,000 persons) [3]; screening had to include a commercial TST or ELISA/ELISPOT based IGRA; TST had to be read 48–72 h after administration; and investigators had to use ≥10 mm induration diameter for a positive TST result. Studies not included in this systematic review were those which used self-reported TST results due to high potential for misreporting and bias; performed in an immunocompromised population—including HIV, chronic kidney disease, diabetes, or on immunocompromising medications (e.g. steroids, TNF-α inhibitors)—as they typically have higher rates of TB [3]; and used outdated TST techniques, such as Heaf or Tine testing, which are no longer the norm. I performed the literature search (JRC) and uncertainty was discussed with Dr. Marra.

2.2.2 Data Extraction

Jane Krot and I extracted the data independently and discrepancies were discussed with Dr. Marra. Data extracted included the study author, location and date, total number of participants included, immigrant class, age, gender, country of origin, number of participants included in the analysis, type of testing received, BCG vaccination status, TST induration diameter cut-off used in each study, number of participants who had positive versus negative results for TST and/or IGRA, and outcomes data including number diagnosed with LTBI, active TB, and number who developed active TB over the follow-up period. Further contact with authors was sought when relevant information was unclear.

2.2.3 Study Quality

Due to lack of a gold standard for diagnosing LTBI, evaluation of diagnostic accuracy is impossible and thus evaluation of study quality is not standardized. In light of this and the fact that evaluating data quality is necessary in any systematic review, we used a modified version of the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist for Studies of Diagnostic Accuracy [253]. Our version only used the applicable aspects of this checklist, including how patients were enrolled and excluded, the appropriateness of the patient population used, the reading of the diagnostic test, and the final number of patients included in the analysis. Articles scoring 6 or higher (out of 8) were deemed to have a low risk of bias due to study methodology. Prospective and retrospective studies were deemed high quality and acceptable, respectively. Study quality was assessed independently.

2.2.4 Data Analysis

Prevalence of positive tests, LTBI diagnosis, active TB diagnosis, and active TB follow-up data in the population for each study were analyzed for all included studies. We further analyzed studies that reported their data according to age—for most studies data was reported as <18 years of age (child) or ≥18 years of age (adult). For studies which reported their data according to TB incidence rate in country of origin, we chose to analyze according to the Canadian definition of high versus low (moderate to very high, ≥30 cases per 100,000 population; low, <30 cases per 100,000 population) [3], but we also conducted a sensitivity analysis using the WHO definition of low being <10/100,000; moderate to very high ≥10/100,000 [70] and a more conservative definition of low being

<50/100,000; moderate to very high ≥50/100,000 [249]. The IGRAs (three versions of the QuantiFERON test and the T-SPOT.*TB* test) were analyzed as aggregated data due to the small number of studies using platforms other than the QFT-GIT, but we also separated by QuantiFERON platform or T-SPOT.*TB* test, where enough data existed.

Fisher's exact test or the χ^2 test was used, as appropriate, to compare outcome data and prevalence of positive tests in different strata. Comparisons were made between age categories, incidence categories, and between tests within the same category. Within these categories, comparisons between studies that actively excluded those with active TB and those that did not were made, where possible, due to the likely differences in test performance in these different populations. Due to the high heterogeneity of studies, these analytical tests were not applied to aggregate results of all included studies.

2.3 Results

The literature search yielded 4,990 citations; 2,625 citations remained after duplicate removal. Title and abstract review removed a further 2,266 studies. A further 308 studies were removed as no English translation was available, the citations were abstracts, the studies were not performed in immigrants, the studies did not use an IGRA or TST, the data was not provided in a manner suitable for this review, or the TST cut-off was not 10 mm, leaving 51 papers for analysis [100,101,127,207,254–300] (**Figure 2-1**).

Of the 51 studies included in the review, 32 were ranked high quality [100,101,127,207,254–269,285–288,293–300] and 19 were ranked acceptable quality [270–284,289–292]. Across the 51 studies, 34 studies looked at TST alone [100,101,127,254–284] and 9 studies looked at IGRAs alone [207,285–292]; 8 studies compared TST and IGRAs [293–300]. Just 8 studies excluded those with active TB from their study [100,101,262,278,293,295,296,298]. Only 16 studies reported on BCG vaccination with 9 using BCG scar as evidence of vaccination [207,258,262,263,281,283,287,298,299], 5 using BCG self-reporting as evidence [101,259,264,293,296], and 2 using BCG vaccination schedule in country of origin as a proxy for BCG vaccination [276,300], although BCG vaccination rates varied considerably across studies (0–100%). The characteristics of the 51 included studies are included in **Table 2-1**, which summarizes each of the 51 studies included in the review.

2.3.1 Studies Evaluating Clinical Outcomes of LTBI in Immigrants

Using the results of TST or IGRA, CXR and/or clinical history, 15 studies evaluated LTBI as a clinical outcome using the TST [100,101,127,254,256,263,267,273–277,279,280,284] as the diagnostic test while 3 studies

used the IGRA test [285,288,297] (**Table 2-2**). Of the 9,349 immigrants with a positive TST, 5,041 (53.9%) were recommended LTBI treatment compared to 511 (43.1%) of the 1,186 immigrants with a positive IGRA being recommended for LTBI treatment ($p < 0.0001$). In the TST group, two studies excluded those with active TB [100,101], however the prevalence of positive tests did not differ significantly between studies that did and did not exclude active TB ($p > 0.05$).

We found only 3 longitudinal follow-up studies for development of active TB. In the first TST study [274], 5 of the 4,990 TST positive immigrants followed for 5 years developed active TB. The second TST study [280] found 8 of 154 TST positive immigrants followed for 3 years developed active TB. The IGRA study [288] followed up active TB development in the 238 QFT-GIT positive immigrants not treated for LTBI and found 8 cases in their approximately 2 years of follow-up. This data results in an active TB incidence rate ratio of 0.030 (95% CI 0.011–0.065) in those tested with a TST compared to QFT-GIT.

A secondary outcome of active TB diagnosis using chest X-ray and/or sputum in immigrants at the time of entry was reported in 14 studies using the TST [127,255–258,260,267,273,274,276,280,282,297] and in 6 studies using an IGRA [285,287–290,297] (**Table 2-2**). Only 88 (0.8%) of the 10,579 immigrants with a positive TST had a diagnosis of active TB, yielding an active TB discovery rate of 8.3 cases per 1,000 persons screened. Three of these TST studies reported presence of active TB in those with negative TST results [127,256,273], with only 12 (0.15%) of the 7,862 immigrants with a negative TST having active TB. Using these studies, we calculated a pooled sensitivity of 78.18% (95% CI 64.99–88.19%) and pooled specificity of 55.4% (95% CI 54.58–56.22%) for the TST to detect active TB, however its positive predictive value is only 0.7% (0.6–0.8%). In contrast, 32 (2.0%) of the 1,574 IGRA positive immigrants were diagnosed with active TB, giving an active TB discovery rate of 20.3 cases per 1,000 persons screened. In the one study reporting this information [288], only 1 (0.2%) of the 577 IGRA negative immigrants was diagnosed with active TB; this study estimated QFT-GIT sensitivity at 88.89% (95% CI 51.7–98.2%) and specificity at 70.8% (95% CI 67.5–73.9%) for detecting active TB, although its positive predictive value was 3.3% (95% CI 1.4–6.3%). Removing the one study [285] using T-SPOT.*TB* from our analysis did not significantly affect our findings ($p > 0.05$). Active TB diagnosis was significantly higher in IGRA positive immigrants ($p < 0.0001$), however no difference was noted in those who were IGRA negative ($p > 0.05$), compared to those who were TST negative.

2.3.2 Studies Evaluating the Prevalence of LTBI Screening Test Positivity in Immigrants: Adults Versus Children

When stratified according to different age groups 10 studies had TST results for those ≥18 years old [100,261–263,271,279–281,298,299] and 8 had IGRA results [207,286–288,291,292,298,299]. There were 7 studies with TST results for those <18 years [127,264–268,282] and 3 with IGRA data in this age group [207,291,292] (**Table 2-3**).

Studies totalling 3,307 immigrants ≥18 years of age tested with a TST resulted in 1,479 (44.7%) being TST positive. Studies with TST results in those <18 years of age included 6,784 immigrants, of which 1,628 (24.0%) were positive, significantly lower than those ≥18 years of age ($p < 0.0001$). Three studies in immigrants ≥18 years of age tested with a TST excluded those with active TB [100,262,298], resulting in a significant increase in the prevalence of positive tests compared to studies that didn't exclude active TB ($p < 0.0001$). There were 4,914 immigrants ≥18 years of age tested with an IGRA, with 1,282 (26.1%) being positive. Comparatively, of the 331 immigrants <18 years of age tested with an IGRA, 46 (13.9%) were positive, significantly lower than those ≥18 years of age ($p < 0.0001$). Removal of the lone IGRA study excluding active TB [298] did not change the results of the analysis. Comparing TST and IGRA results across age groups, prevalence of positive test results were significantly lower in those tested with IGRAs who were both ≥18 years of age ($p < 0.0001$) and <18 years of age ($p < 0.0001$). We compared the QFT-GIT in those ≥18 years of age to the TST and the results remained significantly different ($p < 0.0001$), in addition the QFT-GIT did not differ from the QFT-G in this age group ($p > 0.05$).

2.3.3 Studies Evaluating Prevalence of LTBI Screening Test Positivity in Immigrants: Country of Origin

When using a cut-off of <30 per 100,000 population as low TB incidence, we found 5 TST studies [127,264,272,278,279] and 1 IGRA study [291], using the QFT-GIT, which examined prevalence of positive tests by TB incidence in country of origin (**Table 2-4**). A total of 5,207 immigrants from low TB incidence countries and 21,513 immigrants from moderate to very high TB incidence countries had TST results, with a total of 1,331 (25.6%) and 8,924 (41.5%) of immigrants from low incidence and moderate to very high incidence countries being TST positive, respectively. Prevalence of positive tests was significantly lower in those from low incidence countries ($p < 0.0001$). Removal of the one study [278] excluding those with active TB did not significantly affect

this conclusion ($p < 0.05$). The lone IGRA study included 16 immigrants from low incidence countries of which 0 (0%) were IGRA positive, while prevalence of positive tests was significantly higher in the 484 immigrants from moderate to very high incidence countries with 166 (34.3%) being IGRA positive ($p < 0.0001$). The prevalence of positive IGRA results was lower than the TST when compared in low incidence countries ($p < 0.0001$) and in moderate to very high incidence countries ($p < 0.0001$).

In our sensitivity analysis comparing prevalence of positive TST's to IGRA's using different definitions for low and moderate to very high incidence (**Table 2-4)**, 15 TST studies [100,127,255,259,264,265,269,270,272,273,277–279,281,282] and 5 IGRA studies [207,286,288,291,299], all using the QFT-GIT, were included when defining low incidence as <50 cases per 100,000 population. A total of 16,313 immigrants from low TB incidence countries and 54,017 immigrants from moderate to very high TB incidence countries had TST results, with a total of 5,199 (31.9%) and 22,015 (40.8%) of immigrants from low incidence and moderate to very high incidence countries being TST positive, respectively. Prevalence of positive tests was significantly lower in those from low incidence countries ($p < 0.0001$). Positive test prevalence was not significantly affected after removing the two studies that excluded those with active TB [100,278] ($p > 0.05$). In studies involving IGRAs, 707 immigrants from low incidence countries and 4,184 immigrants from moderate to very high incidence countries were examined. A total of 96 (13.6%) immigrants from low incidence countries were IGRA positive, while 1,135 (27.1%) were positive from moderate to very high incidence countries. Positive IGRA prevalence was significantly lower in those from low incidence countries compared to moderate to very high incidence countries ($p < 0.0001$). The prevalence of positive IGRA results was lower than the TST when compared in low incidence countries ($p < 0.0001$) and in moderate to very high incidence countries ($p < 0.0001$).

When defining low incidence as <10 cases per 100,000 population, we only found 1 TST study [279] and one IGRA study [291]. In the lone TST study, 16 immigrants from low incidence countries and 307 immigrants from moderate to very high incidence countries were included. No positive test was found in the 16 immigrants from low incidence countries (0%) while 153 (49.8%) of those from moderate to very high incidence countries were positive, indicating a higher positive test prevalence in those from moderate to very high incidence countries ($p < 0.0001$). Similarly, the lone IGRA study included 16 and 484 immigrants from low and moderate to very high incidence countries, respectively. None of the immigrants from low incidence countries tested positive (0%), although 166 (34.3%) from moderate to very high incidence countries were positive, yielding a higher positive test

prevalence in those from moderate to very high incidence countries ($p < 0.0001$). There was no significant difference in TST or IGRA test positivity in those from low incidence countries ($p > 0.05$), however the prevalence of positive IGRA results was significantly lower ($p < 0.0001$) in those from moderate to very high incidence countries when compared with the TST.

In all three incidence definitions, the prevalence of positive tests in immigrants from moderate to very high incidence countries was significantly higher with the TST than IGRA ($p < 0.0001$). Prevalence of positive tests in immigrants from low incidence countries was significantly higher when the TST was used compared to the IGRA using the <50/100,000 and <30/100,000 incidence definitions ($p < 0.0001$), however there was no difference when the <10/100,000 definition was used ($p > 0.05$).

2.3.4 Studies Evaluating Prevalence of LTBI Screening Test Positivity in Immigrants: TST Versus IGRA

Of the 8 studies comparing the TST and IGRA, concordance values between the two tests could be calculated in all but one [293] and in the remaining studies, 5 used the QFT-GIT as their IGRA platform [294–296,299,300]. The percentage of test agreement varied from 66.0–80.2%, and κ values varied from 0.316–0.555, with three of the seven studies showing "fair" agreement between tests [294,298,300] and the remaining showing "moderate". Of the 2,796 immigrants that received TST and IGRA, 1,128 (40.3%) and 896 (32.0%) were positive, respectively (**Table 2-5**). Overall, those tested with a TST were significantly more likely to test positive ($p < 0.0001$). When only QFT-GIT studies were included, positive test prevalence was still significantly higher in those tested with a TST ($p < 0.0001$). Comparing the QFT-GIT to the other IGRA platforms, however, yielded significant differences ($p < 0.01$). Studies that excluded those with active TB [295,296,298], had significantly higher prevalence of positive TST ($p < 0.01$) and IGRA ($p < 0.001$).

2.3.5 Predictors of LTBI Screening Test Positivity

Significant associations between TST positivity and the male gender were noted in several studies [100,254–256,260,273,277,278]; this association was not seen in four studies [257,262,270,293]. BCG vaccination was found to be significantly associated with TST positivity in four studies [259,278,283,293], however one study found an association with negative TST results [260]. Country and/or region of origin were found to be significantly

associated with TST positivity in numerous studies [127,255–257,260,270,273,277,278] and found to not be significant in only 4 studies [101,272,293,294]. Increased age was also found to be significantly associated with a positive TST in majority of the studies [101,254–256,270,273,277,278,283]. Age was not significant in 4 studies [127,257,264,294] although two studies [127,264] were performed in subjects <18 years old and therefore were not able to look at older age categories.

Male gender was not found to be significantly associated with IGRA positivity in three studies [287,290,292], however two concluded significant association [207,289]. Country of origin was significantly associated with IGRA positivity in several studies [207,286,289,291,293,299], however three saw no association [287,290,294]. Increasing age was a significant factor for a positive IGRA in three studies [289,291,299], however the same conclusion was not found in one [294]. BCG vaccination was not found to be significantly associated with a positive IGRA in one study [287].

2.4 Discussion

This is the first systematic evaluation of outcomes and prevalence of positive LTBI diagnostic tests in the immigrant population in low-incidence, immigrant-receiving countries. We found that the number of newly arrived immigrants recommended for preventative treatment was significantly lower in those tested with an IGRA rather than with a TST and that long-term, more test positive immigrants tested with an IGRA developed active TB compared to a TST, providing evidence for increased use of the IGRA in LTBI detection. Although the use of IGRAs is still a moving field in terms of active TB detection, IGRA performance was similar to the TST in terms of active TB detection sensitivity. Interestingly, their similar performance in active TB detection provides conditional evidence of expanded use of the IGRA in regular LTBI screening as the test has better specificity and thus identifies fewer people for preventative treatment without an increase in risk of missing current active TB cases.

The prevalence of positive tests was significantly higher in immigrants tested with a TST rather than an IGRA in each age and TB incidence subgroup. Our age-related findings of higher TST positivity rates in those ≥18 years of age has been shown in a previous study [251] and is presumably related to the duration of exposure in the country of origin. Higher IGRA positivity rates were also found in those ≥18 years of age, however with only three studies examining IGRA results in those <18 years of age, more studies in younger populations are required to better characterize the behaviour of this test before recommending widespread use in the young immigrant

populations. Positive test prevalence for both the IGRA and TST was significantly higher in immigrants coming from moderate to very high incidence countries compared to low incidence countries, and this result was not sensitive to changing low-incidence definition, except in the case of those from countries of <10 TB cases per 100,000 population, likely due to the very small sample size (17 total immigrants).

Our results coincide with the Munoz *et al.* [250] study which evaluated the two diagnostic tests in populations of contacts, anti-tumor necrosis factor candidates, and asylum seekers, even though this review was specific to generally healthy, immunocompetent immigrants, demonstrating demographic independent trends. A review of BCG and tuberculin reactivity in populations from areas of varying TB incidence [251] noted similar results of increasing TST positivity with age in both BCG vaccinated and non-vaccinated groups, as well as increased TST positivity in people from countries with high TB incidence, although this review was narrow in focus. Several research papers and new TB guidelines have suggested that targeted LTBI screening in those from high incidence populations is likely to be the most cost-effective method and have the greatest impact in quelling TB in low-incidence countries, due to the increased likelihood of discovering LTBI and further benefit of subsequent treatment. A number of countries, including the UK, have already changed their screening guidelines [3,96,117,205,243,249].

This chapter is not without limitations. The studies included are heterogeneous, examining populations from very different regions and lifestyles (e.g., diet, hygiene, living situations, fitness, exposure); comparing groups of similar age and TB incidence in country of origin, further analyzing studies using different IGRAs, or excluding active TB helped minimize heterogeneity. Even so, rates of BCG vaccination in each country, living conditions, and healthcare-related factors could not be considered, and these may have an effect on LTBI rates. The majority of studies did not report BCG vaccination status, not allowing for comparison of rates between populations that were BCG vaccinated and those that were not, a likely key reason for the high prevalence of positive TST in certain studies. Pooling of data from the different IGRAs, given their different characteristics and performance is a limitation of this chapter, however this technique is used by others conducting reviews and meta-analyses, due to the small numbers of studies using the various IGRA platforms [25,301,302]. We attempted to analyze data based on time since arrival, but were unable to do so as nearly all studies were performed in populations who had landed <5 years prior to study commencement and data were not reported by time since arrival. Even though new data

[244] suggest that LTBI reactivation, and likely positive test prevalence, is nearly constant after entry, it may be worthwhile to perform a meta-analytical comparison based on time of arrival if data becomes available.

This review included studies that took place between 1980 and 2014. Over that time period TB rates, and subsequently LTBI rates, have dropped substantially in certain countries. This time frame was used to ensure an adequate number of studies were included to see any possible differences between age groups, TB incidence, and diagnostic tests. Comparison of TST studies from 2006 or earlier to those from 2007 onwards revealed no significant differences in prevalence of positive diagnostic tests, suggesting that the large time period did not have a significant effect on our overall conclusions. Furthermore, the IGRA is a new diagnostic tool and literature on long-term follow-up, use in immigrant populations, and use in children, is limited. These limitations could cause us to have misestimated rates of LTBI, active TB, and active TB development in the immigrant population.

No gold standard for LTBI diagnosis exists, complicating decision making in the clinic and at the policy level. Best estimates for true test performance come from meta-analytical studies evaluating active TB as the surrogate reference standard for LTBI or from evaluating test performance in populations of negligible TB risk. Muddling the decision of which test to use are the inherent disadvantages of each test. TST specificity is influenced by BCG vaccination history and, less commonly, exposure to NTM; further disadvantages include variability in interpretation of results and requirement for provider training [39]. Additionally, the requirement of test reading 48–72 h after injection leads to low TST screening completion (69%; 95% CI 69–70%) [303]. In contrast, the IGRA does not require follow-up, but does have significant sources of variability, poor reproducibility, and is more expensive to administer. Furthermore, each of the IGRA tests have differing sensitivity and specificity [247,248,286,291]. As these disadvantages may vary in certain groups, recommendation of which test to use in each situation can be a foggy area.

More literature directly comparing TSTs to IGRAs is needed to improve decision making on situational use of either test in immigrants. Licensing of LTBI diagnostic tests stem from estimation of sensitivity using TB as a surrogate marker; future studies evaluating these tests would be wise to include active TB detection rates, especially in age-specific strata, where decisions to screen are still cloudy. Ideally the comparison would look at LTBI diagnosis, treatment, and long-term development of active TB. Performing longitudinal studies on new immigrants is made increasingly difficult when considering cultural differences, fear of refusal of citizenship should they become ill, language barriers, and further difficulties in gaining a permanent residence. Culturally sensitive,

engaging studies, explained clearly to the participants in their chosen language are required to truly estimate long-term active TB development in immigrants.

This chapter took a qualitative approach to answer questions about LTBI outcomes and positivity rates between different TB endemicities and age classes. A quantitative meta-analysis could be utilized to explore possible relationships between TST and IGRA positivity rates in gender, country of origin, and more specific age classes across several studies, although given that many studies do not provide raw, comparative data, advanced methodologies would need to be used.

2.5 Conclusions

Compared to TST, significantly fewer immigrants tested positive with the IGRA and thus were considered for preventative treatment. The IGRA performs similarly to the TST in active TB detection, and more IGRA positive immigrants develop active TB long-term, lending evidence to its expanded use in regular LTBI screening, however with so few studies in this area, more are required to draw more robust conclusions. Children/adolescents and immigrants from low TB incidence countries have a lower prevalence of positive test results than adults and immigrants from high TB incidence countries, respectively. More comparative longitudinal studies are required to improve screening decisions in immigrant populations, as this would be as close to gold-standard evidence for policy as possible.

2.6 Tables

Table 2-1. Characteristics of the included studies

Study (Publication Year)	Immigrant Class	Time of Study	Number of Included Participants	Mean Age (Years)	Gender (% Male)	Country/Region (% Distribution)[c]	BCG Vaccinated (% Vaccinated)[d]	SIGN Score[e]
Levesque et al [101] (2004)	Refugee	February to October 1999	197	23.2	64	39% Indian Subcontinent, 29% Sub-Saharan Africa, 11% Eastern Europe, 10% South America, 11% Other	48%	High Quality 8
Trauer et al [254] (2011)	Refugee	February 2006 to January 2009	458	15[a]	44	59% Africa, 22% Middle East, 19% Southeast Asia	Not reported	High Quality 8
Lifson et al [255] (2002)	Refugee	1999	2249	23	53	73% Sub-Saharan Africa, 23% Eastern Europe, 3% Southeast Asia, 1% Other	Not reported	High Quality 8
Tafuri et al [256] (2011)	Refugee	March to April 2009	982	25	86	87% Sub-Saharan Africa, 5% Middle East, 4% Asia, 4% North Africa	Not reported	High Quality 8
Sanfrancisco et al [257] (2001)	Immigrant	1998	2216	25.4	89	27% Nigeria, 13% Mali, 8% Sierra Leone, 7% Congo, 45% Other Africa	Not reported	High Quality 8
Perez-Stable et al [258] (1986)	Immigrant	August 1983 to March 1984	1232	28	56	37% El Salvador, 30% Mexico, 19% Nicaragua, 14% Other	42%	High Quality 8
Menzies et al [259] (1992)	Immigrant	~1990	1198	21.3	N/A	65% Highly Endemic Regions, 35% Other	33%	High Quality 8
El-Hamad et al [260] (2001)	Immigrant	April 1996 to October 1997	993	All Ages[b]	58	40% Sub-Saharan Africa, 23% Eastern Europe, 16% North Africa, 21% Other	Not reported	High Quality 8
Asgary et al [261] (2011)	Immigrant	2007 to 2008	43	38.7	48	65% Africa, 23% Central America, 12% Other	Not reported	High Quality 8
Robertson et al [262] (1996)	Immigrant	November 1992	121	35	78	100% Vietnam	0%	High Quality 8
Padovese et al [263] (2013)	Immigrant	December 2010 to June 2011	500	26.5	81	83% Somalia, 8% Eritrea, 9% Other	19%	High Quality 7

[a]Median age, [b]Median/Mean age not provided

[c]Percent distribution of country of origin of included study participants, [d]Total percent of included participants who were BCG vaccinated, where data is available

[e]High quality: low risk of bias, prospective study (score 6-8); Acceptable Quality: low risk of bias, retrospective study (score 6-8)

Table 2-1. Continued

Study (Publication Year)	Immigrant Class	Time of Study	Number of Included Participants	Mean Age (Years)	Gender (% Male)	Country/Region (% Distribution)[c]	BCG Vaccinated (% Vaccinated)[d]	SIGN Score[e]
Carvalho et al [100] (2005)	Immigrant	June to December 2001	213	27	70	39% Sub-Saharan Africa, 22% North Africa, 15% Eastern Europe, 24% Other	Not reported	High Quality 8
Alperstein et al [264] (1996)	Immigrant	1992 to 1996	353	3-9[b]	N/A	52% South Asia, 15% Middle East, 33% Other	76%	High Quality 8
Minodier et al [127] (2010)	Immigrant	1997 to 2007	3401	12.2	52	33% Established Market Economy, 19% Western Pacific, 13% Eastern Europe, 10% Southeast Asia, 25% Other	Not reported	High Quality 7
Geltman et al [265] (2001)	Refugee	July 1995 to June 1998	1737	0-17[b]	52	33% Former Soviet Union, 14% Former Yugoslavia, 11% Africa, 10% East Asia, 32% Other	Not reported	High Quality 8
Sheikh et al [266] (2009)	Refugee	May 2005 to December 2006	216	0-17[b]	47	38% East Africa, 19% Central Africa, 19% Western Africa, 16% Asia, 8% Middle East	Not reported	High Quality 8
Gray et al [267] (2012)	Refugee	May 2005 to June 2010	328	0.5-17.5[b]	54	N/A	Not reported	High Quality 8
Losi et al [268] (2011)	Immigrant	January 2006 to December 2008	621	13	N/A	40% Africa, 27% Eastern Europe, 33% Other	Not reported	High Quality 6
Hladun et al [269] (2014)	Immigrant	February 2001 to February 2005	309	≥15[b]	58	49% Americas, 25% Eastern Mediterranean, 17% Western Pacific, 7% Southeast Asia, 1% Africa, 1% Europe	Not reported	High Quality 7
Baussano et al [270] (2013)	Immigrant	January 1991 to December 2010	26,554	All Ages	59	29% Romania, 15% Morocco, 11% Sub-Sahara, 9% Nigeria, 6% Albania, 30% Other	Not reported	Acceptable 8
Kowatsch-Beyer et al [271] (2013)	Refugee	2008	224	30[a]	52	55% Africa, 31% Southeast Asia, 13% East Asia, 1% Other	Not reported	Acceptable 7

[a]Median age, [b]Median/Mean age not provided
[c]Percent distribution of country of origin of included study participants, [d]Total percent of included participants who were BCG vaccinated, where data is available
[e]High quality: low risk of bias, prospective study (score 6-8); Acceptable Quality: low risk of bias, retrospective study (score 6-8)

Table 2-1. Continued

Study (Publication Year)	Immigrant Class	Time of Study	Number of Included Participants	Mean Age (Years)	Gender (% Male)	Country/Region (% Distribution)[c]	BCG Vaccinated (% Vaccinated)[d]	SIGN Score[e]
Martin et al [272] (2006)	Refugee	January 2003 and December 2004	2033	All Ages[b]	52	60% Sub-Saharan Africa, 20% North Africa, 10% South Asia, 10% Other	Not reported	Acceptable 8
Varkey et al [273] (2007)	Refugee	January 1997 to December 2001	9842	All Ages[b]	52	67% Africa, 27% Europe, 6% Asia	Not reported	Acceptable 8
MacIntyre et al [274] (1999)	Refugee	July 1989 to January 1990	938	33	54	Southeast Asia	Not reported	Acceptable 8
Chai et al [275] (2013)	Asylum Seeker and Refugee	September 2003 to August 2007	115 and 496[f]	22 and 31[a,f]	50 and 59[f]	59% Africa, 41% Other and 63% Africa, 37% Other[f]	Not reported	Acceptable 8
Hobbs et al [276] (2002)	Refugee	January 1999 to December 2000	869	All Ages[b]	68	19% Iran, 16% Afghanistan, 15% Sri Lanka, 15% Czech Republic, 35% Other	Not reported	Acceptable 8
Bran et al [277] (2006)	Immigrant	2001	728	≤35[b]	78	77% Africa, 11% South America, 8% Asia, 4% Other	Not reported	Acceptable 8
Li et al [278] (2010)	Immigrant	January 2002 to August 2004	20 808	All Ages[b]	46	14% Dominican Republic, 9% China, 8% Ecuador, 6% Jamaica, 6% Mexico, 6% Haiti, 4% Colombia, 47% Other	91%	Acceptable 8
Desale et al [279] (2013)	Immigrant	2006 to 2010	391	34	63	27% Mexico, 16% El Salvador, 15% Honduras, 42% Other	Not reported	Acceptable 8
Truong et al [280] (1997)	Immigrant	1992 to 1994	160	30[a]	53	45% India, 43% Tibet, 12% Other	Not reported	Acceptable 8

[a]Median age, [b]Median/Mean age not provided
[c]Percent distribution of country of origin of included study participants, [d]Total percent of included participants who were BCG vaccinated, where data is available
[e]High quality: low risk of bias, prospective study (score 6-8); Acceptable Quality: low risk of bias, retrospective study (score 6-8)
[f]For asylum seeker and refugee, respectively

Table 2-1. Continued

Study (Publication Year)	Immigrant Class	Time of Study	Number of Included Participants	Mean Age (Years)	Gender (% Male)	Country/Region (% Distribution)[c]	BCG Vaccinated (% Vaccinated)[d]	SIGN Score[e]
Mulder et al [281] (2013)	Immigrant	April 2009 to March 2011	643	≥18[b]	43	45% Asia, 24% Europe/Americas, 16% Sub-Saharan Africa, 15% North Africa/Middle East	85%	Acceptable 7
Hayes et al [282] (1998)	Refugee	January 1994 to December 1995	128	10	58	48% East Africa, 17% Former Yugoslavia, 13% Former Soviet Union, 22% Other	Not reported	Acceptable 8
Fortin et al [283] (2007)	Immigrant	January 1998 to December 2001	515	0.3-19[b]	28	51% Western Pacific, 14% Americas, 14% Southeast Asia, 9% Europe, 12% Other	73%	Acceptable 7
Brassard et al [284] (2006)	Immigrant	September 1998 to August 2003	2524	4-18[b]	N/A	N/A	Not reported	Acceptable 8
Bodenmann et al [285] (2009)	Immigrant	January to July 2007	125	34.8	53	51% Latin America, 19% Sub-Saharan Africa, 30% Other	Not reported	High Quality 8
Pareek et al [207] (2011)	Immigrant	January 2008 to July 2010	1229	≤ 35[b]	49	60% Indian Subcontinent, 20% Sub-Saharan Africa, 13% Other Asia, 7% Other	43%	High Quality 8
Mulder et al [286] (2012)	Immigrant	April 2008 to March 2011	1468	34	46	46% Asia, 24% Europe/Americas, 15% Sub-Saharan Africa, 15% North Africa/Middle East	Not reported	High Quality 8
Garfein et al [287] (2011)	Immigrant	October 2008	133	35[a]	37	75% Oaxca Mexico, 25% Other Mexico	76%	High Quality 8
Harstad et al [288] (2010)	Asylum Seeker	September 2005 to June 2006	823	≥18[b]	75	45% Asia, 42% Africa, 13% Europe	Not reported	High Quality 7
Bennett et al [289] (2014)	Refugee	January 2010 to October 2012	4280	31[a]	50.3	87% Middle East, 7% Asia, 6% Sub-Saharan Africa	Not reported	Acceptable 7
Banfield et al [290] (2012)	Refugee	January 2006 to December 2007	1004	19.8	49	92% Africa, 8% Asia	Not reported	Acceptable 7
Simpson et al [291] (2013)	Immigrant	January 2008 to June 2009	533	29	49	42% Burma, 16% Bhutan, 9% Iraq, 33% Other	Not reported	Acceptable 7

[a]Median age, [b]Median/Mean age not provided

[c]Percent distribution of country of origin of included study participants, [d]Total percent of included participants who were BCG vaccinated, where data is available

[e]High quality: low risk of bias, prospective study (score 6-8); Acceptable Quality: low risk of bias, retrospective study (score 6-8)

Table 2-1. Continued

Study (Publication Year)	Immigrant Class	Time of Study	Number of Included Participants	Mean Age (Years)	Gender (% Male)	Country/Region (% Distribution)[c]	BCG Vaccinated (% Vaccinated)[d]	SIGN Score[e]
Paxton et al [292] (2012)	Refugee	July 2006 to October 2009	810	All Ages[b]	50	Karen refugees (Thailand/Burma)	Not reported	Acceptable 8
Orlando et al [293] (2010)	Immigrant	July 2005 to July 2007	899 TST, 1115 IGRA	35.3[a]	44	50% Latin America, 27% Eastern Europe, 16% Africa, 7% Asia	6%	High Quality 7
Saracino et al [294] (2009)	Immigrant	September 2004 to December 2005	279	27.1	96	48% Africa, 47% Eastern Mediterranean, 5% Other	Not reported	High Quality 8
Baker et al [295] (2009)	Refugee	July 2006 to March 2007	195	19[a]	34	76% Somalia, 13% Ethiopia, 11% Other	Not reported	High Quality 8
Weinfurter et al [296] (2011)	Refugee	June 2004 to August 2006	594	All Ages[b]	52	Only Ethnicities Reported	92%	High Quality 8
Pottumarthy et al [297] (1999)	Refugee	November 1996 to February 1998	237	28[a]	N/A	N/A	Not reported	High Quality 7
Carvalho et al [298] (2007)	Immigrant	January to May 2004	100	28[a]	75	35% Sub-Saharan Africa, 22% Eastern Europe, 21% Asia, 16% North Africa, 6% Other	64%	High Quality 8
Winje et al [299] (2008)	Asylum Seeker	September 2005 to June 2006	912	29[a]	71	46% Asia, 36% Africa, 17% Europe, 1% Other	72%	High Quality 6
Painter et al [300] (2013)	Immigrant	December 2008 to January 2010	479	≥15[b]	48	Vietnam	100%	High Quality 8

[a]Median age, [b]Median/Mean age not provided

[c]Percent distribution of country of origin of included study participants, [d]Total percent of included participants who were BCG vaccinated, where data is available

[e]High quality: low risk of bias, prospective study (score 6-8); Acceptable Quality: low risk of bias, retrospective study (score 6-8)

Table 2-2. Diagnostic data from the TST and IGRA studies with outcomes data

Study	Test Type	Number of Included Participants	TST		Recommended LTBI Treatment[a]	Diagnosed with Active TB		Active TB Case Detection[b] (per 1000)
			Testing Positive	Testing Negative		Testing Positive	Testing Negative	
Levesque et al [101]	TST	197	49 (25%)	148 (75%)	35	-	-	-
Trauer et al [254]	TST	458	146 (32%)	312 (68%)	121	-	-	-
Lifson et al [255]	TST	2249	1059 (47%)	1190 (53%)	-	13	-	12.2
Tafuri et al [256]	TST	982	596 (61%)	386 (39%)	596	7	7	11.7
Sanfrancisco et al [257]	TST	2216	722 (32%)	1494 (68%)	-	2	-	2.8
Perez-Stable et al [258]	TST	1232	650 (53%)	582 (47%)	-	2	-	3.1
El-Hamad et al [260]	TST	993	392 (39%)	601 (61%)	-	8	-	20.4
Padovese et al [263]	TST	500	248 (50%)	252 (50%)	19	-	-	-
Carvalho et al [100]	TST	213	124 (58%)	89 (42%)	55	-	-	-
Minodier et al [127]	TST	3401	777 (23%)	2624 (77%)	573	0	0	0
Gray et al [267]	TST	328	92 (28%)	236 (72%)	81	11	-	119.6
Losi et al [268]	TST	621	104 (17%)	517 (83%)	-	4	-	38.5
Varkey et al [273]	TST	9842	4990 (51%)	4852 (49%)	2446	36	5	7.2
MacIntyre et al [274]	TST	938	561 (60%)	377 (40%)	124	0	-	0
Chai et al [275]	TST	611	239 (39%)	372 (61%)	184	-	-	-
Hobbs et al [276]	TST	869	316 (36%)	553 (64%)	160	4	-	12.7
Bran et al [277]	TST	728	351 (48%)	377 (52%)	61	-	-	-
Desale et al [279]	TST	391	164 (42%)	227 (58%)	101	-	-	-
Truong et al [280]	TST	160	154 (96%)	6 (4%)	110	0	-	0
Hayes et al [282]	TST	128	45 (35%)	83 (65%)	-	1	-	22.2
Brassard et al [284]	TST	2524	542 (21%)	1982 (79%)	375	-	-	-
Pottumarthy et al [297]	TST	237	86 (36%)	151 (64%)	-	0	-	0
Bodenmann et al [285]	T-SPOT.*TB*	125	24 (19%)	101 (81%)	14	2	-	83.3
Garfein et al [287]	QFT-GIT	133	53 (40%)	80 (60%)	-	0	-	0
Harstad et al [288]	QFT-GIT	823	246 (30%)	577 (70%)	8	8	1	32.5
Bennett et al [289]	QFT-GIT	4280	916 (21%)	3364 (79%)	489	14	-	15.3
Banfield et al [290]	QFT-G & QFT-GIT	1004	264 (26%)	740 (74%)	-	8	-	30.3
Pottumarthy et al [297]	QFT	237	71 (30%)	166 (70%)	-	0	-	0

TST: Tuberculin Skin Test; QFT: QuantiFERON; QFT-G: QuantiFERON-Gold; QFT-GIT: QuantiFERON-Gold-In-Tube

[a]Recommended treatment with a positive TST or IGRA; [b]In those testing positive

Table 2-3. Diagnostic data from the TST and IGRA studies with age-specific data

Study	Test Type	Number of Included Participants	<18 years of age		≥18 years of age	
			Testing Positive (%)	Testing Negative (%)	Testing Positive (%)	Testing Negative (%)
Asgary et al [261]	TST	43	-	-	24 (56%)	19 (44%)
Robertson et al [262]	TST	121	-	-	35 (29%)	86 (71%)
Padovese et al [263]	TST	500	-	-	248 (49%)	252 (51%)
Carvalho et al [100]	TST	213	-	-	124 (58%)	89 (42%)
Alperstein et al [264]	TST	353	99 (28%)	254 (72%)	-	-
Minodier et al [127]	TST	3401	777 (23%)	2624 (77%)	-	-
Geltman et al [265]	TST	1737	440 (25%)	1297 (75%)	-	-
Sheikh et al [266]	TST	216	71 (33%)	145 (67%)	-	-
Gray et al [267]	TST	328	92 (28%)	236 (72%)	-	-
Losi et al [268]	TST	621	104 (17%)	517 (83%)	-	-
Kowatsch-Beyer et al [271]	TST	224	-	-	102 (46%)	122 (54%)
Desale et al [279]	TST	391	-	-	164 (42%)	227 (58%)
Truong et al [280]	TST	160	-	-	154 (96%)	6 (4%)
Mulder et al [281]	TST	643	-	-	273 (42%)	370 (58%)
Hayes et al [282]	TST	128	45 (35%)	83 (65%)	-	-
Carvalho et al [298]	TST	100	-	-	44 (44%)	56 (56%)
Winje et al [299]	TST	912	-	-	311 (34%)	601 (66%)
Pareek et al [207]	QFT-GIT	36 and 604[a]	7 (19%)	29 (81%)	152 (25%)	452 (75%)
Mulder et al [286]	QFT-GIT	1468	-	-	296 (20%)	1172 (80%)
Garfein et al [287]	QFT-GIT	133	-	-	53 (40%)	80 (60%)
Harstad et al [288]	QFT-GIT	823	-	-	246 (30%)	577 (70%)
Simpson et al [291]	QFT-GIT	87 and 272[a]	6 (7%)	81 (93%)	93 (34%)	179 (66%)
Paxton et al [292]	QFT-G	208 and 602[a]	33 (16%)	175 (84%)	163 (27%)	439 (73%)
Carvalho et al [298]	QFT-G	100	-	-	15 (15%)	85 (85%)
Winje et al [299]	QFT-GIT	912	-	-	264 (29%)	648 (71%)

TST: Tuberculin Skin Test; QFT: QuantiFERON; QFT-G: QuantiFERON-Gold; QFT-GIT: QuantiFERON-Gold-In-Tube

[a]Values for those tested who were <18 and ≥18 years of age, respectively.

Table 2-4. Diagnostic data from the TST and IGRA studies with incidence-specific data, stratified according to several cut-offs

Study	Test Type	Number of Included Participants	Testing Positive	Testing Negative	Testing Positive	Testing Negative
			<10 cases per 100,000 persons		**≥10 cases per 100,000 persons**	
Desale et al [279]	TST	1 and 307[a]	0 (0%)	1 (100%)	153 (50%)	154 (50%)
Simpson et al [291]	QFT-GIT	16 and 484[a]	0 (0%)	16 (100%)	166 (34%)	318 (66%)
			<30 cases per 100,000 persons		**≥30 cases per 100,000 persons**	
Alperstein et al [264]	TST	27 and 326[b]	5 (19%)	22 (81%)	94 (29%)	232 (71%)
Minodier et al [127]	TST	1091 and 2229[b]	29 (3%)	1062 (97%)	743 (33%)	1486 (67%)
Martin et al [272]	TST	616 and 1517[b]	289 (47%)	327 (53%)	789 (52%)	728 (48%)
Li et al [278]	TST	3356 and 17,250[b]	950 (28%)	2406 (72%)	7203 (42%)	10,047 (58%)
Desale et al [279]	TST	117 and 191[b]	58 (49%)	59 (51%)	95 (50%)	96 (50%)
Simpson et al [291]	QFT-GIT	16 and 484[b]	0 (0%)	16 (100%)	166 (34%)	318 (66%)
			<50 cases per 100,000 persons		**≥50 cases per 100,000 persons**	
Lifson et al [255]	TST	585 and 1952[c]	250 (43%)	335 (57%)	987 (51%)	965 (49%)
Menzies et al [259]	TST	418 and 780[c]	89 (21%)	329 (79%)	288 (37%)	492 (63%)
Carvalho et al [100]	TST	24 and 57[c]	15 (63%)	9 (37%)	36 (63%)	21 (37%)
Alperstein et al [264]	TST	38 and 315[c]	8 (21%)	30 (79%)	91 (29%)	224 (71%)
Minodier et al [127]	TST	1479 and 1841[c]	175 (12%)	1304 (88%)	597 (32%)	1244 (68%)
Geltman et al [265]	TST	31 and 1705[c]	8 (26%)	23 (74%)	431 (25%)	1274 (75%)
Hladun et al [269]	TST	152 and 157[c]	32 (21%)	120 (79%)	55 (35%)	102 (65%)
Baussano et al [270]	TST	4114 and 22,440[c]	1119 (27%)	2995 (73%)	8061 (36%)	14,379 (64%)
Martin et al [272]	TST	670 and 1463[c]	314 (47%)	356 (53%)	764 (52%)	699 (48%)
Varkey et al [273]	TST	2543 and 7299[c]	1096 (43%)	1447 (57%)	3894 (53%)	3405 (47%)
Bran et al [277]	TST	81 and 624[c]	22 (27%)	59 (73%)	302 (48%)	322 (52%)
Li et al [278]	TST	5830 and 14,776[c]	1915 (33%)	3915 (67%)	6238 (42%)	8538 (58%)
Desale et al [279]	TST	187 and 121[c]	92 (49%)	95 (51%)	61 (50%)	60 (50%)
Mulder et al [281]	TST	156 and 487[c]	64 (41%)	92 (59%)	209 (43%)	278 (57%)
Hayes et al [282]	TST	5 and 123[c]	0 (0%)	5 (100%)	45 (37%)	78 (63%)
Pareek et al [207]	QFT-GIT	50 and 1179[c]	2 (4%)	48 (96%)	243 (21%)	936 (79%)
Mulder et al [286]	QFT-GIT	376 and 1086[c]	48 (13%)	328 (87%)	267 (25%)	819 (75%)
Harstad et al [288]	QFT-GIT	103 and 693[c]	18 (17%)	85 (83%)	224 (32%)	469 (68%)
Simpson et al [291]	QFT-GIT	63 and 437[c]	6 (10%)	57 (90%)	160 (37%)	277 (63%)
Winje et al [299]	QFT-GIT	115 and 789[c]	22 (19%)	93 (81%)	241 (31%)	548 (69%)

TST: Tuberculin Skin Test; QFT: QuantiFERON; QFT-G: QuantiFERON-Gold; QFT-GIT: QuantiFERON-Gold-In-Tube

[a]Values listed for those from countries with incidences <10 cases per 100,000 persons and ≥10 cases per 100,000 persons, respectively

[b]Values listed for those from countries with incidences <30 cases per 100,000 persons and ≥30 cases per 100,000 persons, respectively

[c]Values listed for those from countries with incidences <50 cases per 100,000 persons and ≥50 cases per 100,000 persons, respectively

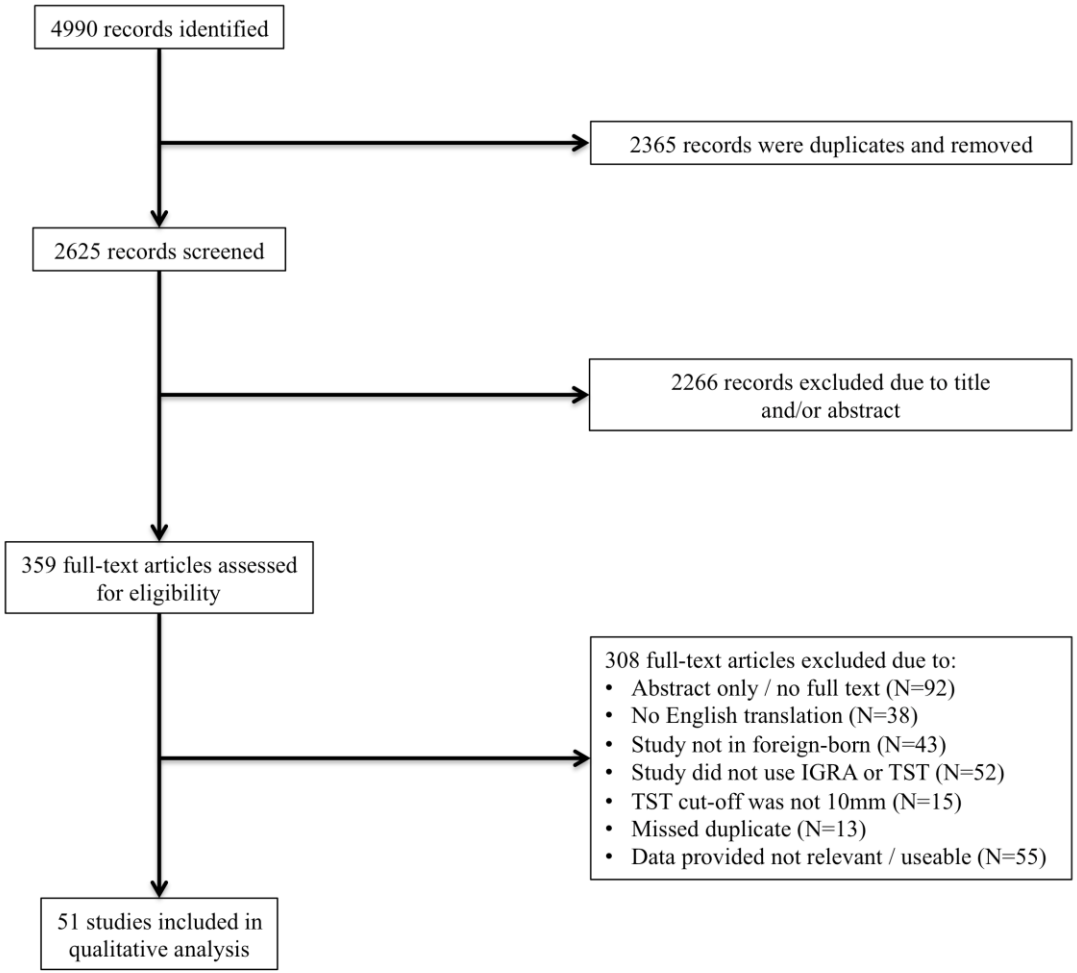
Table 2-5. Diagnostic data and concordance of the studies that used both the TST and IGRA in immigrants

Study	IGRA Platform	Number of Included Participants	TST		IGRA		Concordance (κ)
			Testing Positive (%)	Testing Negative (%)	Testing Positive (%)	Testing Negative (%)	
Orlando et al [293]	QFT-GIT	899 TST, 1115 IGRA	407 (45%)	492 (55%)	337 (30%)	778 (70%)	Data not provided
Saracino et al [294]	QFT-GIT	279	72 (26%)	207 (74%)	107 (38%)	172 (62%)	Fair (0.346)
Baker et al [295]	QFT-GIT	195	108 (55%)	87 (45%)	105 (54%)	90 (46%)	Moderate (0.555)
Weinfurter et al [296]	QFT-GIT	594	271 (46%)	323 (54%)	171 (29%)	423 (71%)	Moderate (0.461)
Pottumarthy et al [297]	QFT	237	86 (36%)	151 (64%)	71 (30%)	166 (70%)	Moderate (0.554)
Carvalho et al [298]	QFT-G	100	44 (44%)	56 (56%)	15 (15%)	85 (85%)	Fair (0.367)
Winje et al [299]	QFT-GIT	912	311 (34%)	601 (66%)	264 (29%)	648 (71%)	Moderate (0.506)
Painter et al [300]	QFT-GIT	479	236 (49%)	243 (51%)	161 (34%)	318 (66%)	Fair (0.316)

TST: Tuberculin Skin Test; QFT: QuantiFERON; QFT-G: QuantiFERON-Gold; QFT-GIT: QuantiFERON-Gold-In-Tube

2.7 Figures

Figure 2-1. Flow diagram of the literature search



CHAPTER 3. LATENT TUBERCULOSIS INFECTION SCREENING IN IMMIGRANTS TO LOW-INCIDENCE COUNTRIES: A META-ANALYSIS[2]

3.1 Background

After significant declines in the incidence of TB in many high-income countries, TB persists in these regions, in large part related to immigration of persons from high TB incidence regions [238,304]. New immigrants to low-incidence countries have much higher rates of developing active TB compared to the general population [304]. The highest incidence of TB occurs within the first 5 years post-arrival, but many develop TB years after migration [244]. The high incidence of TB in immigrants, coupled with the majority of all TB cases attributed to immigrants, have highlighted the need to reconsider TB screening methods in low-incidence countries [3,205]. Recent literature regarding TB screening of immigrants shows much variation between national screening procedures [241–243]. Many countries employ different criteria for screening new immigrants for active TB and LTBI, while nearly one half of low-incidence countries do not have a LTBI screening program in place [241].

The diagnosis of LTBI relies on a combination of medical history, immune assays, and chest radiography. The backbone of LTBI diagnostics are the immune assays, including the TST and the newer IGRAs [108]. The TST is an inexpensive and sensitive method for LTBI testing, but has poor specificity in BCG-vaccinated individuals [305]. IGRAs do not suffer from the same false-positive results in BCG-vaccinated individuals and only require one visit, however long-term evidence to support their use is less robust and they are more expensive [247]. The determination of which test to use is a topic of current debate, with the increased cost of the IGRA only justifiable if it is more cost-effective than the TST.

For clinicians and policy makers, deciding on whom and how to screen for LTBI is a difficult choice marred by the lack of a gold standard test, different test costs, failure to accept and/or return for testing, and uncertainty as to the population of highest priority. In chapter 2, we conducted a qualitative systematic review where we highlighted the lack of definitive knowledge in immigrant LTBI diagnosis. The review evaluated screening

[2]Adapted with permission from: Campbell JR, Chen W, Johnston J, Cook V, Elwood K, Krot J, Marra F. Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis. *Mol Diagn Ther* 2015;19(2):107-17

outcomes, concurrent TST and IGRA performance, and test behaviour by age and TB incidence. In building upon this work this chapter aims to quantitatively explore associations implied by the results of the review and attempt to discern the implications. The primary outcome of this meta-analysis was to explore concurrent TST and IGRA in terms of positive test prevalence and concordance as well as each test's behaviour in immigrants from varying TB incidence levels. Secondary outcomes assessed were recommendation of LTBI treatment and possible predictors of diagnostic test positivity by TST and IGRA, exclusive of each other.

3.2 Methods

3.2.1 Literature Search Strategy and Study Selection

A literature search (January 1980–April 2014) was performed in eight electronic databases including: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CAB Direct, CINAHL, Web of Knowledge, and PubMed. The searches varied with each database, however key Medical Subject Headings used were: tuberculosis, immigrants and emigrants, immigration and emigration, refugees, tuberculin test, interferon gamma release tests, and mass screening. The Web of Knowledge search strategy utilized was: ("immigra*" OR "refugee*" OR "migra*" OR "foreign born*") AND ("tuberculosis") AND ("test*" OR "screen*"). I performed the literature search. Uncertainty and revisions were discussed with Dr. Marra.

Inclusion criteria applied to the studies ensured that: the study took place in a low TB incidence country (defined as <30 culture positive cases per 100,000 persons) [3]; TST, ELISA and/or ELISPOT based IGRA were used; the study population included immigrants or listed results for immigrant populations; data were stratified by at least one of gender, age, country of origin, BCG status or test result; a 10 mm induration diameter was used as a cut-off for a positive TST; and the TST was read between 48 and 72 h after administration. Exclusion criteria applied to this meta-analysis were: self-reported results; immunocompromised populations—including HIV; and the use of outdated TST techniques.

3.2.2 Data Extraction

Jane Krot and I extracted the data independently. Discrepancies were resolved through discussion and, if necessary, Dr. Marra made the final decision. Data extracted from the studies included the location and date of the study, total number of participants included in the analysis, age, gender, country of origin, type of testing, BCG

vaccination, TST and/or IGRA results, TST induration diameter cut-off, and test results by age, gender, incidence in country of origin, and BCG status where possible.

3.2.3 Study Quality

The review was conducted according to the PRISMA statement [252] and study quality was assessed using the SIGN Methodology Checklist for Studies of Diagnostic Accuracy [253], a commonly used grading system for diagnostic studies. Due to the lack of a gold standard test, only certain aspects of the grading system were used, including evaluation of: how patients were enrolled, appropriateness of selected patients, how patients were excluded, the final number of included patients in the analysis, and reading of the diagnostic test.

3.2.4 Data Analysis

3.2.4.1 Primary Analysis

Four different commercially available IGRA tests: QFT, QFT-G, QFT-GIT (QIAGEN Inc, Valencia, CA) and T-SPOT.*TB* (Oxford Immunotec, Oxford, UK) were pooled in this analysis, to maximize data due to lack of available data surrounding the use of the QFT, QFT-G, and T-SPOT.*TB* in immigrant populations.

Our primary analysis consisted of creating a forest plot for the logit-transformed proportions (e.g. log-odds) of positive test prevalence for studies comparing the TST and IGRA in the same immigrants using a random effects model in Review Manager 5 (The Cochrane Collaboration, Oxford, UK).

To further explore the relationship between the TST and IGRA, concordance between the TST and IGRA was assessed using the kappa statistic as a measure of test agreement. This was carried out using Stata software, version 12.1 (StataCorp, College Station, TX).

Evaluation of test positivity based on TB incidence in country of origin was carried out in a random-effects meta-regression using Stata and visualized graphically based on cut-points of <30 cases per 100,000 persons, 30–99 cases per 100,000 persons, 100–199 cases per 100,000 persons, and ≥200 cases per 100,000 persons [3,96].

3.2.4.2 Secondary Analysis

Studies reporting recommendation of LTBI treatment in those tested with a TST or IGRA were meta-analyzed using Stata for proportion of immigrants testing positive and the proportion of positive immigrants

recommended treatment, respectively. Logit-transformed proportions were used in the random-effects meta-analysis and the weighted-pooled point estimates were back-transformed into proportions.

To further understand the behaviour of the TST and IGRA, forest plots for the logit-transformed proportions of positive test prevalence of each identified predictor were created. Positivity rates for the TST and IGRA were explored by: gender (male vs. female), BCG status (vaccinated vs. unvaccinated), TB incidence in country of origin (moderate to very high, ≥30 cases per 100,000 persons vs. low, <30 cases per 100,000 persons), and age (<35 years old vs. ≥35 years old) in corresponding subgroup analyses. TB incidence in country of origin was subjected to a sensitivity analysis using low-end cut-points of <10 cases per 100,000 persons [70] and <50 cases per 100,000 population [249] due to the varying definitions seen worldwide. Using a random effects model, Review Manager 5 was used to perform the subgroup analyses.

Heterogeneity was assessed using the I^2 statistical test. Heterogeneity was defined as low ($I^2 \leq 33\%$), moderate ($33\% < I^2 \leq 66\%$), and high ($I^2 > 66\%$) [306]. For measures in the moderate or high region, interpretation was tempered and further investigation into the source of heterogeneity was performed. To discover the source of heterogeneity, a similar method to one employed by Rangaka et al. [25] was used. Investigation was undertaken by stratifying by: study quality (high quality, prospective vs. acceptable, retrospective), country income (high vs. low and moderate), TB incidence per 100,000 persons for the majority of participants (<30 cases vs. ≥30 cases), age of the majority of participants (<18 years vs. ≥18 years), and type of IGRA platform used. If heterogeneity could not be described by any of these criteria, we stressed caution on interpreting the result. Jackknife sensitivity analysis was performed for each meta-analysis to determine the effect on the odds ratio (OR) of study removal.

3.3 Results

3.3.1 Studies Identified

As shown in **Figure 3-1**, 45 studies were ultimately included in the various analyses. Twenty-nine of the included studies received a high quality grade [100,101,127,207,254–259,262–265,267–269,285–288,294–300,307] while 16 received an acceptable grade [270,272–284,289,291] according to the SIGN quality assessment.

3.3.2 Primary Results

3.3.2.1 Concurrent Testing: Positive Test Prevalence, Concordance, and Discordance in the TST and IGRA

Eight studies compared TST and IGRA test positivity [268,294–300] with one using the original QFT [296], one using QFT-G [298], and remaining using QFT-GIT. Pooled results demonstrate significantly increased odds of a positive TST compared to IGRA (OR 1.46; 95% CI 1.07–2.01) (**Figure 3-2**) although heterogeneity was high (I^2 = 87%). Removal of individual studies [296,298,300] through jackknife analysis rendered the conclusion insignificant. Analysis of the six studies using the QFT-GIT yielded no difference between the TST and QFT-GIT (OR 1.31; 95% CI 0.93–1.85; p = 0.13; I^2 = 89%). These results suggest the IGRA has conditional added value in immigrant LTBI screening.

Seven studies compared TSTs and IGRAs in terms of concordant and discordant results [294–300]. Concordance of TST and IGRA was moderate (κ 0.45; 95% CI 0.38–0.52), although there was high heterogeneity (I^2 = 76%) in this result. Age as a predictor for test discordance was reported in four studies [268,295,296,298] with conflicting evidence. Two studies [296,298] found no difference in test discordance among age groups, while the remaining studies saw decreasing discordance with age [268,295]. Our results suggest test sensitivity at younger ages plays a role in test discordance.

3.3.2.2 Test Positivity by TB Incidence in Country of Origin

Seventeen studies allowed for calculation of prevalence of positive TST by TB incidence within the immigrants' country of origin [100,127,254,255,257,258,262,264,265,269,272,273,277–279,281,282]. The prevalence of positive TST was 19.9% (95% CI 4.4-57.2%) in immigrants from <30 cases, was 38.5% (95% CI 32.3-45.0%) in immigrants from 30-99 cases, was 32.7% (95% CI 28.3-37.5%) in immigrants from 100-199 cases, and was 41.6% (95% CI 35.7-47.8%) in immigrants from ≥200 cases per 100,000 population. There was no significant difference between TST positivity and TB incidence between the 30–99, 100–199, and ≥200 cases per 100,00 population levels (p > 0.05), while there was a significant increase in TST positivity going from <30 cases to 30–99 cases per 100,000 population (p = 0.05). A bubble plot and prediction interval for TST positivity by TB incidence is shown in **Figure 3-3**.

Five IGRA studies allowed the same calculation as above [207,286,288,291,299]. The prevalence of positive IGRA was 2.9% (95% CI 0.2-31.7%) in immigrants from <30 cases, was 15.9% (95% CI 12.6-19.8%) in immigrants from 30-99 cases, was 20.3% (95% CI 18.4-22.3%) in immigrants from 100-199 cases, and 33.6% (95% CI 26.3-41.7%) in immigrants from ≥200 cases per 100,000 population. There were not enough studies in our lowest group (<30 cases per 100,000 population) preventing any testing with this group. There was a significant increase in IGRA positivity going from 100–199 cases to ≥200 cases per 100,000 population ($p = 0.03$), while no significant change was noted going from 30–99 to 100–199 cases per 100,000 population ($p > 0.05$). **Figure 3-4** displays the bubble plot and prediction interval for IGRA positivity by TB incidence.

3.3.3 Secondary Results

3.3.3.1 Recommendation of LTBI Treatment

Three studies evaluated IGRA positivity and recommendations for LTBI treatment [285,288,289], while 15 performed the same analysis with the TST [100,101,127,254,256,263,267,273–277,279,280,284]. In IGRA studies, a pooled estimate of 23.7% (95% CI 17.7–30.8%) tested positive with IGRA, with an estimate of 27.5% (95% CI 4.2–76.6%) of those testing positive recommended LTBI treatment. A pooled estimate of 44.7% (95% CI 36.4–53.3%) tested positive in TST-based studies, with 59.0% (95% CI 47.7–69.5%) of those recommended LTBI treatment.

3.3.3.2 Predictors for a Positive TST

Twenty-three studies were included in the analysis of predictors for a positive TST. Of those included, 5 assessed age [254,257,258,278,281], 11 assessed gender [254,255,257,262,270,273,277–279,281,300], 5 assessed TB incidence in country of origin [127,264,272,278,279], and 7 assessed BCG vaccination, one via BCG vaccination schedule [278], three via self-reporting [259,264,307], and three via BCG scar [258,281,283].

Figure 3-5 demonstrates that age is a predictor of TST positivity resulting in a higher likelihood of a positive TST in those ≥35 years of age (OR 1.59; 95% CI 1.32–1.92). Male gender was found to be a predictor of TST positivity as shown in **Figure 3-6** (OR 1.38; 95% CI 1.20–1.58). Those from moderate to very high TB incidence countries are at increased odds of a positive TST (**Figure 3-7**) (OR 2.38; 95% CI 1.14–4.98). BCG-vaccinated immigrants had a higher likelihood for a positive TST (OR 2.10; 95% CI 1.54–2.88) as seen in **Figure 3-**

8. Jackknife analyses did not affect any of our conclusions, indicating the results are very robust, albeit heterogeneous.

In our sensitivity analysis, 15 studies provided data on TB incidence in country of origin using <50 cases per 100,000 as the low incidence cut-off [100,127,255,259,264,265,269,270,272,273,277–279,281,282] finding that those from moderate to very high TB incidence countries are at increased odds of a positive TST (OR 1.71; 95% CI 1.40–2.09). Using a low incidence cut off of <10 cases per 100,000 only included one study [279], with only one participant falling into that category, not allowing for analysis.

3.3.3.3 Predictors for a Positive IGRA

Predictors for a positive IGRA were assessed in eight studies, with T-SPOT.*TB* [285] and QFT-GIT [207,286–288,291,299,300] used. All studies assessed gender and one assessed TB incidence in country of origin [291]. Males were found to have a higher likelihood of positive IGRAs (**Figure 3-9**) (OR 1.34; 95% CI 1.08–1.66). With only one study comparing immigrants from low incidence to moderate to very high incidence TB countries, a meta-analysis could not be performed. As a stand-alone study, however, an OR of 17.25 (95% CI 1.03–289.34) was calculated for positive test results in those from moderate to very high TB incidence compared to low TB incidence countries. The results of the gender analysis were robust, as jackknife analysis did not alter the conclusions.

In the sensitivity analysis evaluating varying definitions of low-incidence countries, using <50 cases per 100,000 resulted in five studies, all using the QFT-GIT, assessing TB incidence in country of origin being included [207,286,288,291,299] with increased odds of a positive IGRA in those from moderate to very high TB incidence countries (OR 2.26; 95% CI 1.79–2.87). Dropping the definition to <10 cases per 100,000 resulted in the same conclusion initially garnered, with only one study included [291].

3.4 Discussion

The results of this meta-analysis suggest that the odds of a positive TST are 1.46 times the odds of a positive IGRA in immigrant populations, although this result was highly heterogeneous and inconsistent when including only studies using the QFT-GIT. IGRA and TST test agreement was moderate, with most discordance coming from people testing positive with a TST and negative with an IGRA. The lack of BCG vaccination status reporting in many studies prevents a clear link between vaccination and discordance, however we suspect BCG vaccination is the cause of the differential behaviour of the TST and IGRA as TB incidence increases. We found that

age ≥35 years, male gender, origin from a moderate to very high TB incidence country, and BCG vaccination history were all independent predictors for a positive TST in immigrants. For IGRAs, male gender and origin from a moderate to very high TB incidence country were associated with positivity, while lack of available studies assessing similar age subgroups and BCG vaccination did not allow for further analysis in those receiving IGRAs.

Evaluating the proportion of those recommended LTBI treatment is useful as a benchmark expectation for potential cost of screening immigrants, however given the different country guidelines regarding LTBI treatment worldwide the applicability of this type of evaluation may be limited. Ideally we would have liked to have evaluated person-years incidence rates of disease, stratified by test results, yet this was not possible to do as there were only three long-term follow-up studies for active TB prevention. Two studies evaluated active TB development in those tested with TST. In one study, five of 4990 TST-positive immigrants who were followed for 5 years developed active TB [274]; in the second study, eight of 154 who were followed for 3 years developed active TB [280]. The third study followed immigrants for approximately 2 years but evaluated the QFT-GIT test; nine of 238 positive immigrants developed active TB [288]. More comparative studies, disaggregated by risk-factors, with an extended follow up are required to fully understand the active TB risk in test-positive immigrant populations.

Building on the results of Chapter 2, this meta-analysis is the first to assess predictors for positive LTBI diagnostic tests in exclusively immigrant populations and builds on the results of Chapter 2. Similar meta-analyses have been performed in non-immigrant populations. Wang *et al*. [308] performed an analysis on a range of populations and reported increased risk of a positive TST in BCG vaccinated compared to unvaccinated subjects (relative risk 2.15; 95% CI 1.50–3.00), similar to the results reported here. A meta-analysis by Diel *et al*. [309] did not find any significant association between IGRA positivity and BCG vaccination, a result not calculable in immigrants in this study due to lack of available data.

Shortage of available studies and consistent age reporting did not allow us to calculate if age was a predictor for positive IGRAs. It has been reported elsewhere that increasing age results in higher levels of interferon-gamma production in non-immigrants [310,311]. IGRA sensitivity has been shown to vary with age, with sensitivity lower in children aged ≤5 years [312], but decreasing past 30 years of age [313]. TST sensitivity also varies by age, with estimates lower in children than in adults [24]. This age-dependent behaviour of diagnostic tests may be the reason for decreasing discordance between tests as immigrant's age. Further studies into the behaviour of

each of these diagnostic tests in relation to age in immigrants is required as this has the ability to confer levels of clinician confidence into screening results.

Obstacles exist to determining true test sensitivity and specificity in immigrant populations as studies generally use low-risk populations to estimate specificity and use active TB as a surrogate to determine sensitivity [24,34]. These values were estimated previously with limited data in Chapter 2. Next steps to answering these questions could be to devise longitudinal studies evaluating TB development in immigrants tested for LTBI.

Policy makers should reconsider the use of the TST as standard practice in immigrant populations. BCG vaccination is likely the culprit for the inflated number of positive TSTs as there is no significant difference between test specificity in unvaccinated populations and test sensitivity is not significantly different between the TST and versions of the QFT [24]. Furthermore, considering that many countries now employ dual testing in populations at high risk for TST false positives (e.g. immigrants), the sole use of an IGRA may lead to time and money savings [3,205].

Determining whether screening is necessary is aided by knowledge of test result predictors. The true value of this knowledge, however, is only quantifiable through a cost-effectiveness analysis of screening in populations with varying risk-factor profiles for test positivity. As of now, while several factors with statistically significant associations with test results are identified, their clinical significance is uncertain.

This meta-analysis has several limitations. Comparing studies over a large time interval, given the trends of TB infection worldwide, may muddle any TST to IGRA comparison. However, when we stratified study inclusion based on our earliest IGRA study (pre- and post-1996) there were no significant differences, suggesting that immigrant TB trends have not changed drastically over the past several decades. Our selection of a 10 mm cut-off for inclusion, based on this being the most common standard used worldwide, can limit applicability of our results in several populations, such as immunocompromised populations or children, which may use 5 mm or populations at high risk of being BCG vaccinated in which a 15 mm cut-off is more commonly used, however this meta-analysis was focused on generally healthy immigrant populations where 10 mm is the standard. Combination of several IGRA platforms into one analysis is not ideal given the varying sensitivities and specificities of each test [24], however this limitation is widely recognized [25,301,302] and the relatively limited IGRA data in this area necessitated this.

As in many meta-analyses, the low number of studies reporting diagnostic tests by age, gender, TB incidence, and BCG limited the interpretation of results. The low number of studies reporting on immigrants from low-incidence countries, especially studies using IGRAs, limited our evaluation of the relationship between TB incidence and test positivity. Evaluation of sensitivity and specificity was not possible in these studies due to the infrequent follow-up, lack of clarity on how LTBI was ultimately diagnosed, and lack of data available on those who had a negative diagnostic test but were subsequently diagnosed with LTBI or active TB. Furthermore, there was considerable heterogeneity among all analyses except when considering TB incidence in relation to IGRA positivity. Only one study examined T-SPOT.*TB*; further studies into the test's utility in immigrants are needed to allow comparison of both IGRA diagnostic tests with the TST.

3.5 Conclusions

Immigrants are significantly more likely to test positive with a TST than an IGRA, however longitudinal data on active TB development in immigrants are lacking. Further comparative studies are required to definitively determine the most appropriate diagnostic test to use in immigrant populations and whether this will ultimately help decrease foreign-born rates of active disease in low-incidence countries.

3.6 Figures

Figure 3-1. Flow diagram of studies included in the meta-analysis

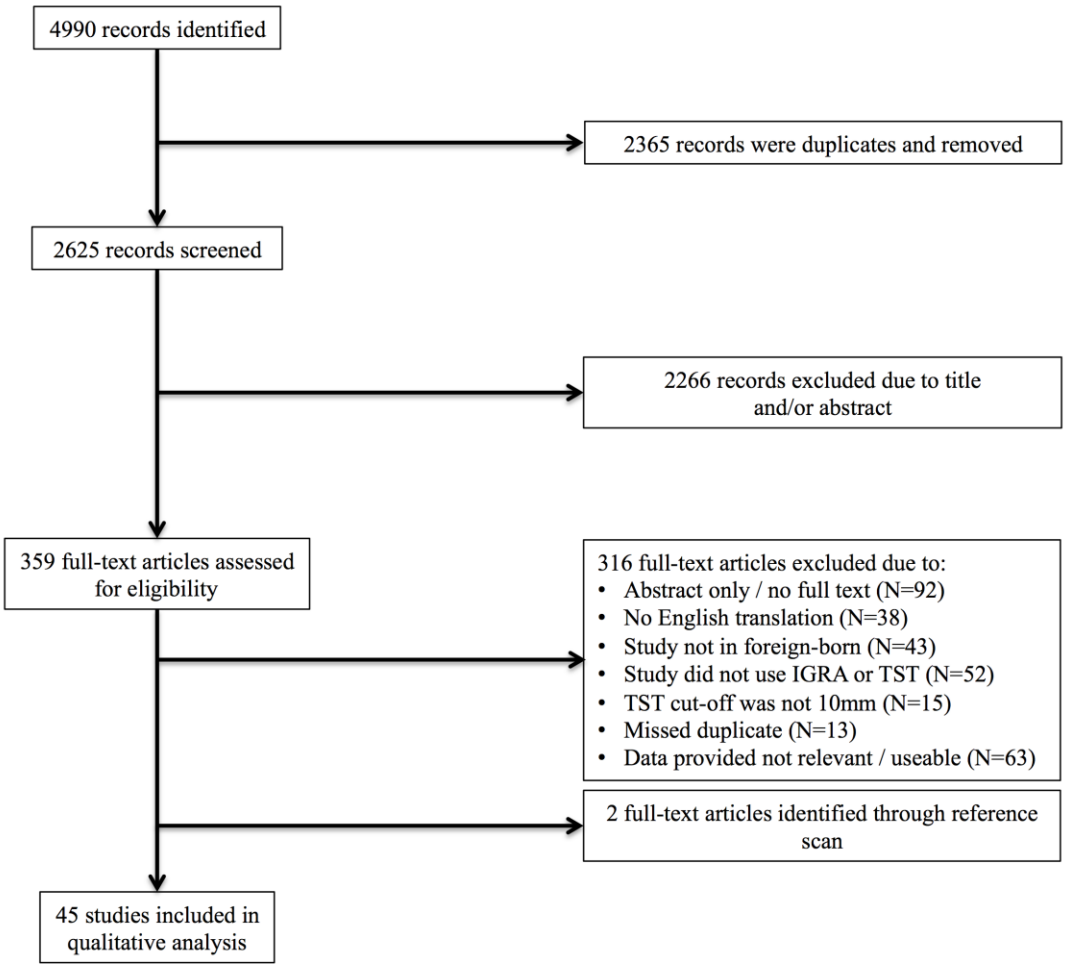


Figure 3-2. Forest plot of the odds of a positive test result between the TST and IGRA

Study or Subgroup	TST Events	TST Total	IGRA Events	IGRA Total	Weight	Odds Ratio M-H, Random, 95% CI
Winje et al	311	912	264	912	14.2%	1.27 [1.04, 1.55]
Baker et al	108	195	105	195	12.1%	1.06 [0.71, 1.59]
Carvalho et al	44	100	15	100	8.9%	4.45 [2.26, 8.75]
Losi et al	104	232	80	232	12.4%	1.54 [1.06, 2.24]
Saracino et al	72	279	107	279	12.6%	0.56 [0.39, 0.80]
Weinfurter et al	271	594	171	594	13.8%	2.08 [1.63, 2.64]
Pottumarthy et al	86	237	71	237	12.3%	1.33 [0.91, 1.95]
Painter et al	236	479	161	479	13.6%	1.92 [1.48, 2.49]
Total (95% CI)		**3028**		**3028**	**100.0%**	**1.46 [1.07, 2.01]**
Total events	1232		974			

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 54.71$, df = 7 ($P < 0.00001$); $I^2 = 87\%$

Test for overall effect: $Z = 2.36$ ($P = 0.02$)

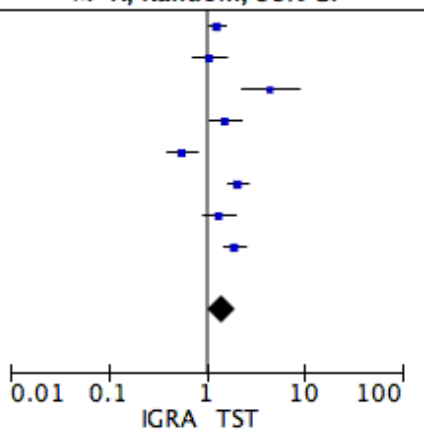


Figure 3-3. TST bubble plot for test positivity by TB incidence in country of origin

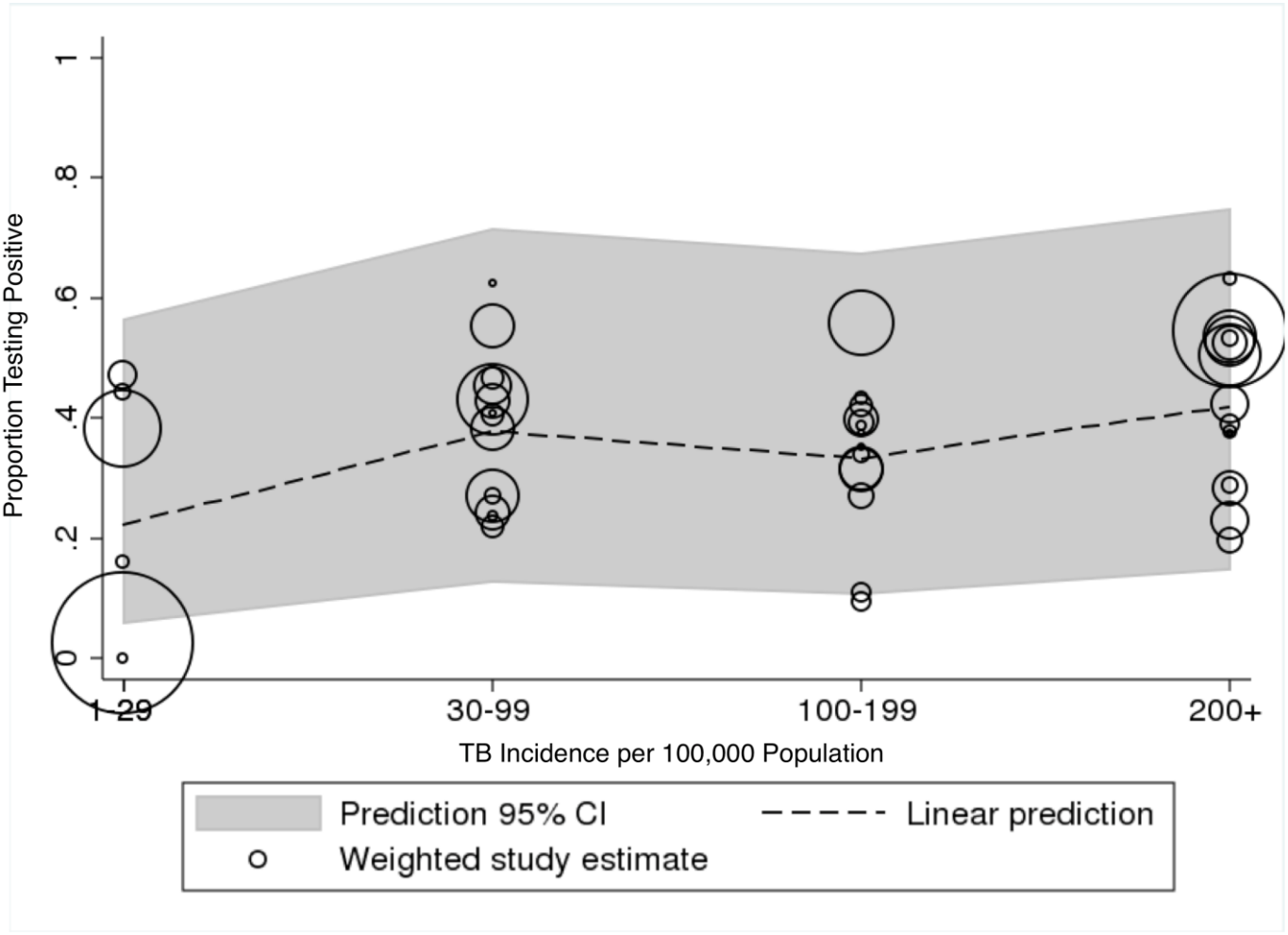


Figure 3-4. IGRA bubble plot for test positivity by TB incidence in country of origin

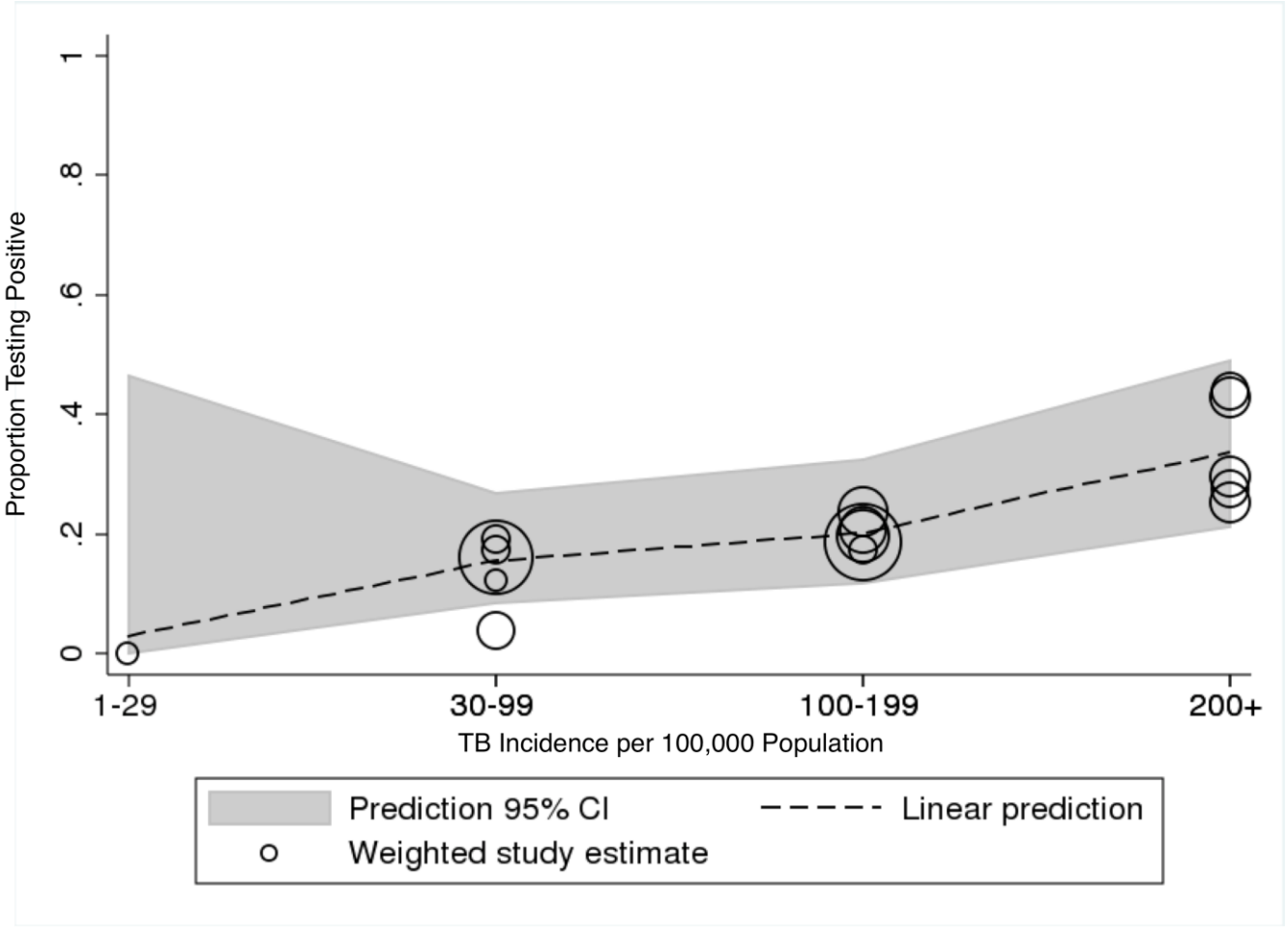


Figure 3-5. Forest plot of association between TST positivity and age ≥35 years old

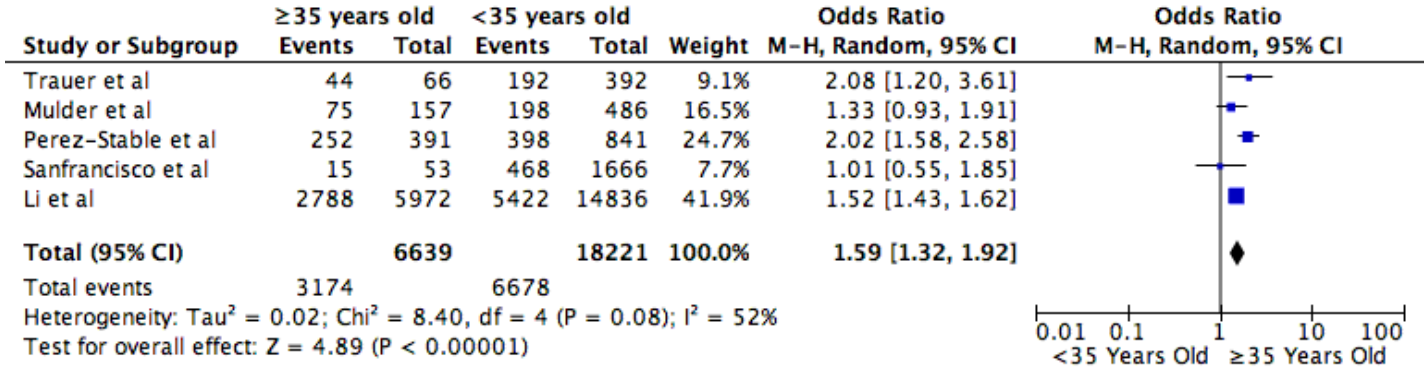


Figure 3-6. Forest plot of association between TST positivity and gender

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Odds Ratio M-H, Random, 95% CI
Painter et al	128	231	108	248	7.3%	1.61 [1.12, 2.31]
Trauer et al	73	203	73	255	6.6%	1.40 [0.94, 2.08]
Varkey et al	2709	4740	1944	4301	13.8%	1.62 [1.49, 1.76]
Bran et al	289	570	62	158	7.3%	1.59 [1.11, 2.28]
Desale et al	108	242	55	148	6.2%	1.36 [0.90, 2.07]
Mulder et al	120	273	153	370	8.2%	1.11 [0.81, 1.53]
Sanfrancisco et al	654	1979	68	244	8.7%	1.28 [0.95, 1.72]
Lifson et al	730	1360	508	1184	12.2%	1.54 [1.32, 1.80]
Robertson et al	31	95	4	26	1.3%	2.66 [0.84, 8.40]
Li et al	4178	9626	4059	11182	14.2%	1.35 [1.27, 1.42]
Baussano et al	5517	15705	3663	10849	14.2%	1.06 [1.01, 1.12]
Total (95% CI)		**35024**		**28965**	**100.0%**	**1.38 [1.20, 1.58]**
Total events	14537		10697			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 94.36$, df = 10 ($P < 0.00001$); $I^2 = 89\%$

Test for overall effect: $Z = 4.59$ ($P < 0.00001$)

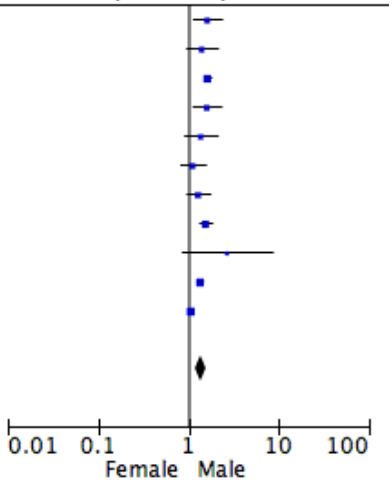


Figure 3-7. Forest plot of association between TST positivity and source country TB incidence

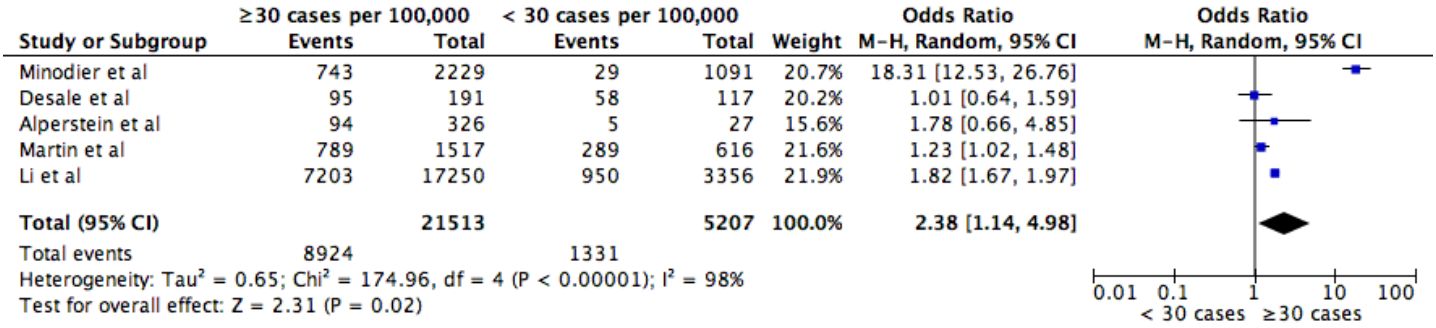


Figure 3-8. Forest plot of association between TST positivity and BCG vaccination

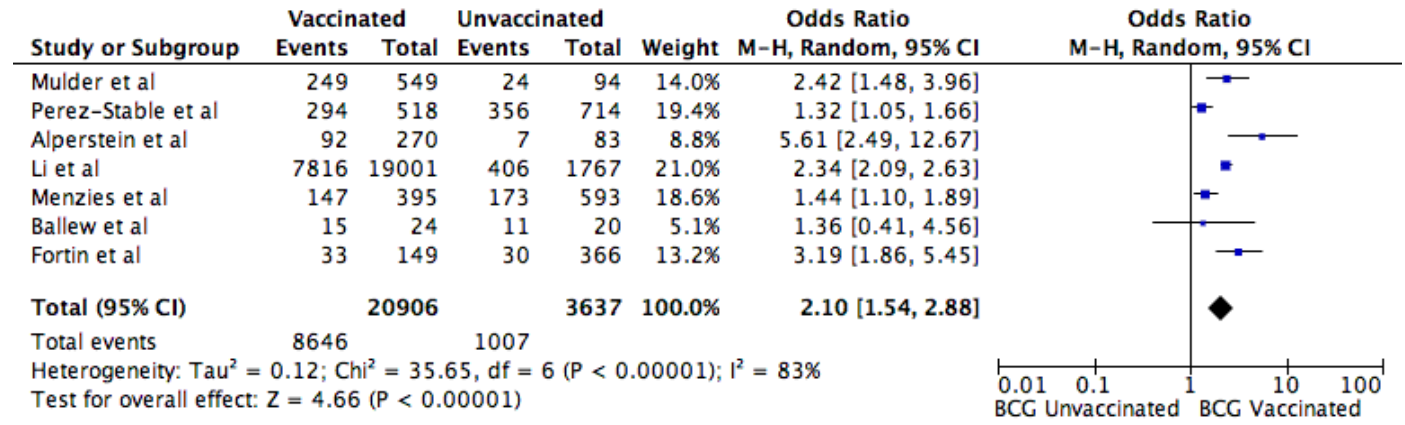
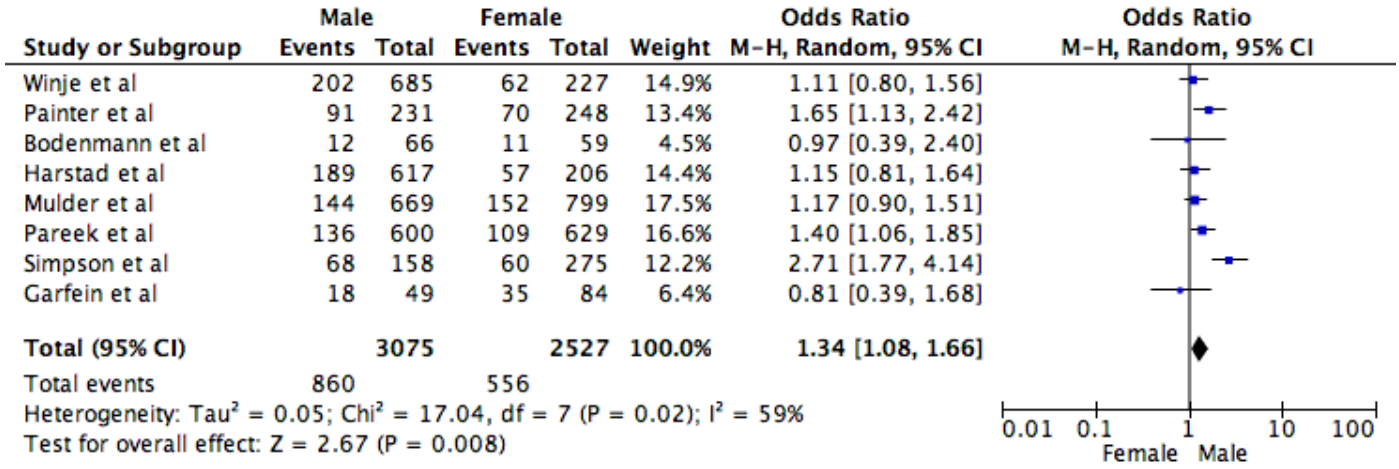


Figure 3-9. Forest plot of association between IGRA positivity and gender



CHAPTER 4. COST-EFFECTIVENESS OF POST-LANDING LATENT TUBERCULOSIS INFECTION CONTROL STRATEGIES IN NEW MIGRANTS TO CANADA[3]

4.1 Background

In Canada, over two-thirds of all active TB cases occur in migrants [3,314,315]. Current pre-immigration TB screening protocols are mandatory for permanent residents and select temporary residents. All associated costs are the responsibility of the applicant. Screening consists of a medical history, CXR, and sputum tests to rule out active TB. Migrants diagnosed with active TB must complete an adequate course of therapy before migrating to Canada. Meanwhile, those with a medical history or CXR suggestive of prior TB are flagged for post-landing surveillance—approximately 2% [94]. The follow-up system is passive, with adherence to post-landing surveillance reported to be between 60 to 70% [3,94].

The post-landing surveillance system is successful in identifying people at risk for active TB after arrival; in Ontario one-third of all active TB in the first two years post-migration occurred in those flagged for surveillance. However, genotypic studies estimate that approximately 85% of all TB cases in migrants are due to reactivation of LTBI acquired prior to migration [71–73]. In those with LTBI, approximately 5-10% will progress to active TB over their lifetime, but effective treatment can reduce risk of progression by over 90% [51]. Despite this, it is unknown how many migrants flagged for surveillance are screened for LTBI and for the remaining 98% not flagged, there is no routine LTBI screening protocol, leaving a large group of migrants at risk for active TB and a missed opportunity for TB prevention [94]. Implementation of a LTBI screening system, however, would have to overcome inefficiencies in the LTBI cascade of care. In this context, the cascade of care consists of placing a screening test, evaluating the result, performing a medical evaluation, and initiating and completing treatment. At present, high rates of dropout during screening and treatment result in <20% of those who may benefit from treatment actually completing it [53].

Evidence-based screening and treatment recommendations in new migrants need to support TB elimination efforts in Canada. Implementation of pre- or post-landing LTBI screening protocols have been suggested

[3]Adapted with permission from: Campbell JR, Johnston JC, Sadatsafavi M, Cook VJ, Elwood RK, Marra F. Cost-Effectiveness of Post-Landing Latent Tuberculosis Infection Control Strategies in New Migrants to Canada. *PLoS ONE* 2017;12(10):e0186778.

[3,133,203,222], but no system or policy is in place to execute any of these possible solutions. In this chapter we aim to provide evidence surrounding possible implementation of post-landing LTBI screening. We developed a model to determine the cost and prevalence of LTBI and imported active TB in recent migrants. These estimates were then applied to view the impact LTBI screening post-landing would have on TB incidence in subgroups of a cohort of new migrants to Canada.

4.2 Methods

4.2.1 Study Population

The population studied in the model was the 2014 cohort of new permanent residents to Canada, which consists of 260,600 new permanent residents, of which 6100 were flagged for post-landing medical surveillance. The cohort was characterized by post-landing surveillance flag, derived from Ontario data [94], age and TB incidence in country of origin, derived from Immigration, Refugees and Citizenship Canada (IRCC) [93], and BCG vaccination status, based on data from countries with a current national vaccination policy for all, which was derived from the BCG World Atlas [224] and adjusted based on 36-year average reported immunization rates [316]. To determine the prevalence of LTBI and imported (non-preventable) TB in this population, a calibration scheme was developed. Two-year TB incidence rates in new permanent resident cohorts to Ontario between 2002 and 2011 [94], stratified by TB incidence in country of origin (low <30 cases per 100,000 population, moderate 30-99 cases, high 100-199 cases, and very high ≥200 cases) and surveillance flag were used as optimization targets. Several assumptions were made. Firstly, we assumed 85% of TB cases in those not flagged for surveillance were due to reactivation of LTBI [71–73] and that the rate of reactivation was constant over time [244]. Second, those flagged for surveillance had a reactivation risk 3.9 times higher than those not flagged for surveillance, selected based on TB risks from a long-term study in Britain [317]. Finally, it was assumed that LTBI prevalence in those under surveillance was higher than those who were not. To optimize to the targets, the baseline average reactivation rate was varied between 0.8 and 1.6 reactivation TB cases per 1000 person-years [318–321] and the proportion of TB cases in those flagged for surveillance that were imported was varied between 55% and 85% [244,322]. After optimization, a reactivation rate of 1.1 per 1000 person-years and 70% of TB cases being imported were selected; these estimates were applied proportionally to the demographic profile of the 2014 permanent resident cohort. Optimization targets are reported in **Table 4-1** and results of the optimization are reported in **Table 4-2**.

4.2.2 Discrete Event Simulation Model

A DES model was developed in Simio and run using Simio Replication Runner (Version 8.146.14121, Simio LLC, Sewickley, PA). DES, a microsimulation technique, was chosen as it allowed for modeling time continuously, modeling simultaneous events, and creating many parameters describing each patient (a Markov model would have too many states to accommodate the same level of granularity). Internal validity was examined to ensure the model worked as intended and external validity was investigated against the data source used to inform the model. The model's time horizon was 10 years from arrival to Canada to minimize extrapolation from optimization targets. The model took a healthcare system perspective and used a discount rate of 1.5% for costs and outcomes as recommended by CADTH [190]. The model's main outcomes were cost per QALY gained and cost per TB case prevented. A WTP threshold of $100,000 CAD per QALY [189,323–325] or $20,000 CAD per TB case prevented (i.e. approximately the average cost of managing one TB case) was used to determine if an intervention was cost-effective. Several assumptions were made in the model. Firstly, it was not possible to self-heal from LTBI without treatment. Secondly, multi-drug resistant TB was not considered due to extremely low incidence in Canada and difficulty in accurately costing cases. Finally, direct transmission between migrants in the cohort or to the general population was not modeled, rather we accounted indirectly for this through a certain proportion being remotely infected during the simulation.

The model structure is outlined in **Figure 4-1**. Upon arrival, simulated migrants may import tuberculosis, be flagged for post-landing TB surveillance based on pre-immigration screening, or not be flagged for surveillance at all; those flagged for surveillance may or may not adhere. Migrants adhering are given a LTBI screening test and those completing the test that are positive are all referred and given a medical evaluation (to rule out active TB). Migrants completing the medical evaluation are offered LTBI treatment and should they initiate treatment are simulated to either default at some point during treatment, discontinue due to an adverse event, die due to fatal hepatotoxicity, or fully complete treatment. All migrants, regardless of their simulation pathway, are then simulated to the model's time horizon, with an annual risk of developing TB or dying of background mortality. Upon development of TB, a chance of a remote TB case occurring was simulated to account for the proportion of TB cases in migrants not occurring due to reactivation (17.6%). Those who develop TB and complete treatment are at risk of experiencing TB relapse for the subsequent two years.

4.2.3 Model Characteristics

Input Parameters. Published reports and expert opinion were used to estimate input parameters for the model. Where possible, systematic reviews were used to derive model estimates; in cases where this was not possible, estimates from the literature were used. Background mortality was derived from Canadian life tables [326]. LTBI diagnostic test sensitivity was derived from each test's ability to detect prevalent TB (i.e. a surrogate measure) as described in Chapter 2 [20], while test specificity was derived in populations at very low risk of infection [24,34] and stratified by BCG vaccination status [224,316]. TB reactivation rate was carefully chosen from data from a variety of studies [73,219,318–321,327–329]. A rate of 1.1 per 1000 person years in individuals with LTBI was selected as it results in a cumulative incidence of TB of 5% over approximately 45 years and provides reasonable estimates of LTBI prevalence based on our meta-analysis of IGRA positivity in migrants in Chapter 3 [21]. Transition between all health states was modeled annually, except in the case of transition from adverse events or from TB to a subsequent health state, which had varying transition times. **Table 4-3** lists all model estimates.

Costs. Costs for LTBI screening and treatment were derived from the British Columbia Centre for Disease Control (BCCDC) in 2014 (personal communication), and included the costs of tests, drugs, clinician time, and routine monitoring. Adverse event and hospitalization costs during LTBI and TB treatment were determined from the literature [119,330]. The average cost for each TB case, which includes diagnosis, treatment, contact investigation, and adverse events, was estimated from a Canadian report and cost-effectiveness analysis [221,330]. All model costs were inflated to 2016 Canadian dollars ($) or converted using purchasing power parity.

Health State Utilities. All health state utilities were defined using the SF-6D scores derived from SF-36 responses and were largely informed by a study performed in new migrants to Canada [331–333]. Health state utilities were evaluated for the duration of time in each health state and not subject to fixed duration. The duration of time in the TB health state varied based on whether a patient was or was not under surveillance, as defined by the time from symptom onset to TB diagnosis reported by Khan *et al*. [94] A baseline value of 0.81 was used for all participants without LTBI or TB [331], with adjustments for other health states, where applicable.

4.2.4 Interventions

Several LTBI screening and treatment interventions available in Canada were evaluated, assuming that at each step all migrants evaluated were offered an intervention (i.e. clinician discretion in offering screening and/or

treatment was not simulated and no actual data exist on how often LTBI screening is given). LTBI screening interventions included: (1) TST, a test that requires a follow-up visit to be read and uses ≥10mm cut-point for a positive result; (2) IGRA, a test that may generate indeterminate results and uses the manufacturer's recommendation for a positive result and; (3) sequential screening (SEQ), a two-stage approach where those who test positive with a TST are tested with an IGRA—both tests must be positive for the patient to be considered to have LTBI [204,334].

Subsequently, test positive migrants who completed the medical evaluation and initiated treatment were offered one of two LTBI interventions available in Canada: (1) nine-months of isoniazid, which reduces risk of future TB by 93% and; (2) four-months of rifampin, a shorter regimen with higher completion rates, but uncertain efficacy. In general, only those flagged and adhering with post-landing surveillance are offered LTBI interventions upon arrival and Canadian guidelines recommend screening with a TST and subsequent treatment with isoniazid [3]. Thus, LTBI screening with a TST and treatment with isoniazid in the migrant population under surveillance was considered our base case in all cost-effectiveness analyses. A comprehensive table of interventions is located in **Table 4-4**.

4.2.5 Cost-Effectiveness Analyses

4.2.5.1 Improving the Post-Landing Surveillance System

In this evaluation, the analysis focused solely on the 2.4% of new migrants normally flagged for post-landing surveillance (N=6100), as a system is already in place where LTBI interventions can be easily implemented. In the primary analysis, interventions were compared to the base case under real world care conditions. The total number of discounted TB cases (including imported TB cases), costs, and QALYs were calculated for each intervention. The ICER was calculated for each intervention compared to the base case.

A secondary analysis was performed to determine if improving the cascade of care would be valuable. In this analysis, improving to surveillance adherence to 100%, improving LTBI treatment completion by 30%, and achieving both, was modeled. Based on our WTP threshold ($100,000 per QALY gained), the maximum cost that could be afforded to the healthcare system to implement these improvements was calculated using NMB.

4.2.5.2 Implementation of Mass Post-Landing LTBI Screening

In this evaluation, the entire 2014 entry cohort is included (N=260,600). Post-landing LTBI screening was evaluated through step-wise expansion of the post-landing surveillance system based on TB incidence in country of origin (i.e. screen migrants from very high TB incidence countries, screen migrants from countries of high TB incidence or greater, screen migrants from countries of moderate TB incidence or greater, screen all migrants). We modeled this intervention under the assumption that it was implemented as a supplement to the current post-landing surveillance system, therefore, even if migrants were not subject to mass post-landing screening, they could still be flagged for post-landing surveillance. Each intervention was compared to the base case. Adherence with post-landing screening was assumed to be the same as in migrants flagged for surveillance (60.5%). Discounted costs, QALYs, and TB cases (including imported TB cases) were compared to the base case.

4.2.6 Sensitivity Analysis

Uncertainty around model variables was examined using univariate sensitivity analysis and PSA. Ranges examined for both univariate and PSA can be found in **Table 4-3**. All sensitivity analyses were run for ≥2000 iterations. Results of univariate sensitivity analysis were reported as NMB of the most cost-effective option in our first primary analysis ("Improving the Post-Landing Surveillance System") compared to the base case. A PSA was performed for each primary analysis to evaluate parameter uncertainty. When model variables came from the literature, relevant distributions were used (e.g. log-normal, beta). Most costs were modeled using relevant triangular distributions due to lack of individual data. In the case of LTBI treatment, extreme costs commonly seen in treatment due to adverse events were accounted for by modeling these separately. In the case of TB treatment, expert opinion was used to develop a relevant gamma distribution. Particular health states were correlated to prevent implausible values during PSA (i.e. patients with active TB will always have a lower utility value than healthy patients). Using the average results of our PSA, efficiency frontiers comparing interventions based on costs and QALYs were developed. CEACs were developed based on the probability an intervention provided the most NMB over the ≥2000 iterations run compared to the base case. The expected value of perfect information (EVPI), a measure of the maximum amount of money to invest to absolve all uncertainty in model parameters, was calculated using the ≥2000 iterations (second-order uncertainty) as our outer sample size and the size of the population evaluated as our inner sample size (first-order uncertainty).

4.3 Results

4.3.1 Improving the Post-Landing Surveillance System

In the base case scenario, the migrant population under post-landing surveillance (N=6100) experience, on average, 99.41 cases of TB, incur $3.1 million in costs, and accrue 45,026 QALYs over ten-years (**Table 4-5**). Screening with an IGRA and treating with rifampin was dominant in comparison, preventing 4.90 TB cases (a 4.9% reduction), adding 4.0 QALYs, and saving $353,013. While treating with isoniazid was also dominant, preventing more TB cases (6.71) and adding more QALYs (4.8), it only provided an incremental NMB of $676,330 compared to the incremental NMB provided by rifampin treatment of $753,658, making rifampin the preferred treatment. If the standard of care was no screening, IGRA followed by rifampin was still preferred, with a cost per QALY gained of $11,921 and cost per TB case prevented of $8829.

A NMB of $1,098,510 resulted from improving treatment completion by 30% and $1,557,078 resulted when ensuring 100% adherence with surveillance when screening with an IGRA and treating with rifampin. If both of these improvements could be achieved, a NMB of $2,068,246 resulted. While investing in improving post-landing adherence added more QALYs and prevented more TB cases, the added costs of screening and treatment limit the proportional NMB of such an intervention (**Table 4-6**).

4.3.2 Implementation of Mass Post-Landing LTBI Screening

The most effective intervention to implement for post-landing LTBI screening of every new permanent resident to reduce TB cases was to screen with an IGRA and treat with isoniazid, preventing 125.99 TB cases (a 21.8% reduction) at a cost of $169,986 per TB case prevented; screening with an IGRA and treating with rifampin added the most QALYs, with an additional 78.3 QALYs at a cost of $207,328 per QALY gained. The most cost-effective intervention, was to limit post-landing LTBI screening to every new migrant from countries with a TB incidence ≥30 per 100,000 and screen with an IGRA, followed by treatment with rifampin, which had a cost per TB case prevented of $114,840 and $138,484 per QALY gained (**Table 4-7**).

4.3.3 Sensitivity Analysis

In univariate sensitivity analysis the base case intervention was compared to IGRA followed by rifampin, in migrants under surveillance. Extending the time horizon had the most significant impact in favor of IGRA

followed by rifampin, as the incremental NMB increased by over $1.2 million if extended to 50 years. Reducing the effectiveness of a full course of rifampin to 50% had the most significant impact against IGRA followed by rifampin, reducing the incremental NMB by over $600,000. The decision to favor IGRA screening followed by rifampin treatment over the base case, however, was very robust as no single parameter change resulted in the base case having a higher NMB. The tornado diagram is displayed in **Figure 4-2**.

In PSA of our primary analysis of migrants under surveillance, screening with an IGRA followed by rifampin treatment was the dominant option, resulting in the lowest cost, minimizing TB cases and maximizing QALYs. Screening sequentially or with a TST did not fall on the frontier (**Figure 4-3**). Due to the base case being the most expensive option, probabilities of interventions being cost-effective fell as WTP thresholds increased. Use of IGRA followed by rifampin had a probability of being cost-effective of 64.9% at a WTP of $100,000 per QALY gained, however increasing the WTP impacted the probability minimally (**Figure 4-4**). It was determined that the choice of IGRA followed by rifampin over the base case resulted in an EVPI of $610,102.

In PSA of our analysis in the total migrant cohort, it was found that the base case provided the best value for the least investment. In efficiency frontier analysis, screening with an IGRA followed by treatment with rifampin in all migrants maximized QALYs. No TST screening intervention fell on the frontier (**Figure 4-5**). Use of IGRA followed by rifampin in migrants from countries ≥30 cases per 100,000, the most cost-effective option in deterministic analysis, had a probability of being cost-effective of 43.3% at a WTP of $100,000 per QALY, however use of sequential screening followed by rifampin in migrants from countries ≥200 cases per 100,000 had the highest probability of being cost-effective at this threshold of 47.8% (**Figure 4-6**). In EVPI analysis, it was found that the decision to remain using our base case intervention compared to use of an IGRA followed by rifampin in migrants from countries ≥30 cases per 100,000, resulted in an EVPI of $12,873,338.

4.4 Discussion

The current post-landing TB surveillance system is not effective in achieving the desired decline in TB incidence in Canada. To improve LTBI diagnosis and treatment in new migrants flagged for post-landing surveillance, screening with an IGRA followed by rifampin treatment provides an overall lower cost to the healthcare system, with a reduction in TB cases and an increase in QALYs over a ten-year time horizon. Expanding post-landing LTBI screening and treatment to include all migrants was not cost-effective using any intervention,

however had the ability to significantly increase population QALYs and reduce TB cases. Further targeting post-landing LTBI interventions by TB incidence in country of origin significantly improved cost-effectiveness, yet ICERs still remained above WTP thresholds.

In Canada, the current post-landing TB surveillance system was developed to focus on identifying those at highest risk of TB immediately after arrival and was never intended to be a platform for LTBI identification. Our analysis shows that using this system to screen for LTBI would not significantly impact longitudinal TB incidence, even when improving adherence with surveillance and LTBI treatment. In the present system, gaps in the LTBI cascade of care result in <20% of migrants who may benefit from treatment actually completing LTBI therapy [53]. Ensuring 100% adherence to post-landing surveillance and improving completion of therapy by 30%, still less than one-third of migrants would complete LTBI therapy. Our data and others suggest that there is significant room for investment in improving treatment adherence [335], yet it is evident that filling gaps at each step of the cascade of care is crucial to achieving significant reductions in TB incidence.

Our analysis shows that post-landing LTBI screening decisions guided solely by TB incidence in country of origin are not specific enough to be cost-effective—it is clear that further targeted screening will be necessary. It is likely that determining the socioeconomic factors that underlie TB infection in migrant populations will be necessary to cost-effectively target LTBI screening and treatment. A previous analysis [133] examined LTBI screening in people with co-morbidities such as silicosis, renal disease, and diabetes and found this targeting not to be cost-effective. Considering comorbidity as part of selection criteria for screening in migrant populations where LTBI prevalence is significantly higher may lead to a different conclusion, however.

Previous economic analyses have been performed to assess the cost-effectiveness of mass post-landing screening of new migrants to low-incidence countries, several of which have been highlighted in systematic reviews [192,201,202]. In an analysis by Dasgupta *et al.* [222], post-landing surveillance was evaluated for its ability to prevent TB cases in new immigrants to Montreal. The analysis found that in this setting, post-landing surveillance prevented 1.9 cases of TB per 1000 new immigrants identified, for an incremental cost of $65,126 per TB disease prevented, slightly different from our results of 2.3 cases prevented per 1000 immigrants identified for post-landing surveillance ($36,837 per TB disease prevented).

Oxlade and colleagues evaluated IGRA and TST screening in new immigrants from varying TB incidence groups [204] and found that CXR at entry was cost-effective in immigrants from intermediate-to-high TB incidence

countries, while IGRAs and TSTs were not cost-effective. This is in agreement with our findings, where no screening method was cost-effective in a mass LTBI screening scenario, regardless of TB incidence in country of origin.

An evaluation performed by Khan et al [203] examined mass LTBI interventions in the United States and found it to be net saving. This evaluation, however, assumed no dropout during screening and/or treatment, which would be incredibly difficult to implement in practice. Finally, Linas et al [133] examined LTBI screening in new migrants to the United States and found it to be cost-effective, assuming low rates of dropout in modeled portions of the LTBI cascade of care and different diagnostic test performance in their model than ours.

Our analysis is the first to comprehensively model gaps in the LTBI cascade of care. We have shown that these gaps limit the effectiveness of any mass intervention to target LTBI, with <20% of those who can potentially benefit from LTBI therapy completing a course. This model is also the first to estimate the prevalence of LTBI and migrant TB in new migrant cohorts to Canada based on incident TB, rather than TST reactivity. Further, the use of DES allowed for varying times in different health states for different migrants; this allows for more accurate simulation of real world utility data and the impact each health state has on total quality of life. Our accurate representation of "healthy" utility for new migrants limits our bias of LTBI interventions away from the null, as is seen when healthy utility is assumed to be one [336]. A significant strength of this model was that it was specifically calibrated to Canadian immigration data and the TB profile of new immigrants to Ontario, giving the analysis potential to effectively inform policy decisions in immigrant-receiving provinces and territories in Canada. Further, these results may be generalizable to other low TB incidence countries that also use CXR to identify new migrants at high-risk for TB and have a similar migrant profile to Canada.

This chapter has several limitations. The proportion of remote infections was tied to reactivation TB; in essence, if fewer TB cases occurred due to reactivation, so too did TB cases due to remote transmission, which may not reflect reality where reductions in TB reactivation likely don't exactly match reductions in TB transmission. This model assumes that all migrants reporting to the clinic are offered LTBI screening, which is unlikely. Furthermore, for migrants referred due to a previous diagnosis of TB, LTBI diagnostic tests may not be reliable due to a lasting immune response, however it was not possible to determine how many migrants fell into this category; thus it was unaccounted for in our model although we do not think many individuals would fall into this category, making a real difference in the model results. Moreover, we assumed that dropout at each step of the care cascade is random,

which may not reflect reality, as some patients will never be offered therapy due to age, co-morbid conditions, risk of adverse outcomes, or low likelihood to complete therapy. Nevertheless, this was a necessary assumption in our model due to the level of evidence available. Finally, this model did not consider co-morbid conditions that may increase risk of TB, however the studies informing our rate of reactivation were derived from diverse populations and should approximate a population-wide reactivation rate incorporating co-morbidity and other risk factors.

Future economic analyses of LTBI interventions in migrant populations should focus on varying the timing of screening and/or how to target screening. Research into LTBI screening during pre-immigration medical exams could potentially be highly valuable as a tool for post-landing follow-up. Furthermore, targeting screening post-landing based on a combination of co-morbidities and demographic variables can potentially make strong predictions about future TB risk in individuals.

4.5 Conclusions

Screening new migrants flagged for post-landing surveillance with an IGRA followed by treatment with rifampin was dominant compared to the base case of TST followed by isoniazid. Expanding LTBI screening to all new migrants was cost-prohibitive. Future research should investigate the cost-effectiveness of LTBI screening based on socioeconomic factors and co-morbid conditions.

4.6 Tables

Table 4-1. Optimization targets used in the cost-effectiveness model

	TB Incidence Category			
	<30 cases	30-99 cases	100-199 cases	≥200 cases
Number of TB cases in first 2 years				
Total TB Cases	4.28	23.62	43.22	76.27
Referred for surveillance and adherent	0.92	7.20	8.38	11.76
Referred for surveillance and non-adherent	0.31	2.48	7.07	9.07
Not referred for surveillance	3.05	13.95	27.77	55.44
Population Statistics				
Total Population	74,700	61,600	54,700	69,600
Referred for surveillance and adherent	370	1025	882	1404
Referred for surveillance and non-adherent	295	792	595	726
Not referred for surveillance	74,035	59,783	53,223	67,740

TB: tuberculosis

Table 4-2. Final results of the optimization

	TB Incidence Category			
	<30 cases	30-99 cases	100-199 cases	≥200 cases
LTBI Prevalence in Migrants who were not Referred for Surveillance	0.01094	0.06198	0.13860	0.21826
Proportion of Migrants Referred for Surveillance That Had Imported TB				
Adherent with Surveillance	0.00192	0.00543	0.00637	0.00544
Non-Adherent with Surveillance	0.00048	0.00153	0.00875	0.00956
LTBI Prevalence in Migrants Referred for Surveillance	0.0641	0.1862	0.3659	0.3420

LTBI: latent tuberculosis infection; TB: tuberculosis

Table 4-3. Model parameters and analyses range

Parameter		Estimate	Univariate Analysis Range	Range for PSA	Reference
Costs					
Full INH Treatment		$992	$804, $1179	Triangular, 804-1179	BCCDC, [330,337]
	Drug Costs	$181			
	Nurse and Clinician Costs	$741			
	Follow-up CXR	$42			
	Routine Tests	$28			
Full RIF Treatment		$575	$464, $686	Triangular, 464-686	BCCDC, [330,337]
	Drug Costs	$98			
	Nurse and Clinician Costs	$421			
	Follow-up CXR	$42			
	Routine Tests	$14			
Partial INH		$462	N/A	Triangular, 174-804	BCCDC, [330,337]
Partial RIF		$319	N/A	Triangular, 178-464	BCCDC, [330,337]
Complete TST		$31	$24, $38	Triangular, 24-38	BCCDC, [330,337]
	TST Cost	$11			
	Nurse Costs (Two Visits)	$20			
Incomplete TST		$21	$17, $25	Triangular, 17-25	BCCDC, [330,337]
IGRA		$54	$31, $62	Triangular, 31-62	BCCDC, [330,337]
	Kit and Technician Cost	$47			
	Nurse Costs	$7			
CXR		$42	N/A	Triangular, 32-52	BCCDC, [330,337]
	Cost per X-Ray	$35			
	Nurse Costs	$7			
Tuberculosis		$20,532	$16,730, $24,334	Gamma(4.1064,5000)	Expert Opinion, [221,330]
LTBI Adverse Event		$732	$549, $916	Triangular, 549-916	[330]
Hospitalization		$6641	$5305, $9985	Triangular, 5305-9985	[119]
Death		$26,933	$13,079, $40,788	Triangular, 13,079-40,788	[338]

All costs are in 2016 CAD.

PSA: Probabilistic Sensitivity Analysis; INH: Isoniazid; RIF: Rifampin; BCCDC: British Columbia Centre for Disease Control; TST: Tuberculin Skin Test; IGRA: Interferon-Gamma Release Assay; CXR: Chest X-Ray; LTBI: Latent Tuberculosis Infection; TB: Tuberculosis

Table 4-3. Continued

Parameter	Estimate	Univariate Analysis Range	Range for PSA	Reference
QALYs				
LTBI	0.81	0.75, 1.0	Beta(9.49,2.23)	[331–333]
Healthy	0.81	0.75, 1.0	Beta(7.85,1.84)	[331–333]
Adverse Event Disutility	0.2	0, 0.5	Triangular, ±25%	[119,330]
TB	0.69	0.55, 0.75	Beta(6.84,3.07)	[331–333]
Hospitalization	0.5	0.3, 0.7	Triangular, ±25%	[119]
Dead	0	-	-	-
Screening Parameters				
TST Sensitivity	0.782	0.50, 0.95	Beta(43,12)	Chapter 2, [20,24]
TST Specificity (No BCG)	0.974	0.94, 1	Beta(770,21)	[24,34]
TST Specificity (BCG)	0.602	0.35, 0.87	Beta(239,158)	[24,34]
IGRA Sensitivity	0.889	0.81, 0.95	Beta(8,1)	Chapter 2, [20,24]
IGRA Specificity	0.957	0.86, 1	Beta(900,40)	[24,34]
IGRA Indeterminate	0.06	0, 0.18	Beta(83,1286)	[34]
Complete TST*	0.72	0.72, 1.0	Beta(117.84,45.83)	[53,303]
Complete Medical Evaluation†	0.78	0.6, 1.0	Beta(46.12,13.01)	[53]
Parameters for Population Under Surveillance				
Adherent with Surveillance	0.605	0.7, 0.8	-	[94]
LTBI Prevalence ≥200 cases	0.3420	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
LTBI Prevalence 100-199 cases	0.3659	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
LTBI Prevalence 30-99 cases	0.1862	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
LTBI Prevalence <30 cases	0.0641	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
Overall Imported TB Prevalence	0.0054	-	-	[244]
Parameters for Population Not Under Surveillance				
LTBI Prevalence ≥200 cases	0.3162	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
LTBI Prevalence 100-199 cases	0.2016	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
LTBI Prevalence 30-99 cases	0.0902	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
LTBI Prevalence <30 cases	0.0159	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]

*Number imputed from 43.4% of migrants indicated for screening completing [53] (if 60.5% are adherent with surveillance, 72% must complete TST screening).
†Number imputed from 43.7 of 56 individuals referred for medical evaluation completing [53].
All costs are in 2016 CAD.
QALY: Quality Adjusted Life Year; PSA: Probabilistic Sensitivity Analysis; INH: Isoniazid; RIF: Rifampin; TST: Tuberculin Skin Test; IGRA: Interferon-Gamma Release Assay; CXR: Chest X-Ray; LTBI: Latent Tuberculosis Infection; TB: Tuberculosis; BCG: Bacillus Calmette-Guérin

Table 4-3. Continued

Parameter	Estimate	Univariate Analysis Range	Range for PSA	Reference
Treatment Parameters				
Initiate Therapy*	0.938	0.5, 1	Beta(180.83,11.95)	[53,303]
Complete INH	0.616	0.5, 0.7	Beta(131.66,82.07)	[53]
Complete RIF	0.814	0.7, 0.9	Beta(76.85,17.56)	[53]
Adverse Event INH°	0.060	0.04, 0.12	Beta(134,2095)	[120–123,339]
Adverse Event RIF°	0.027	0.01, 0.07	Beta(56,2043)	[120–123,339]
Hospitalization | AE	0.01	0, 0.02	Beta(1,99)	[119]
Death due to INH	0.00000988	0, 0.0001	Beta(2,202495)	[340]
LTBI Risk Reduction INH	0.93	0.5, 1	Normal(-2.597,0.461)§	[51]
LTBI Risk Reduction RIF	0.8	0.5, 1	Normal(-1.609,0.500)§	[57,59]
Partial Risk Reduction INH	0.346	0, 0.69	Combination of Normal Distributions‡	[51,120–123,339]
Partial Risk Reduction RIF	0	0, 0.69	Normal(-0.693,0.300)§	[57,59]
Adverse Event Duration	7 days	3, 17	Gamma(0.7,10)	Expert Opinion, [119]
TB Parameters				
Death from TB	0.0476	0, 0.08	Beta(76,1523)	[3]
Reactivation Rate	0.0011	0.0009, 0.0013	Beta(90.92,82545.55)	[73,219,318–321,327–329]
Risk Increase if Abnormal CXR	3.9	2.7, 5.5	Normal(1.36,0.15)§	[317]
Extended Therapy	0.124	0, 0.3	Beta(2.366,16.713)	Expert Opinion, [119]
Relapse Rate	0.0359	0.0274, 0.0462	Normal(-3.327,0.365)§	[341]
Model Parameters				
Flagged for surveillance	0.024	Optimization Parameter	Optimization Parameter	[94]
BCG Vaccination (<30 cases)	0.605	-	Beta(45137,29502)	[224]
BCG Vaccination (≥30 cases)	0.998	-	Beta(185381,384)	[224]
BCG Vaccination Uptake	0.837	0.419, 1	-	[316]
Discount Rate	0.015	0, 0.03	-	[190]
Time Horizon	10 years	25, 50 years	-	-

*This model assumes all who complete a medical evaluation and have no indication for active TB, are recommended treatment.
§The result is exponentiated (i.e. is a lognormal distribution).
‡Formula: 0.33*(Normal(-1.168,0.228))+0.374*(Normal(-0.381,0.169))+0.293*1
°Causing treatment cessation
PSA: Probabilistic Sensitivity Analysis; INH: Isoniazid; RIF: Rifampin; AE: Adverse Event; LTBI: Latent Tuberculosis Infection; TB: Tuberculosis; BCG: Bacillus Calmette-Guérin

Table 4-4. Interventions evaluated

Strategy	Description
TST/INH	This is the base case when applied only to the population under medical surveillance. A tuberculin skin test is completed and, if positive via an induration size ≥10mm, nine months of isoniazid is prescribed.
TST/RIF	A tuberculin skin test is completed and, if positive via an induration size ≥10mm, four months of rifampin is prescribed.
IGRA/INH	An interferon-gamma release assay is performed and, if positive via manufacturer's definition, nine months of isoniazid is prescribed.
IGRA/RIF	An interferon-gamma release assay is performed and, if positive via manufacturer's definition, four months of rifampin is prescribed.
SEQ/INH	A tuberculin skin test is completed. If positive via an induration size ≥10mm, a confirmatory interferon-gamma release assay is given, and, if positive via manufacturer's definition, nine months of isoniazid is prescribed.
SEQ/RIF	A tuberculin skin test is completed. If positive via an induration size ≥10mm, a confirmatory interferon-gamma release assay is given, and, if positive via manufacturer's definition, four months of rifampin is prescribed.

TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin

Table 4-5. Discounted results of base case analysis of the population under medical surveillance

Intervention	Total TB Cases (Change from Reference)	Population Costs ($) (Change from Reference)	Population QALYs (Change from Reference)	Incremental Cost per TB Case Prevented ($)	Incremental Cost per QALY gained ($)
TST/INH (Reference)	99.41	3,137,675	45,026.1	-	-
TST/RIF	100.58 (1.17)	2,914,913 (-222,762)	45,025.4 (-0.7)	191,236†	312,952†
IGRA/INH	92.70 (-6.71)	2,946,383 (-191,292)	45,030.9 (4.8)	Dominant	Dominant
IGRA/RIF	94.51 (-4.90)	2,784,661 (-353,014)	45,030.1 (4.0)	Dominant	Dominant
SEQ/INH	100.58 (1.17)	2,853,649 (-284,026)	45,025.8 (-0.3)	242,882†	1,064,235†
SEQ/RIF	101.73 (2.32)	2,756,316 (-381,359)	45,024.8 (-1.3)	164,292†	308,919†
No Intervention	113.56 (14.15)	2,616,436 (-521,239)	45,016.0 (-10.1)	36,836†	51,581†

†The result falls in Quadrant III, worse outcomes with lower cost. The result should be interpreted inversely

TB: Tuberculosis, QALYs: Quality Adjusted Life Years; TST: Tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin

Table 4-6. Results of LTBI cascade of care improvements in the population under medical surveillance

Intervention	Change* in TB Cases	Change* in Population Costs ($)	Change* in Population QALYs	Amount Available to Invest per Cohort at WTP of $100,000 per QALY Gained ($)
Improve Treatment Completion by 30%				
TST/INH	-2.13	38,308	1.7	127,358
TST/RIF	-1.32	-242,145	1.2	366,737
IGRA/INH	-9.70	-188,394	7.5	941,790
IGRA/RIF	-8.73	-407,861	6.9	1,098,510
SEQ/INH	-0.38	-277,563	0.5	331,006
SEQ/RIF	0.30	-407,679	0.1	420,370
Perfect Adherence with Surveillance				
TST/INH	-9.40	430,200	7.7	339,075
TST/RIF	-7.84	54,442	6.0	549,260
IGRA/INH	-20.43	108,094	14.6	1,351,074
IGRA/RIF	-17.79	-161,603	14.0	1,557,078
SEQ/INH	-7.11	-35,082	6.3	660,236
SEQ/RIF	-5.58	-197,657	4.6	660,570
Perfect Adherence with Surveillance and Improve Treatment Completion by 30%				
TST/INH	-12.88	494,333	10.5	559,007
TST/RIF	-11.75	28,971	8.7	836,791
IGRA/INH	-25.44	110,840	18.4	1,733,599
IGRA/RIF	-23.90	-246,880	18.2	2,068,246
SEQ/INH	-10.19	-34,954	8.6	893,888
SEQ/RIF	-9.27	-249,568	7.1	956,461

*Change from Reference Intervention: 99.41 Cases of TB, $3,137,675 Population Costs, and 45,026.1 Population QALYs

TB: Tuberculosis, QALYs: Quality Adjusted Life Years; TST: Tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; WTP: willingness-to-pay; LTBI: latent tuberculosis infection

Table 4-7. Results of expanding post-landing LTBI screening based on TB incidence in country of origin

Intervention	Total TB Cases (Change from Reference)	Population Costs ($) (Change from Reference)	Population QALYs (Change from Reference)	Incremental Cost per TB Case Prevented ($)	Incremental Cost per QALY gained ($)
Reference (TST/INH in those under surveillance)	578.18	13,479,792	1,930,729.6	-	-
Screen all from ≥200 per 100,000					
TST/INH	545.01 (-33.17)	22,413,667 (8,933,875)	1,930,760.6 (31.0)	269,388	288,550
TST/RIF	548.73 (-29.45)	19,439,848 (5,960,056)	1,930,754.0 (24.4)	202,369	244,489
IGRA/INH	520.03 (-58.15)	21,579,890 (8,100,098)	1,930,768.3 (38.7)	139,305	209,222
IGRA/RIF	524.71 (-53.47)	19,079,482 (5,599,690)	1,930,761.6 (32.0)	104,729	175,131
SEQ/INH	550.38 (-27.80)	18,775,849 (5,296,057)	1,930,739.4 (9.8)	190,545	541,408
SEQ/RIF	554.75 (-23.43)	17,301,425 (3,821,633)	1,930,746.1 (16.5)	163,104	231,661
Screen all from ≥100 per 100,000					
TST/INH	517.00 (-67.18)	29,298,355 (15,818,563)	1,930,760.5 (30.9)	258,590	511,673
TST/RIF	524.11 (-54.07)	24,250,547 (10,770,755)	1,930,765.1 (35.5)	199,218	303,254
IGRA/INH	478.42 (-99.76)	26,783,895 (13,304,103)	1,930,792.0 (62.4)	133,369	213,406
IGRA/RIF	486.92 (-91.26)	22,944,405 (9,464,613)	1,930,793.9 (64.3)	103,714	147,350
SEQ/INH	526.43 (-51.75)	22,326,981 (8,847,189)	1,930,757.1 (27.5)	170,962	321,508
SEQ/RIF	531.95 (-46.23)	20,020,938 (6,541,146)	1,930,763.2 (33.6)	141,505	194,940

TB: Tuberculosis, QALYs: Quality Adjusted Life Years; TST: Tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin

Table 4-7. Continued

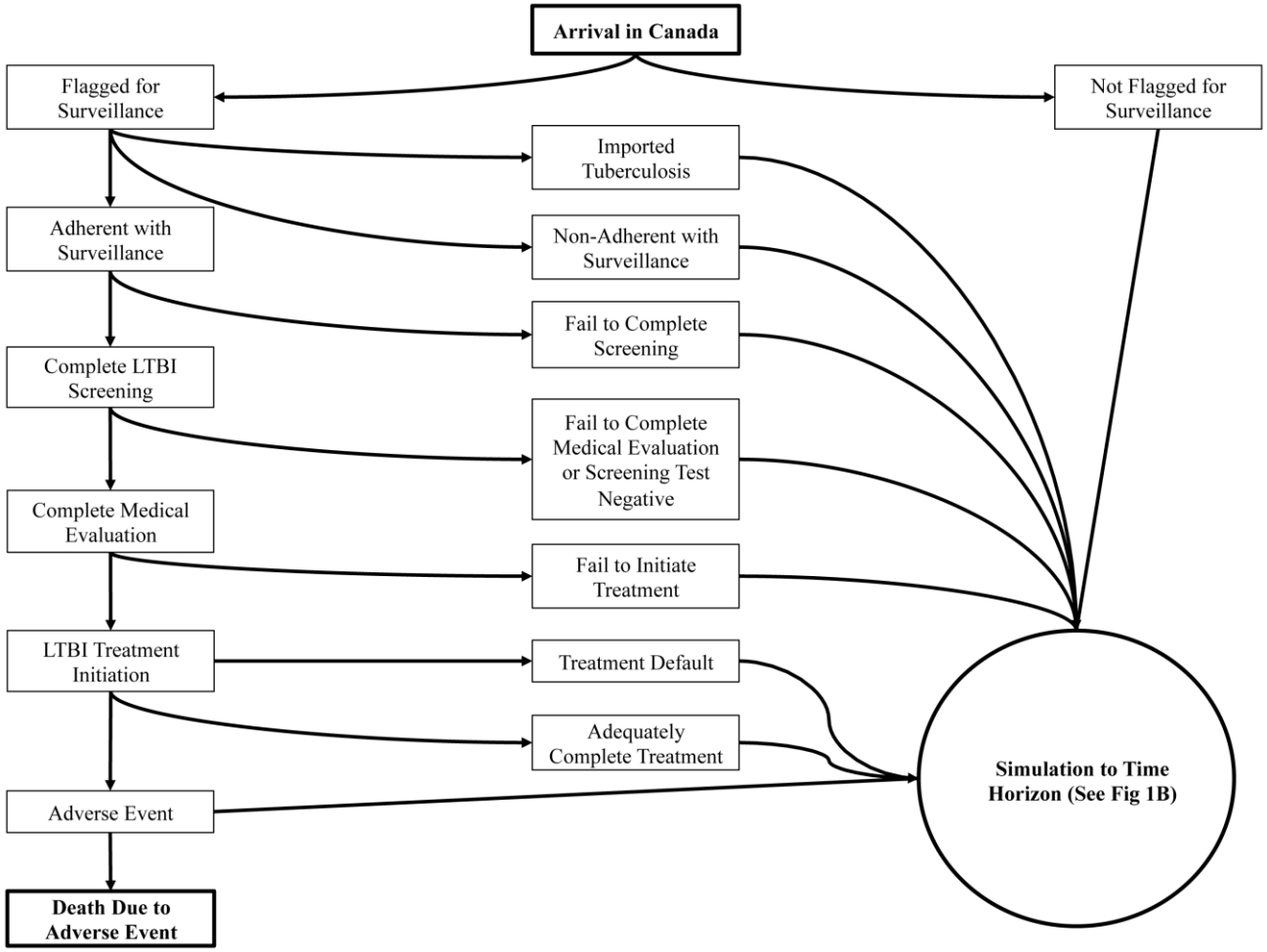
Intervention	Total TB Cases (Change from Reference)	Population Costs ($) (Change from Reference)	Population QALYs (Change from Reference)	Incremental Cost per TB Case Prevented ($)	Incremental Cost per QALY gained ($)
Reference (TST/INH in those under surveillance)	578.18	13,479,792	1,930,729.6	-	-
Screen all from ≥30 per 100,000					
TST/INH	503.00 (-75.18)	36,534,345 (23,054,553)	1,930,767.6 (38.0)	306,672	607,385
TST/RIF	508.41 (-69.77)	29,309,392 (15,829,600)	1,930,784.1 (54.5)	226,898	290,511
IGRA/INH	454.91 (-123.27)	30,992,637 (17,512,845)	1,930,807.5 (77.9)	142,079	224,739
IGRA/RIF	466.44 (-111.74)	26,311,297 (12,831,505)	1,930,822.3 (92.7)	114,840	138,484
SEQ/INH	513.32 (-64.86)	25,263,671 (11,783,879)	1,930,775.8 (46.2)	181,693	255,395
SEQ/RIF	519.41 (-58.77)	22,418,827 (8,939,035)	1,930,774.6 (45.0)	152,121	198,819
Screen all new migrants					
TST/INH	501.14 (-77.04)	42,460,450 (29,980,658)	1,930,780.8 (51.2)	376,180	566,155
TST/RIF	506.55 (-71.63)	33,689,173 (20,209,381)	1,930,778.2 (48.6)	282,148	415,606
IGRA/INH	452.19 (-125.99)	34,895,981 (21,416,189)	1,930,803.5 (73.9)	169,986	289,838
IGRA/RIF	463.67 (-114.51)	29,720,266 (16,240,474)	1,930,808.0 (78.4)	141,825	207,328
SEQ/INH	510.88 (-67.30)	27,535,513 (14,055,721)	1,930,778.0 (48.4)	208,859	290,448
SEQ/RIF	518.21 (-59.97)	24,497,307 (11,017,515)	1,930,770.3 (40.7)	183,724	270,562

TB: Tuberculosis, QALYs: Quality Adjusted Life Years; TST: Tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin

4.7 Figures

Figure 4-1. Model structure and possible transition events. (A) Model Structure: Flow of new migrants through the simulation and the interventions investigated upon arrival in Canada. (B) Possible events that may result in movement between health states after arrival in Canada

(A)



(B)

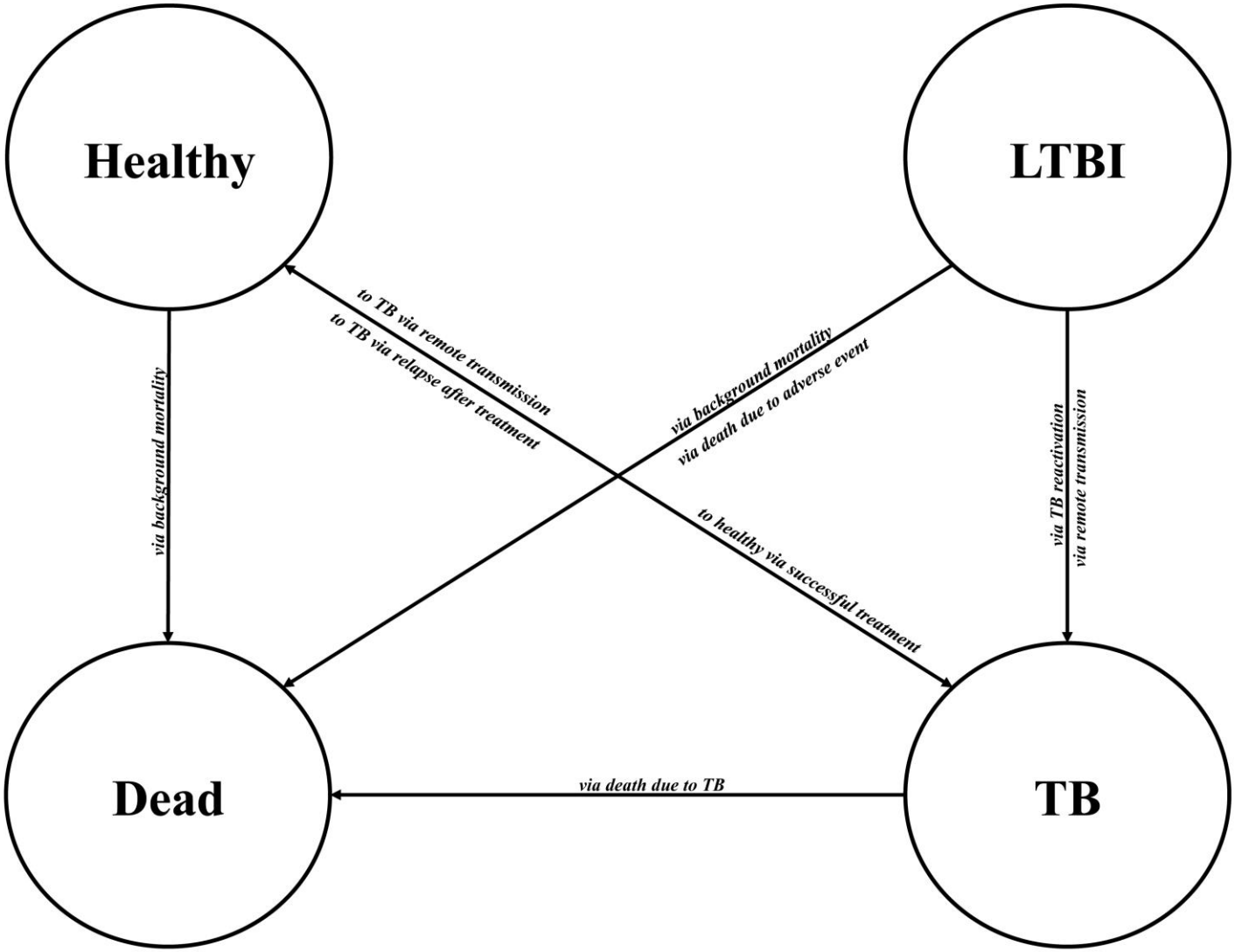

Healthy
LTBI
Dead
TB
to TB via remote transmission
to TB via relapse after treatment
via background mortality
via death due to adverse event
via background mortality
to healthy via successful treatment
via TB reactivation
via remote transmission
via death due to TB

Figure 4-2. Results of the univariate sensitivity analysis using QALYs as effectiveness measure. The figure is ordered in the direction of absolute effect (i.e. not in order of direction of effect) on the net monetary benefit in relation to what was calculated in deterministic analysis.

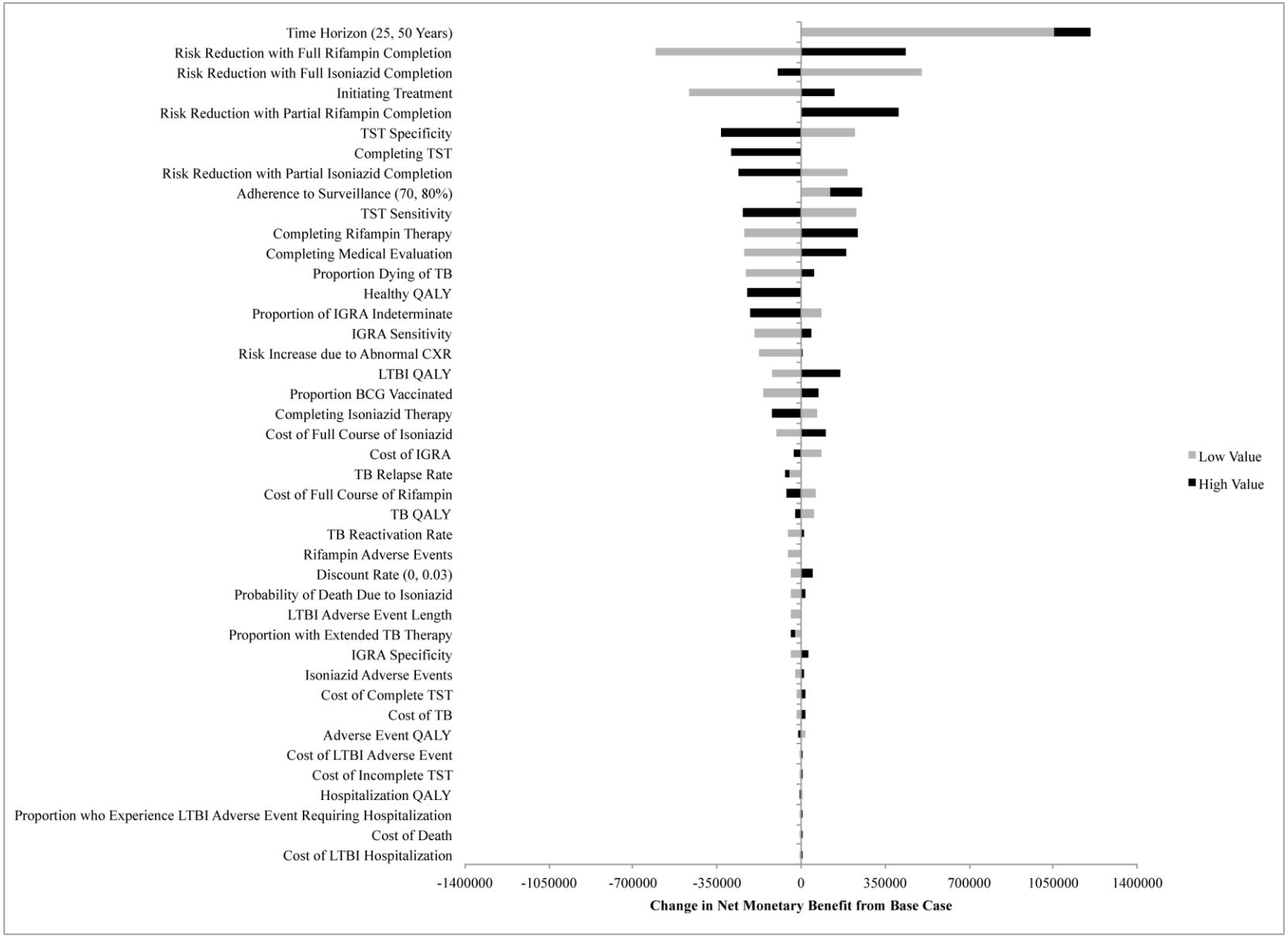


Figure 4-3. Efficiency frontier for the migrants under post-landing surveillance in terms of population QALYs vs. population costs. The frontier is read from left to right, with interventions connected if they fall on the frontier. Interventions subsequent to the initial intervention have an increased cost, but an increased benefit, and represent the next best value at increasing funding thresholds. The slope between two connected interventions represents cost-effectiveness: a steeper slope represents poorer cost-effectiveness between interventions, while a shallow slope represents better cost-effectiveness.

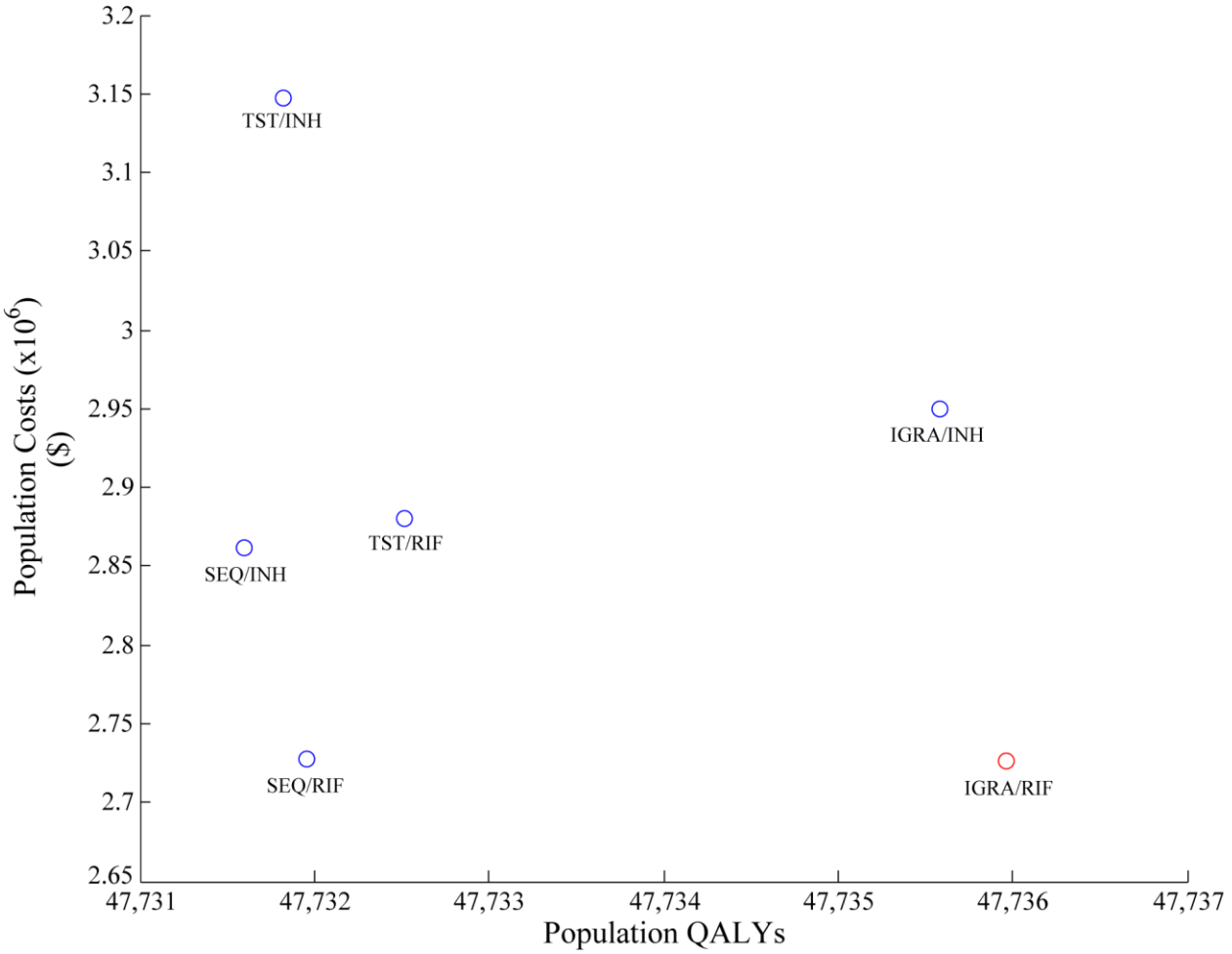


Figure 4-4. Cost-effectiveness acceptability curve for migrants under post-landing surveillance in terms of cost per QALY gained. The graph demonstrates the probability an intervention is cost-effective at various willingness-to-pay thresholds in relation to the base case intervention.

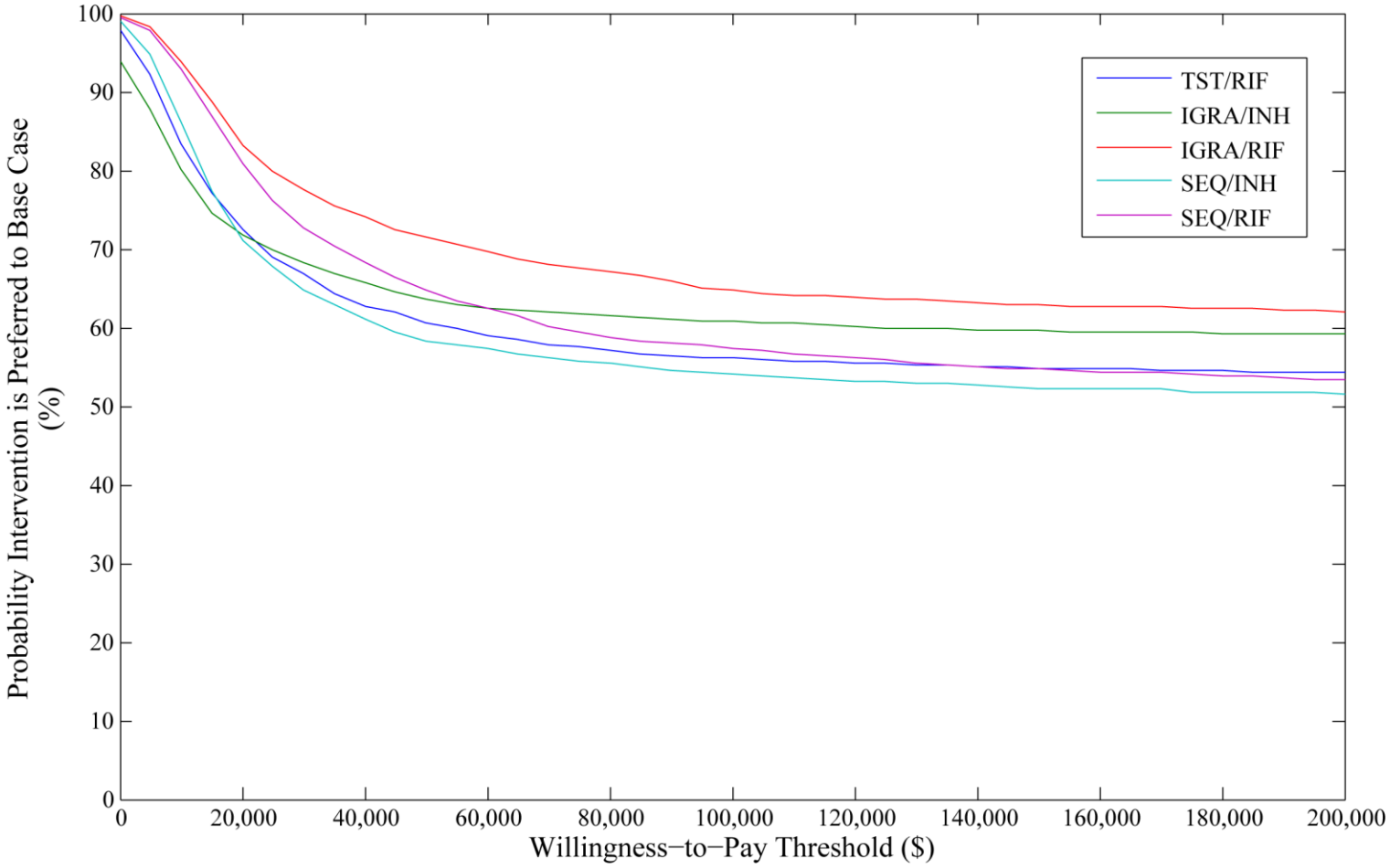


Figure 4-5. Efficiency frontier for the complete cohort of migrants in terms of population QALYs vs. population costs. The frontier is read from left to right, with interventions connected if they fall on the frontier. Interventions subsequent to the initial intervention have an increased cost, but an increased benefit, and represent the next best value at increasing funding thresholds. The slope between two connected interventions represents cost-effectiveness: a steeper slope represents poorer cost-effectiveness between interventions, while a shallow slope represents better cost-effectiveness.

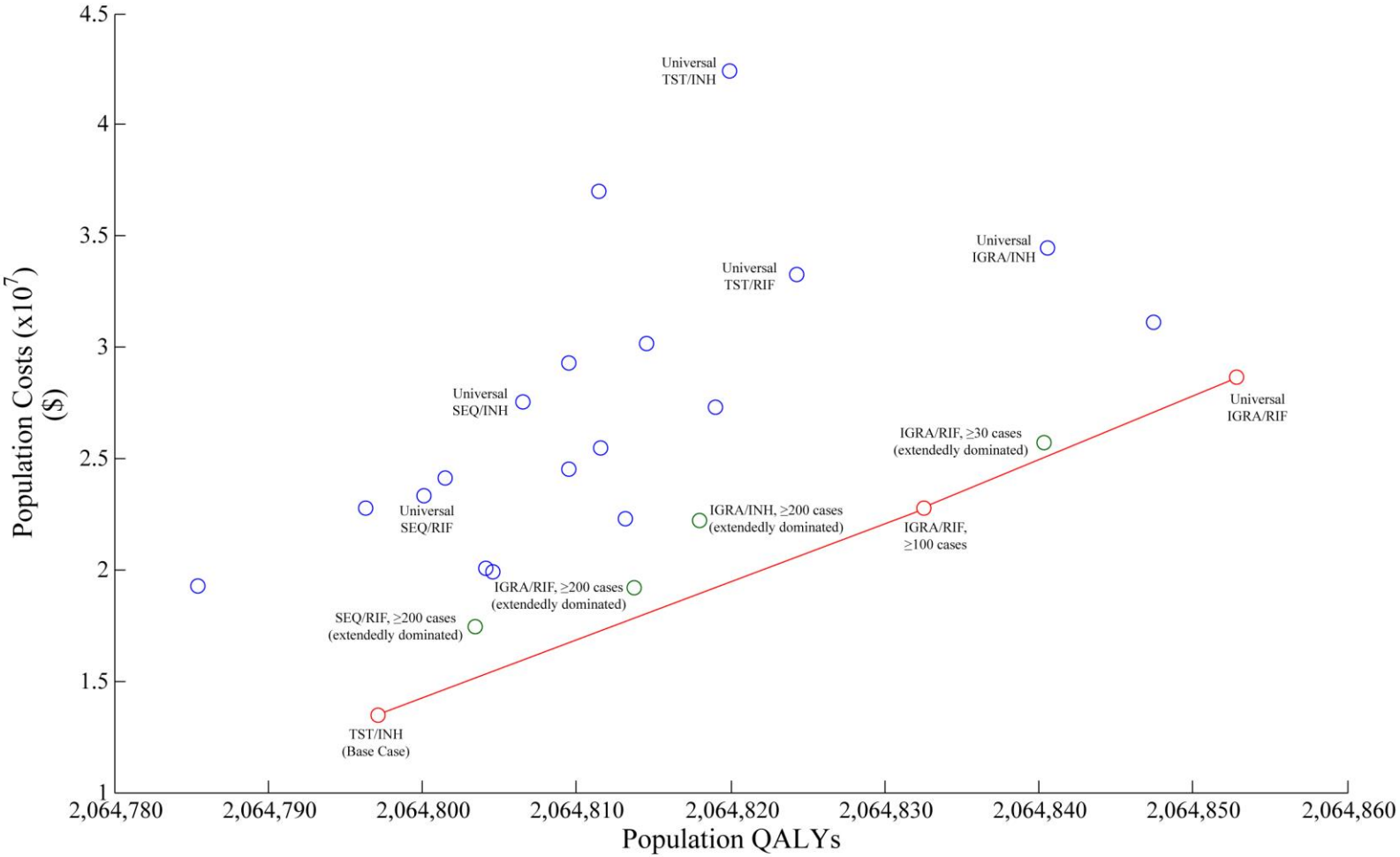
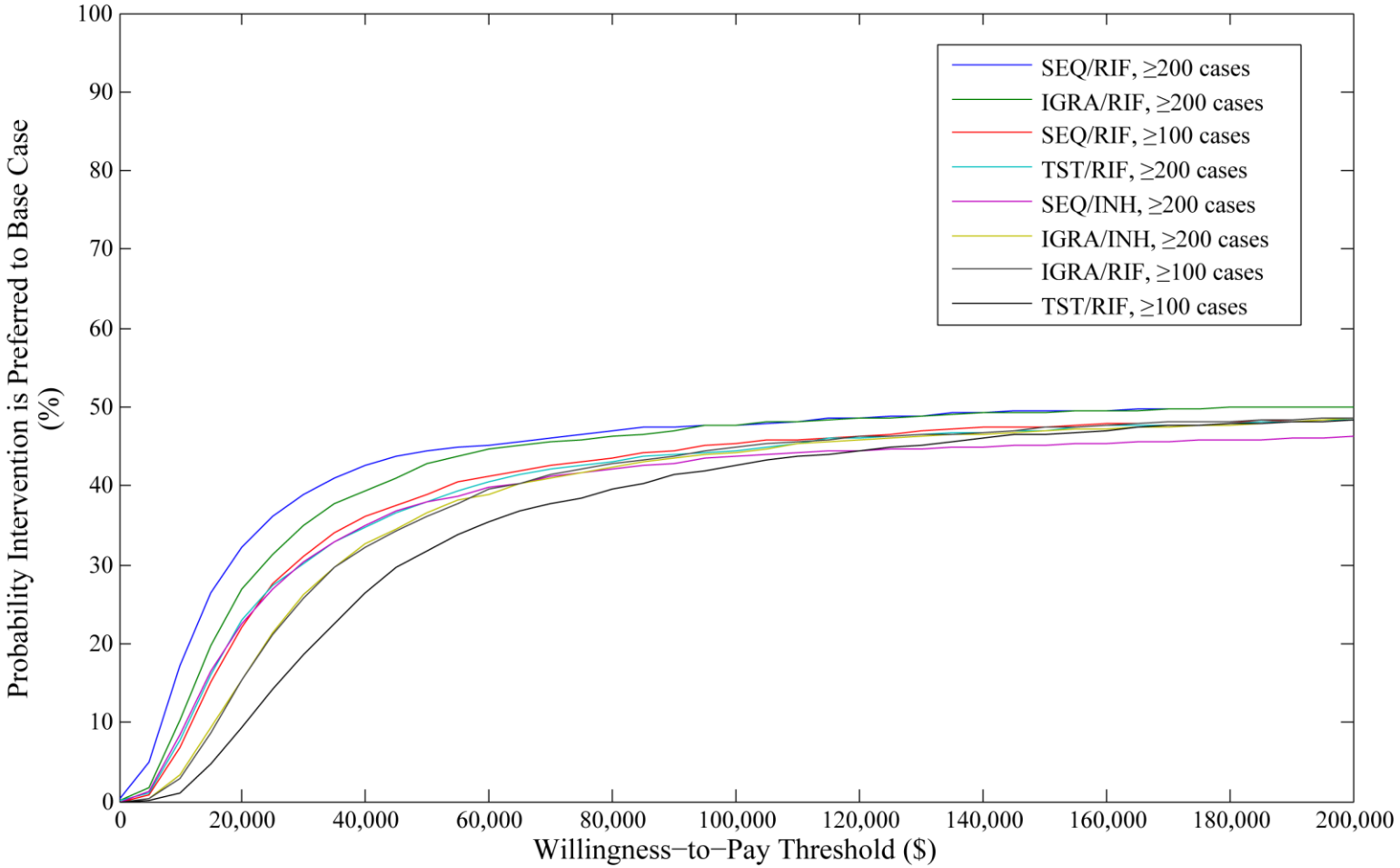


Figure 4-6. Cost-effectiveness acceptability curve for the complete cohort of migrants in terms of cost per QALY gained. The graph demonstrates the probability an intervention is cost-effective at various willingness-to-pay thresholds in relation to the base case intervention.



CHAPTER 5. PRE-IMMIGRATION LATENT TUBERCULOSIS INFECTION SCREENING STRATEGIES IN NEW MIGRANTS TO LOW-INCIDENCE COUNTRIES: A COST-EFFECTIVENESS ANALYSIS

5.1 Background

The WHO has continued their push towards TB elimination, aiming to reduce the TB burden by approximately 90% to <1 case per million persons in low incidence countries [70]. Meeting this target will require new and innovative strategies. Typically, the TB burden in low-incidence countries is focused on migrant populations, with approximately 70% of TB cases occurring in this population in Canada, the United States, and much of Europe [3,4,342]. For the most part, TB prevention in migrants has focused on identifying people with active TB before migration to stop transmission post-arrival. Yet, stagnant rates of TB in migrants suggest this is an ineffective method to accelerate declines in TB incidence [343].

Universal or targeted post-arrival LTBI screening has been suggested by several low-incidence countries as a method to accelerate TB declines [3,344–346], however these domestic LTBI programs exhibit suboptimal performance [53], are resource intensive [97], and as demonstrated in Chapter 4 and elsewhere [192,201,202] have questionable cost-effectiveness in many migrant populations. One major reason for the reduced effectiveness of post-arrival LTBI screening programs is the significant attrition in the LTBI cascade of care. More than half of migrants are lost to follow-up prior to having the opportunity to initiate treatment, which results in less than one-fifth adequately completing a full course of therapy [53].

Currently, several immigrant-receiving, low TB incidence countries employ mandatory pre-immigration medical exams [242]. As part of these medical exams, a CXR and medical evaluation are performed to detect TB prior to migration or identify those who may be at increased risk of TB in the future and these costs are borne by the patient within their country of origin. Only a select few employ some form of mandated LTBI screening [241] and data are scarce on the yield of such programs.

A report sponsored by the United States Centre for Disease Control suggested mandatory LTBI screening and treatment as part of these routine pre-immigration medical exams [347], however this strategy was viewed as

inequitable and unjustly coercive [348] and has never been employed. Alternatively, mandating and fully sponsoring only LTBI screening (i.e. the costs would be borne by the country they are immigrating to) as a formal part of the immigration process would avoid such ethical quandaries and could significantly impact post-arrival TB incidence in migrants. Utilization of screening results as a marker for post-immigration follow-up would improve the yield of post-arrival LTBI screening programs by more than two-fold [53], as all migrants reporting post-immigration would already have completed LTBI screening.

In this chapter, we evaluate the cost-effectiveness of mandating and fully sponsoring LTBI screening in prospective migrants as part of routine pre-immigration medical exams. We evaluate six unique screening and treatment combinations in migrants from four different TB incidence groups to determine the optimal strategy and target TB incidence for this intervention.

5.2 Methods

5.2.1 Model Overview

DES was chosen for this model due to its flexibility in varying transition times between health states in a single simulation, ability to simulate time continuously, and capability to model several different patient covariates (allowing the creation of a highly representative migrant cohort), all of which are resource intensive in traditional Markov models [193]. The populations of interest in this model were migrants from countries belonging to four distinct TB incidence categories: (1) low, <30 cases per 100,000 persons per year; (2) moderate, ≥30 and <100 cases per 100,000 persons per year; (3) high, ≥100 and <200 cases per 100,000 persons per year; (4) very high, ≥200 cases per 100,000 persons per year.

The four populations of interest were further defined by four covariates. (1) Patient age, which was defined based on an age distribution of a reference cohort of permanent residents to Canada in 2014 [93]. (2) BCG vaccination, whose prevalence was determined through presence of a universal BCG vaccination policy in each source country and adjusted by 36-year average BCG vaccine uptake [93,224,316]. (3) CXR; a reference cohort of permanent residents to Ontario between 2002 and 2011 was used to identify prevalence of abnormal CXR [94], which increases risk of active TB 3.9-fold [317]. (4) LTBI prevalence, which in each migrant population was calibrated using two-year TB incidence in permanent resident cohorts to Ontario between 2002 and 2011 [94]. LTBI prevalence was estimated using several assumptions. Firstly, it was assumed that 85% of reported TB cases in the

cohorts from Ontario resulted from reactivation of imported LTBI [71–73]. Secondly, it was assumed that TB reactivation did not change over time post-migration [244] with a rate of 1.1 cases per 1000 person years in individuals with LTBI [73,219,319,328,349]. Lastly, the distribution of LTBI prevalence was assumed to approximately match reported rates of IGRA positivity in migrants from each of the four TB incidence categories reported in Chapter 3 [21].

The model evaluates three pre-immigration LTBI screening techniques and two post-arrival LTBI treatment options, for a total of six unique strategies to compare to the base case in each population of interest (**Table 5-1**). Individuals could be screened with a TST, IGRA, or SEQ where TST-positive individuals were given a confirmatory IGRA. A positive TST result was defined as an induration measuring ≥10mm, while a positive IGRA result was defined based on manufacturer's recommendations with IGRA performance being a composite measure of commercially available products [20,24,34]. While testing pre-immigration was mandated, post-immigration follow-up and treatment were not mandated and instead assumed to be passive, as per current standard, following published rates of follow-up post-arrival in several countries [322]. Test-positive migrants that successfully reported post-arrival could be treated with nine-months of isoniazid or four-months of rifampin. The base case in this model was considered to be pre-immigration TB screening (CXR, medical history, symptom screen) without any evaluation for LTBI pre- or post-immigration.

The model took a healthcare system perspective for the fully sponsored and mandated pre-immigration LTBI screening (i.e. all LTBI screening costs pre-immigration were the responsibility of the receiving healthcare system, as well as typical post-arrival costs), utilized the standard 3% annual discount rate for costs and outcomes [189], and had a twenty-five year time horizon from immigration. The main outcomes of the model were QALYs, number of TB cases, and costs (2016 CAD) per 1000 migrants from each of the four populations analyzed. These data were used to calculate other outcomes in comparison to the base case: the ICER for QALYs gained, the incremental NMB, and percent reduction in longitudinal TB. A WTP threshold of $100,000 per QALY gained was adopted based on recommendations of the WHO and other economic experts [189,324,325,350].

A simplified model structure is displayed in **Figure 5-1**. Migrants modeled to intervention were given a mandatory LTBI diagnostic test simultaneously with the rest of their medical exam; test-positive migrants were referred for post-immigration follow-up. All migrants were followed up 25-years from arrival. Post-immigration follow-up was passive. Those with untreated LTBI adhering with post-immigration follow-up were recommended

LTBI therapy. After initiating treatment, migrants could complete a full course, partially complete treatment, or cease treatment due to an adverse event that may result in death. After treatment, all migrants were simulated to the time horizon, with annual risks of TB reactivation and death. Several assumptions were made. Migrants with previous TB or an abnormal CXR [94] identified during the pre-immigration medical exam were also referred for follow-up post arrival. Losses to follow-up during the LTBI cascade of care were eliminated when an intervention was part of a pre-immigration medical exam as this was modeled to be mandatory (e.g. in domestic LTBI programs 78% of individuals complete a medical evaluation; in this model there would be 100% completion). Self-cure from LTBI was not modeled. It was assumed that all test-positive migrants were offered LTBI treatment, to limit extrapolation of care provider decisions to offer and/or initiate treatment. Drug resistant TB was not considered in this model. All reactivation TB cases had a 17.6% chance of causing a secondary case; further transmission was not modeled. The model's internal validity was examined through several experiments to ensure it operated as intended and its outputs were then compared to the data source used to inform it to ensure external validity.

All modeling was completed in Simio (Version 8.146.14121, Simio LLC, Sewickley, PA) and run using Simio Replication Runner.

5.2.2 Model Parameters

All model estimates were derived from the literature or expert opinion, with preference to systematic reviews and meta-analyses (**Table 5-2**). A meta-analysis provided evidence for domestic LTBI program performance (e.g. treatment completion) [53], therapy efficacy was derived from the literature [51,57,59], and adverse events were retrieved from several randomized controlled trials [120–123,339]. Diagnostic performance of LTBI screening tests was derived from Chapter 2 and several systematic reviews and was modeled to be the same in each country [20,24,34]. Canadian life tables provided estimates of background mortality [326]. Adherence with post-immigration follow-up in test-positive migrants was estimated via re-analysis of post-immigration follow-up data [94,222,351–361] reported in a recent meta-analysis [322] (**Figure 5-2**). Death from tuberculosis [3], probability of TB therapy extension [119], and relapse rate [341] were derived from Canadian sources.

All costs were derived from Canadian sources and it was assumed the costs of LTBI diagnostic tests were equal to costs incurred in Canada when performed prior to immigration (i.e. the cost of a TST in Canada was assumed to be the same in a migrant's country of origin). Costs for LTBI treatment and screening were derived from

the BCCDC (personal communication). These costs included the cost of drugs, screening tests, routine monitoring, and clinician time. Adverse event costs, including hospitalization rates and time, were estimated from the literature [119,330]. The cost of managing a TB case was derived from Canadian data [221,330]. All costs were converted or inflated to 2016 Canadian dollars ($).

Health utility data were derived from a Canadian study [331] in new migrants who reported for post-immigration follow-up. Health utility adjustments due to adverse events or hospitalization were derived from the literature [119,330,333].

5.2.3 Sensitivity Analysis

A PSA was performed to capture uncertainty around model estimates. Uncertainties around input parameters form the literature were modeled using relevant distributions (e.g. beta, log-normal); cost estimates were modeled using triangular and gamma distributions. In situations where the uncertainty was difficult to define, expert opinion was used. The PSA was performed with an outer sample size of 2000 and inner sample size of 50,000. CEACs were created for the base case vs. the intervention with the largest incremental NMB at each WTP threshold. Efficiency frontiers [200] for costs and QALYs were created using the average results of the PSA.

Various exploratory sensitivity analyses were performed. We analyzed the impact of limiting LTBI screening by age on outcomes. We then analyzed the impact certain parameters may have on cost-effectiveness including: modeling low LTBI therapy uptake post-landing, ensuring 100% adherence in post-landing follow-up, ensuring 100% adherence and participation in all steps of the LTBI cascade of care, extending the time horizon, altering TB reactivation rate, and modeling high and low estimates of costs. Parameters chosen for each exploratory analysis are listed in **Table 5-2**.

5.3 Results

5.3.1 Overall Results

The most effective screening intervention was the IGRA, reducing incident TB by more than 40% in migrants from all TB incidences. TST screening identified the most migrants for post-arrival follow-up, while sequential screening identified the fewest. Isoniazid treatment was associated with fewer cases of TB, however significantly higher costs than rifampin. Summary results are presented in **Table 5-3** stratified by TB incidence in country of origin.

5.3.1.1 Low Incidence Countries

No intervention was cost-effective when applied in low incidence countries. Utilizing any screening method other than IGRA resulted in a net loss in population QALYs due to the poor specificity of the TST. Screening with an IGRA followed by post-arrival treatment with rifampin was the most attractive option if screening was to be implemented, with a cost per QALY gained of $581,942.

5.3.1.2 Moderate Incidence Countries

IGRA screening with post-arrival rifampin treatment was the optimal intervention in moderate incidence countries with a cost per QALY gained of $48,993 and the largest incremental NMB at $92,059. Sequential screening followed by rifampin treatment provided the lowest cost per QALY ($47,374), but yielded a lower incremental NMB ($84,977).

5.3.1.3 High Incidence Countries

Similar to moderate incidence countries, IGRA followed by rifampin treatment was the optimal intervention, having a cost per QALY gained of $49,035 and maximizing the incremental NMB ($102,124). A cost per QALY gained of $46,303 was found with sequential screening and rifampin, yet similar to moderate incidence countries, it provided a lower incremental NMB of $98,750.

5.3.1.4 Very High Incidence Countries

IGRA screening was the most cost-effective intervention in very high incidence countries. While follow-up rifampin treatment provided a lower ICER ($33,696) than isoniazid treatment ($43,290) they had nearly identical incremental NMB's of $223,683 and $223,704, respectively, suggesting both are attractive options.

5.3.2 Probabilistic Sensitivity Analysis

5.3.2.1 Low Incidence Countries

In low incidence countries, IGRA screening followed by rifampin treatment yielded the highest incremental NMB (**Table 5-4**). This intervention had a probability of resulting in a higher NMB than the base case of 48.4% at a WTP threshold of $100,000 per QALY (**Figure 5-3**) and was the only intervention to fall on the efficiency frontier (**Figure 5-4**).

5.3.2.2 Moderate Incidence Countries

When evaluating screening in moderate incidence countries, IGRA screening followed by rifampin treatment provided the largest incremental NMB (**Table 5-4**). When comparing this intervention to the base case, past a WTP threshold of $50,000 per QALY, this intervention had a probability of providing the highest NMB >50% (**Figure 5-5**). Similar to low incidence countries, this intervention was the only intervention on the efficiency frontier (**Figure 5-6**)

5.3.2.3 High Incidence Countries

In high incidence countries, sequential screening followed by rifampin treatment had the largest incremental NMB (**Table 5-4**). When compared only to the base case, this intervention had a probability >50% for yielding the highest NMB past a WTP threshold of $30,000 (**Figure 5-7**). IGRA screening followed by rifampin or isoniazid also fell on the frontier, however they provided smaller incremental NMB than sequential screening followed by rifampin and should not be considered at a WTP threshold of $100,000 per QALY (**Figure 5-8**).

5.3.2.4 Very High Incidence Countries

In very high incidence countries, IGRA screening followed by rifampin treatment resulted in the largest incremental NMB (**Table 5-4**). This intervention had a probability of having a higher NMB than the base case alone of >50% past a WTP threshold of $20,000 per QALY (**Figure 5-9**) and was the only intervention to be included in the efficiency frontier (**Figure 5-10**).

5.3.3 Exploratory Sensitivity Analysis

Results of the exploratory analysis are reported in **Table 5-5**, **Table 5-6**, **Table 5-7**, and **Table 5-8**, for migrants from low, moderate, high, and very high TB incidence countries, respectively. Changes from the base case were consistent between migrants from different TB incidences.

Only screening certain portions of new migrants based on age did not significantly impact cost per QALY gained, but did lessen the overall reductions in TB incidence seen. In the case of limiting screening to those ≤35 years old, the reduction in TB incidence was halved. Mandating post-arrival follow-up improved the reduction in TB incidence by 40% compared to a passive system and did not significantly impact ICERs. On the contrary, if we modelled initiation of LTBI therapy at an extreme low value of 63.5%, reduction in TB incidence was reduced by

approximately 30%. This further impacted decisions on which intervention was likely to be the most cost-effective. Fully mandating all parts of the LTBI cascade of care (i.e. all test-positive migrants must report, initiate, and complete treatment, except in cases of adverse events) increased overall costs of interventions approximately 40%, but overall reductions in TB incidence exceeded 80% and ICERs were significantly lower when compared to the base case.

When assuming rifampin was just as effective as isoniazid, pre-immigration screening with an IGRA followed by post-arrival rifampin treatment was the most cost-effective option with an ICER of $24,273 per QALY gained in very high incidence countries. Using a lifetime time horizon significantly improved cost-effectiveness of interventions, yielding an ICER <$100,000 per QALY gained for at least one intervention, regardless of TB incidence in country of origin. Adjusting reactivation rate or costs did not significantly impact ICERs, but did impact the overall cost of interventions. In the case of adjusting reactivation rate, this was due to increasing or decreasing the number of individuals with LTBI.

5.4 Discussion

Fully sponsored and mandated pre-immigration LTBI screening followed by post-arrival treatment in new migrant applicants from countries with a TB incidence ≥30 cases per 100,000 persons appears to be an impactful and cost-effective method for reducing TB incidence post-landing. IGRA screening followed by post-arrival rifampin treatment provided the largest incremental NMB in each TB incidence category. This intervention reduced TB incidence by >40% in migrants and yielded ICER's <$50,000 per QALY.

Sensitivity analyses indicated that pre-immigration IGRA screening followed by rifampin treatment post-arrival to be the logical choice of intervention, providing the highest benefit at the second lowest cost. Our baseline assumption of poorer effectiveness of rifampin (80%) compared to isoniazid (93%) and assumption that partial treatment of rifampin did not result in any benefit, did not preclude rifampin from being the most cost-effective treatment option in migrants from moderate to very high TB incidence countries. A multicenter randomized controlled trial [362] assessing the effectiveness of rifampin compared with isoniazid may inform future analyses and may further emphasize rifampin as the favored agent for LTBI therapy.

Setting aside the ethical implications, the impact of mandating post-arrival follow-up is significant—improving TB reduction by approximately 40% with no major changes in the cost-effectiveness compared with the

current standard of practice. Looking broader and considering treatment, fully sponsoring and mandating LTBI treatment doubled the reduction in TB incidence, resulting in more than 80% of future incident TB cases being averted with no increase in the ICER. Indeed, these analyses show the true potential of a fully sponsored and optimized LTBI program, enabling target setting.

Due to the low prevalence of LTBI in migrants from countries with a TB incidence <30 cases per 100,000 persons, LTBI screening is not cost-effective and may unnecessarily expose a significant number of uninfected individuals to treatment. Further scrutiny is required to decide which, if any, migrants to screen from low incidence countries. Other factors, such as medical history, co-morbid conditions, and demographic characteristics may need to be considered for such an intervention to be economically sound and not expose a significant amount of individuals to unnecessary treatment. Further stressing this fact is the disagreement between changes in TB incidence and population QALYs. While it would be expected for population QALYs to increase as TB incidence decreases, in migrants from low incidence countries, this trend was not seen with many interventions, suggesting the harm of inappropriate LTBI treatment outweighed the benefit of averted TB.

While these results suggest significant domestic benefit to mandating and fully sponsoring pre-immigration LTBI screening in moderate to very high TB incidence countries, several factors would need to be carefully examined. Firstly, IGRA use in high-income settings suffers from variability, in part related to several operational issues [363]. Similarly, TST variability remains an issue [29,364]. In both cases, test variability may be exacerbated in low-income settings. This model did not consider the costs of program initiation and maintenance, necessitating a comprehensive pilot testing and evaluation prior to implementation. A crude method of calculating the maximum to invest in program initiation and/or maintenance per year would be to calculate the incremental NMB using a healthcare providers WTP threshold. In this study, using IGRA screening in very high incidence countries results in a value of approximately $223,000 per 1000 migrants. This value can be juxtaposed against the operating costs of such a program to guide investment.

This model assumes that the costs of the pre-immigration medical exam are currently borne by the immigrant applicant and that the additional LTBI screening step is the responsibility of the receiving healthcare system. In countries where this is not the case, the addition of the cost of a pre-immigration CXR ($54) and cost of TB treatment ($10) proportional to the active TB discovery rate during these exams (0.05%) did not result in any conclusion changes. Additionally, this model only considered the costs of individuals that began and completed the

immigration process. Based on Canadian data, however, it appears that only approximately 50-60% of those who begin the immigration process successfully land in Canada [3,94]. In migrants from very high incidence countries, doubling pre-immigration screening costs resulted in an ICER of approximately $50,000 (a 48% increase) when the intervention was IGRA and rifampin. Additionally, the feasibility of this intervention must be considered. In a country like Canada, two to three percent of migrants are currently requested to follow-up post arrival based on pre-immigration medical exams [3,94]. Implementing pre-immigration IGRA screening only in migrants from moderate to very high incidence countries would result in 17.6% requiring follow-up in a typical migrant cohort [93,94]. Despite this large number, the total number of TB cases in Canada could drop 3.4% in the first year [3,93,94].

Mandatory pre-immigration LTBI screening may pose an ethical dilemma, as there will always be a proportion of the population without LTBI exposed to therapy unnecessarily. While this is particularly evident in migrants from low incidence countries, the effect of poor test specificity is always present, with nearly 30 per 1000 uninfected individuals IGRA screened misdiagnosed with LTBI [24,34].

Regardless of how pre-immigration LTBI screening is implemented, investment in LTBI infrastructure in high TB incidence settings will be essential for global TB elimination. Evidence suggests that introduction of routine pre-immigration TB screening by many high-income, low TB incidence countries has contributed to improving infrastructure for TB programs in low-income areas [365]. Further introducing LTBI screening as part of these routine medical exams may have similar impact.

The concept of pre-immigration LTBI screening has previously been explored from a cost-effectiveness perspective. Schwartzman and Menzies [209] examined the idea of pre-immigration LTBI screening in addition to standard pre-immigration CXR. The cost per TB case prevented was approximately $67,000 (1997 CAD). In our study, using this strategy in very high incidence countries resulted in a cost per TB case prevented of approximately $77,000 (2016 CAD). Schwartzman and colleagues [210] revisited this idea and investigated the cost associated with performing a TST in all new legal immigrants from Mexico (a low TB incidence country), resulting in a cost per TB case prevented of $648,379 (2003 USD). Using this same strategy in our study resulted in a cost per TB case prevented of $979,417 (2016 CAD). Other studies have been performed that suggest investigation of pre-immigration LTBI screening due to the economic constraints of post-immigration interventions [94,133,222]. With more recent data, our study demonstrates the potential impact this intervention can have in variable settings.

In this chapter we assumed that all individuals were recommended treatment when they are test-positive. This is not necessarily the case as the benefit of treatment may be outweighed by the risk of serious adverse events in specific individuals. In migrants from low TB prevalence countries this was clearly elicited from the results of our analysis, yet it is an important consideration for migrants from moderate to very high incidence countries as well. Migrants from these regions will be at variable risk of reactivation dependent on social factors and co-morbidities. We have shown in this model that the public benefits of mass treatment applied to individuals from moderate to very high TB incidence countries testing positive with an IGRA pre-immigration outweigh the potential benefits and risks to the individual receiving rifampin therapy post-arrival. Yet, when migrants attend the clinic post-arrival it is a concern of the attending physician what the potential risks and benefits of LTBI treatment are and treatment may not be offered in such a universal manner. An analysis of further scrutinizing LTBI treatment in these populations to those at increased risk of TB will be required to determine where best to focus treatment. While the recommendations stemming from this subsequent analysis may well result in a reduction the overall public benefit, it will certainly reduce the number of people exposed to treatment when the risks outweigh the benefits on an individual level.

This chapter is not without further limitations. Two-year TB incidence data from several consecutive cohorts were used to estimate LTBI prevalence. These data however fit well with reported LTBI prevalence estimates [21]. The reactivation rate of LTBI was derived from the literature, yet as many were based on TB incidence in those who were TST positive, it is possible that literature estimates have underestimated true reactivation due to the predictive value of the TST. Further to this point, a universal reactivation rate was assumed of 1.1 per 1000 per years. While this rate reflects a population "average" a more nuanced analysis of cost-effectiveness decisions change based on reactivation rates is required to better target therapy and not unnecessarily expose lower-risk individuals. Finally, we assumed that TB reactivation was constant, which while demonstrated [244,366], goes against the common paradigm of decreasing risk over time [367]. Where possible, sensitivity analyses were performed to view the impact our limitations may have on our results in an effort to better inform decision makers.

5.5 Conclusions

Mandated pre-immigration LTBI screening with an IGRA has the potential to be highly cost-effective when applied in moderate, high, and very high TB incidence countries. Further research into better targeting this

intervention to population subgroups at highest risk of progression is required to limit the individual risk associated with LTBI treatment. Implementing and evaluating pilot screening programs in countries with elevated TB incidence to population subgroups with already identified risk factors to TB is likely to be of value to high-income, immigrant receiving countries.

5.6 Tables

Table 5-1. Interventions explored

Intervention	Description	
	Pre-Immigration Intervention	**Post-Arrival Intervention (if required)**
Base Case	TB screening as part of routine pre-immigration medical exams, consisting of a CXR, medical history, and symptom screen. If a migrant is diagnosed with TB, they must complete treatment before immigrating.	None.
TST/INH	In addition to the base case, a TST is placed at the time of the medical exam. If the result is positive (as defined by an induration ≥10mm) the migrant is referred for follow-up post-arrival. If the TST result is negative, no further action is taken.	Test-positive migrants are recommended to follow-up post-arrival (passively). Should they report, a nine-month course of INH would be recommended.
TST/RIF		Test-positive migrants are recommended to follow-up post-arrival (passively). Should they report, a four-month course of RIF would be recommended.
IGRA/INH	In addition to the base case, an IGRA is placed at the time of the medical exam. If the result is positive (as defined by the manufacturer) the migrant is referred for follow-up post-arrival. If the IGRA result is negative, no further action is taken. If the IGRA result is indeterminate, a second is performed and the correct action taken; a second consecutive indeterminate is treated as a negative.	Test-positive migrants are recommended to follow-up post-arrival (passively). Should they report, a nine-month course of INH would be recommended.
IGRA/RIF		Test-positive migrants are recommended to follow-up post-arrival (passively). Should they report, a four-month course of RIF would be recommended.
SEQ/INH	In addition to the base case, a TST is placed at the time of the medical exam. If the result is positive (as defined by an induration ≥10mm) the migrant is referred for a second test with an IGRA. If the subsequent IGRA result is positive (as defined by the manufacturer) the migrant is referred for follow-up post-arrival. If the initial TST is negative or if the subsequent IGRA is negative, no further action is taken. If the IGRA result is indeterminate, a second is performed and the correct action taken; a second consecutive indeterminate is treated as a negative.	Test-positive migrants are recommended to follow-up post-arrival (passively). Should they report, a nine-month course of INH would be recommended.
SEQ/RIF		Test-positive migrants are recommended to follow-up post-arrival (passively). Should they report, a four-month course of RIF would be recommended.

TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; CXR: chest x-ray; TB: tuberculosis

Table 5-2. Model parameters and values for sensitivity analyses

Parameter		Estimate	Range for PSA	Values in Exploratory Sensitivity Analysis	Reference
Costs					
Full INH Treatment		$992	Triangular, 804-1179	$804, $1179	BCCDC, [330,337]
	Drug Costs	$181			
	Nurse and Clinician Costs	$741			
	Follow-up CXR	$42			
	Routine Tests	$28			
Full RIF Treatment		$575	Triangular, 464-686	$464, $686	BCCDC, [330,337]
	Drug Costs	$98			
	Nurse and Clinician Costs	$421			
	Follow-up CXR	$42			
	Routine Tests	$14			
Partial INH		$462	Triangular, 174-804	$174, $804	BCCDC, [330,337]
Partial RIF		$319	Triangular, 178-464	$178, $464	BCCDC, [330,337]
Complete TST		$31	Triangular, 24-38	$24, $38	BCCDC, [330,337]
	TST Cost	$11			
	Nurse Costs (Two Visits)	$20			
Incomplete TST		$21	Triangular, 17-25	$17, $25	BCCDC, [330,337]
IGRA		$54	Triangular, 31-62	$31, $62	BCCDC, [330,337]
	Kit and Technician Cost	$47			
	Nurse Costs	$7			
CXR		$42	Triangular, 32-52	-	BCCDC, [330,337]
	Cost per X-Ray	$35			
	Nurse Costs	$7			
Tuberculosis		$20,532	Gamma(4.1064,5000)	$16,730, $24,334	Expert Opinion, [221,330]
LTBI Adverse Event		$732	Triangular, 549-916	$549, $916	[330]
Hospitalization		$6641	Triangular, 5305-9985	$5305, $9985	[119]
Death		$26,933	Triangular, 13,079-40,788	$13,079, $40,788	[338]

All costs are in 2016 CAD.
PSA: Probabilistic Sensitivity Analysis; INH: Isoniazid; RIF: Rifampin; BCCDC: British Columbia Centre for Disease Control; TST: Tuberculin Skin Test; IGRA: Interferon-Gamma Release Assay; CXR: Chest X-Ray; LTBI: Latent Tuberculosis Infection; TB: Tuberculosis

Table 5-2. Continued

Parameter	Estimate	Range for PSA	Values in Exploratory Sensitivity Analysis	Reference
QALYs				
LTBI	0.81	Beta(9.49,2.23)	-	[331–333]
Healthy	0.81	Beta(7.85,1.84)	-	[331–333]
Adverse Event Disutility	0.2	Triangular, ±25%	-	[119,330]
TB	0.69	Beta(6.84,3.07)	-	[331–333]
Hospitalization	0.5	Triangular, ±25%	-	[119]
Dead	0	-	-	Standard
Screening Parameters				
TST Sensitivity	0.782	Beta(43,12)	-	Chapter 2, [20,24]
TST Specificity (No BCG)	0.974	Beta(770,21)	-	[24,34]
TST Specificity (BCG)	0.602	Beta(239,158)	-	[24,34]
IGRA Sensitivity	0.889	Beta(8,1)	-	Chapter 2, [20,24]
IGRA Specificity	0.957	Beta(900,40)	-	[24,34]
IGRA Indeterminate¶	0.06	Beta(83,1286)	-	[34]
Complete TST†	1	-	-	[53,303]
Complete Medical Evaluation°	1	-	-	[53]
Population Characteristics				
LTBI Prevalence: Very High Incidence	0.3162	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
LTBI Prevalence: High Incidence	0.2016	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
LTBI Prevalence Moderate Incidence	0.0902	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
LTBI Prevalence Low Incidence	0.0159	Varied with Reactivation Rate	Varied with Reactivation Rate	[94]
Abnormal CXR or Previous TB	0.024	-	-	[94]
Adherence of Post-Landing Follow-up*	0.684	Beta(404.50,186.87)	1	[322]

¶Treated as a negative result if it occurred; was equally likely to occur in those with and without LTBI

†Without being mandatory, this value is 63.5% (imputed from 43.4% of migrants completing screening when 68.4% adhere with a follow-up appointment) [53]

°Without being mandatory, this value is 78% (imputed from 43.7 of 56 individuals completing medical evaluation) [53]

*See **Figure 5-2**.

Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000

QALY: Quality Adjusted Life Year; PSA: Probabilistic Sensitivity Analysis; INH: Isoniazid; RIF: Rifampin; TST: Tuberculin Skin Test; IGRA: Interferon-Gamma Release Assay; CXR: Chest X-Ray; LTBI: Latent Tuberculosis Infection; TB: Tuberculosis

Table 5-2. Continued

Parameter	Estimate	Range for PSA	Values in Exploratory Sensitivity Analysis	Reference
Treatment Parameters				
Initiate*	0.938	Beta(180.83,11.95)	0.635, 1	[53]
Complete INH	0.616	Beta(131.66,82.07)	1†	[53]
Complete RIF	0.814	Beta(76.85,17.56)	1†	[53]
Adverse Event INH	0.060	Beta(134,2095)	0.12	[120–123,339]
Adverse Event RIF	0.027	Beta(56,2043)	0.07	[120–123,339]
Hospitalization | AE	0.01	Beta(1,99)	0.02	[119]
Death INH	0.00000988	Beta(2,202495)	-	[340]
LTBI Risk Reduction INH	0.93	Normal(-2.597,0.461)§	-	[51]
LTBI Risk Reduction RIF	0.8	Normal(-1.609,0.500)§	0.93	[57,59]
Partial Risk Reduction INH	0.346	Combination of Normal Distributions§ǂ	-	[51,120–123,339]
Partial Risk Reduction RIF	0	Normal(-0.693,0.300)§	-	[57,59]
Adverse Event Duration	7 days	Gamma(0.7,10)	-	Expert Opinion, [119]
TB Parameters				
Death from TB	0.0476	Beta(76,1523)	-	[3]
Reactivation Rate	0.0011	Beta(90.92,82545.55)	0.0009, 0.0013	[73,219,318–321,327–329]
Abnormal CXR Risk Change	3.9	Normal(1.36,0.15)§	-	[317]
Extended Therapy	0.124	Beta(2.366,16.713)	-	Expert Opinion, [119]
Relapse Rate	0.0359	Normal(-3.327,0.365)§	-	[341]
Model Parameters				
BCG Vaccination (<30 cases)	0.605	Beta(45137,29502)	-	[224]
BCG Vaccination (≥30 cases)	0.998	Beta(185381,384)	-	[224]
BCG Vaccination Uptake	0.837	-	-	[316]
Discount Rate	0.03	-	0	[189]
Time Horizon	25 years	-	Lifetime	-

*This model assumes all who report post-landing due to a positive pre-immigration LTBI diagnostic test are offered treatment. Exploratory analysis adjusts this assumption so that only the number of migrants who would complete TST screening begin treatment.
†This is assuming 100% of those who do not default to due adverse event will complete therapy (e.g. for isoniazid, this will equate 94% of people completing with an adverse event rate of 6%).
§Results from this distribution are exponentiated
ǂFormula: 0.33*(Normal(-1.168,0.228))+0.374*(Normal(-0.381,0.169))+0.293*1
PSA: Probabilistic Sensitivity Analysis; INH: Isoniazid; RIF: Rifampin; AE: Adverse Event; LTBI: Latent Tuberculosis Infection; TB: Tuberculosis

Table 5-3. Results of implementing pre-immigration LTBI screening as part of routine medical examinations

Intervention	Percent Identified for Post-Arrival Follow-up (%)	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)	Incremental Net Monetary Benefit ($)
Low TB Incidence							
Base Case	0.82	8,988	13,762.3	0.42	-	-	
TST/INH	22.99	166,309	13,762.3	0.26	38.22	Dominated	-164,278
TST/RIF	22.99	124,062	13,762.0	0.27	35.87	Dominated	-152,614
IGRA/INH	6.43	98,336	13,762.5	0.24	43.64	655,630	-75,720
IGRA/RIF	6.43	86,720	13,762.5	0.25	40.93	581,942	-64,374
SEQ/INH	4.02	71,255	13,762.3	0.27	35.65	Dominated	-67,842
SEQ/RIF	4.02	64,156	13,762.1	0.29	31.89	Dominated	-82,075
Moderate TB Incidence							
Base Case	2.88	55,294	13,736.6	2.58	-	-	-
TST/INH	38.96	286,636	13,738.5	1.55	39.97	120,246	-38,951
TST/RIF	38.96	214,987	13,738.2	1.61	37.49	Strict Dominance	2,913
IGRA/INH	14.52	168,965	13,738.0	1.46	43.49	Strict Dominance	35,343
IGRA/RIF	14.52	143,717	13,738.4	1.53	40.67	48,993	92,059
SEQ/INH	11.99	152,372	13,738.3	1.62	37.14	Strict Dominance	77,225
SEQ/RIF	11.99	131,792	13,738.2	1.69	34.36	47,374	84,977
High TB Incidence							
Base Case	2.79	119,282	13,703.5	5.57	-	-	-
TST/INH	44.24	353,091	13,705.8	3.40	39.05	100,935	-2,165
TST/RIF	44.24	274,602	13,705.6	3.55	36.23	Strict Dominance	63,343
IGRA/INH	23.60	257,282	13,705.7	3.18	42.89	62,440	83,014
IGRA/RIF	23.60	217,539	13,705.5	3.36	39.63	49,035	102,124
SEQ/INH	19.13	236,934	13,705.7	3.56	36.07	53,790	101,074
SEQ/RIF	19.13	204,434	13,705.3	3.70	33.61	46,303	98,750
Very High TB Incidence							
Base Case	3.87	178,665	13,668.7	8.34	-	-	-
TST/INH	49.82	421,783	13,672.2	5.15	38.23	Strict Dominance	106,622
TST/RIF	49.82	334,567	13,672.1	5.38	35.48	Strict Dominance	176,048
IGRA/INH	33.86	349,429	13,672.7	4.81	42.38	43,290	223,704
IGRA/RIF	33.86	292,344	13,672.1	5.07	39.27	33,696	223,683
SEQ/INH	27.45	325,391	13,672.0	5.40	35.28	Strict Dominance	180,529
SEQ/RIF	27.45	279,006	13,671.9	5.61	32.79	32,013	213,098

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin
Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.
Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000
All costs in 2016 CAD

Table 5-4. Average PSA results of implementing pre-immigration LTBI screening as part of routine medical examinations

Intervention	Percent Identified for Post-Arrival Follow-up (%)	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)	Incremental Net Monetary Benefit ($)
Low TB Incidence							
Base Case	0.82	8,896	14,885.7	0.42	-	-	
TST/INH	23.00	166,872	14,885.9	0.26	36.99	Strict Dominance	-140,366
TST/RIF	23.00	123,624	14,886.1	0.26	38.58	Strict Dominance	-75,952
IGRA/INH	6.45	93,524	14,885.8	0.24	42.48	Strict Dominance	-75,165
IGRA/RIF	6.45	81,392	14,886.1	0.24	42.44	164,626	-28,459
SEQ/INH	4.03	70,505	14,885.6	0.28	33.39	Dominated	-73,318
SEQ/RIF	4.03	62,764	14,885.9	0.27	35.54	Extended Dominance	-36,328
Moderate TB Incidence							
Base Case	2.88	55,109	14,857.8	2.59	-	-	
TST/INH	39.53	287,763	14,859.3	1.57	39.53	Strict Dominance	-81,973
TST/RIF	39.53	213,132	14,859.5	1.54	40.41	Strict Dominance	15,574
IGRA/INH	14.60	164,699	14,859.3	1.47	43.11	Strict Dominance	48,372
IGRA/RIF	14.60	136,858	14,859.6	1.45	44.07	44,027	103,929
SEQ/INH	12.07	151,490	14,859.6	1.65	36.46	Strict Dominance	86,234
SEQ/RIF	12.07	128,432	14,859.2	1.62	37.51	Extended Dominance	71,115
High TB Incidence							
Base Case	2.79	119,446	14,820.5	5.61	-	-	
TST/INH	44.35	354,495	14,823.3	3.43	38.80	Strict Dominance	48,802
TST/RIF	44.35	270,572	14,823.7	3.39	39.62	Strict Dominance	173,360
IGRA/INH	23.77	253,997	14,823.8	3.22	42.55	39,832	203,243
IGRA/RIF	23.77	207,945	14,823.8	3.16	43.68	26,467	245,875
SEQ/INH	19.29	236,174	14,823.2	3.60	35.76	Strict Dominance	154,262
SEQ/RIF	19.29	199,288	14,823.8	3.56	36.55	23,955	253,460
Very High TB Incidence							
Base Case	3.87	179,085	14,782.6	8.41	-	-	
TST/INH	50.00	424,059	14,786.6	5.21	38.03	Strict Dominance	154,322
TST/RIF	50.00	328,767	14,786.9	5.13	39.03	Strict Dominance	283,535
IGRA/INH	34.13	347,234	14,787.2	4.89	41.90	Strict Dominance	294,474
IGRA/RIF	34.13	281,369	14,787.4	4.80	42.97	21,022	384,281
SEQ/INH	27.45	325,448	14,786.6	5.48	34.88	Strict Dominance	253,042
SEQ/RIF	27.45	272,233	14,786.9	5.40	35.77	Extended Dominance	334,586

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin
Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.
Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000
All costs in 2016 CAD

Table 5-5. Results of exploratory sensitivity analyses in migrants from low TB incidence countries

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
Only Screen ≤60 year olds					
TST/INH	160,167	13,762.1	0.27	36.32	Dominated
TST/RIF	119,619	13,762.2	0.28	33.25	Dominated
IGRA/INH	94,632	13,762.5	0.25	41.35	Strict Dominance
IGRA/RIF	83,610	13,762.6	0.26	38.58	292,362
SEQ/INH	68,616	13,762.5	0.28	33.36	Extended Dominance
SEQ/RIF	61,820	13,762.1	0.29	30.43	Dominated
Only Screen ≤35 year olds					
TST/INH	120,224	13,761.8	0.35	17.67	Dominated
TST/RIF	90,638	13,761.8	0.35	16.70	Dominated
IGRA/INH	71,057	13,762.3	0.34	18.88	Dominated
IGRA/RIF	63,647	13,762.3	0.35	17.30	Dominated
SEQ/INH	51,639	13,762.4	0.35	16.53	1,798,852
SEQ/RIF	47,226	13,761.9	0.35	16.05	Dominated
Only Screen 10-60 year olds					
TST/INH	136,122	13,762.2	0.28	34.31	Dominated
TST/RIF	101,937	13,762.7	0.29	31.89	245,212
IGRA/INH	81,713	13,762.1	0.27	36.83	Dominated
IGRA/RIF	71,982	13,761.8	0.27	35.38	Dominated
SEQ/INH	59,744	13,762.3	0.29	31.29	Dominated
SEQ/RIF	53,656	13,762.1	0.30	29.11	Dominated
Only 63.5% Initiate Therapy After Arrival					
TST/INH	127,463	13,762.2	0.31	27.07	Dominated
TST/RIF	98,791	13,762.5	0.31	26.30	584,302
IGRA/INH	88,413	13,762.4	0.29	30.21	Extended Dominance
IGRA/RIF	80,510	13,762.2	0.30	28.54	Dominated
SEQ/INH	65,238	13,762.3	0.32	24.64	Extended Dominance
SEQ/RIF	60,315	13,762.2	0.32	23.45	Dominated

Base Case Results – Costs: $8988; QALYs: 13,762.3; TB Cases: 0.42

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; PY: person years

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-5. Continued

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
100% Adherence to Post-Arrival Follow-up					
TST/INH	224,798	13,762.0	0.19	55.42	Dominated
TST/RIF	163,173	13,762.1	0.21	50.48	Dominated
IGRA/INH	113,581	13,762.8	0.16	61.45	153,143
IGRA/RIF	96,644	13,762.2	0.18	56.35	Strict Dominance
SEQ/INH	80,439	13,762.4	0.21	51.08	Extended Dominance
SEQ/RIF	69,889	13,762.1	0.22	47.02	Dominated
No Losses in the LTBI Cascade of Care					
TST/INH	264,985	13,762.1	0.11	73.72	Dominated
TST/RIF	169,565	13,762.2	0.15	63.55	Dominated
IGRA/INH	123,478	13,762.2	0.08	81.34	Dominated
IGRA/RIF	97,413	13,762.6	0.12	71.33	Strict Dominance
SEQ/INH	86,288	13,762.7	0.14	66.92	242,510
SEQ/RIF	70,137	13,762.4	0.17	58.84	Extended Dominance
Reactivation Rate is 0.9 cases per 1000 PY*					
TST/INH	167,480	13,761.6	0.26	38.43	640,400
TST/RIF	124,898	13,761.1	0.27	35.10	Dominated
IGRA/INH	100,117	13,761.5	0.24	42.60	480,838
IGRA/RIF	87,975	13,760.8	0.25	39.54	Dominated
SEQ/INH	72,718	13,761.4	0.27	35.38	Extended Dominance
SEQ/RIF	65,058	13,761.0	0.28	32.80	Dominated
Reactivation Rate is 1.3 cases per 1000 PY†					
TST/INH	165,457	13,762.8	0.25	38.84	Dominated
TST/RIF	123,581	13,762.9	0.27	34.60	Dominated
IGRA/INH	97,220	13,762.7	0.24	43.01	Dominated
IGRA/RIF	86,075	13,763.0	0.25	38.82	Dominated
SEQ/INH	70,254	13,763.0	0.27	34.75	Dominated
SEQ/RIF	63,297	13,762.7	0.28	33.12	Dominated

Base Case Results – Costs: $8988; QALYs: 13,762.3; TB Cases: 0.42; *Base Case Results – Costs: $9004; QALYs: 13,761.3; TB Cases: 0.42; †Base Case Results – Costs: $8939; QALYs: 13,763.1; TB Cases: 0.42

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; PY: person years

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-5. Continued

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
Rifampin and Isoniazid are Equally Effective					
TST/INH	166,309	13,762.3	0.26	38.22	Dominated
TST/RIF	123,503	13,762.0	0.25	41.55	Dominated
IGRA/INH	98,336	13,762.5	0.24	43.64	655,630
IGRA/RIF	86,336	13,761.9	0.23	45.22	Dominated
SEQ/INH	71,255	13,762.3	0.27	35.65	Dominated
SEQ/RIF	63,615	13,762.2	0.26	37.61	Dominated
Lifetime Time Horizon*					
TST/INH	168,517	20,737.6	0.36	37.44	Strict Dominance
TST/RIF	126,277	20,736.6	0.38	35.18	Dominated
IGRA/INH	100,567	20,738.1	0.34	41.25	Strict Dominance
IGRA/RIF	89,047	20,738.4	0.36	38.12	71,775
SEQ/INH	73,594	20,737.6	0.38	34.48	Extended Dominance
SEQ/RIF	66,453	20,736.2	0.39	31.99	Dominated
Minimum Estimated Costs†					
TST/INH	139,390	13,762.3	0.26	38.22	Dominated
TST/RIF	101,829	13,762.0	0.27	35.87	Dominated
IGRA/INH	67,826	13,762.5	0.24	43.64	445,222
IGRA/RIF	57,474	13,762.5	0.25	40.93	376,739
SEQ/INH	54,733	13,762.3	0.27	35.65	Dominated
SEQ/RIF	48,395	13,762.1	0.29	31.89	Dominated
Maximum Estimated Costs°					
TST/INH	193,327	13,762.3	0.26	38.22	Dominated
TST/RIF	146,379	13,762.0	0.27	35.87	Dominated
IGRA/INH	113,103	13,762.5	0.24	43.64	750,510
IGRA/RIF	100,220	13,762.5	0.25	40.93	669,265
SEQ/INH	84,466	13,762.3	0.27	35.65	Dominated
SEQ/RIF	76,606	13,762.1	0.29	31.89	Dominated

Base Case Results – Costs: $8988; QALYs: 13,762.3; TB Cases: 0.42; *Base Case Results – Costs: $12,418; QALYs: 20,737.4; TB Cases: 0.58; †Base Case Results – Costs: $7152; QALYs: 13,762.3; TB Cases: 0.42; °Base Case Results – Costs: $10,825; QALYs: 13,762.3; TB Cases: 0.42

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-6. Results of exploratory sensitivity analyses in migrants from moderate TB incidence countries

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
Only Screen ≤60 year olds					
TST/INH	276,197	13,738.2	1.60	37.89	Strict Dominance
TST/RIF	208,099	13,738.3	1.68	35.00	Strict Dominance
IGRA/INH	162,573	13,738.4	1.51	41.33	Strict Dominance
IGRA/RIF	139,309	13,737.8	1.60	38.02	Extended Dominance
SEQ/INH	146,990	13,738.5	1.68	35.01	47,547
SEQ/RIF	127,704	13,737.8	1.74	32.52	Extended Dominance
Only Screen ≤35 year olds					
TST/INH	211,292	13,737.8	2.10	18.68	Strict Dominance
TST/RIF	164,665	13,737.5	2.14	17.24	Strict Dominance
IGRA/INH	124,773	13,737.9	2.06	20.06	52,931
IGRA/RIF	111,559	13,737.5	2.09	18.99	Strict Dominance
SEQ/INH	114,236	13,737.5	2.13	17.51	Strict Dominance
SEQ/RIF	103,441	13,737.6	2.16	16.35	46,347
Only Screen 10-60 year olds					
TST/INH	243,224	13,738.4	1.67	35.41	Strict Dominance
TST/RIF	184,581	13,737.9	1.73	32.99	Strict Dominance
IGRA/INH	148,718	13,738.5	1.59	38.37	48,065
IGRA/RIF	127,107	13,737.9	1.65	36.17	Strict Dominance
SEQ/INH	135,299	13,738.3	1.74	32.80	44,789
SEQ/RIF	117,678	13,738.2	1.80	30.38	38,103
Only 63.5% Initiate Therapy After Arrival					
TST/INH	224,524	13,738.0	1.85	28.42	Strict Dominance
TST/RIF	176,021	13,737.8	1.89	26.63	Strict Dominance
IGRA/INH	150,573	13,738.0	1.77	31.33	Strict Dominance
IGRA/RIF	133,634	13,737.7	1.83	29.03	Strict Dominance
SEQ/INH	137,792	13,737.6	1.91	25.93	Strict Dominance
SEQ/RIF	123,263	13,738.2	1.93	25.06	41,245

Base Case Results – Costs: $55,294; QALYs: 13,736.6; TB Cases: 2.58

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; PY: person years

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-6. Continued

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
100% Adherence to Post-Arrival Follow-up					
TST/INH	380,822	13,738.3	1.13	56.28	Strict Dominance
TST/RIF	276,111	13,738.3	1.22	52.70	Strict Dominance
IGRA/INH	196,893	13,738.8	0.99	61.81	Strict Dominance
IGRA/RIF	159,917	13,738.8	1.09	57.69	69,496
SEQ/INH	175,263	13,738.3	1.23	52.44	Strict Dominance
SEQ/RIF	144,997	13,738.7	1.33	48.73	65,266
No Losses in the LTBI Cascade of Care					
TST/INH	442,208	13,739.1	0.65	74.84	Strict Dominance
TST/RIF	281,905	13,738.9	0.89	65.53	Strict Dominance
IGRA/INH	212,095	13,739.9	0.47	81.97	47,049
IGRA/RIF	156,712	13,739.1	0.72	72.14	40,504
SEQ/INH	187,965	13,739.1	0.80	69.01	Extended Dominance
SEQ/RIF	142,342	13,738.4	1.02	60.59	Extended Dominance
Reactivation Rate is 0.9 cases per 1000 PY*					
TST/INH	291,580	13,732.5	1.56	39.93	Strict Dominance
TST/RIF	218,700	13,732.4	1.63	36.92	Strict Dominance
IGRA/INH	178,420	13,732.8	1.46	43.56	Strict Dominance
IGRA/RIF	150,147	13,732.9	1.54	40.70	63,760
SEQ/INH	160,399	13,732.6	1.63	37.03	Strict Dominance
SEQ/RIF	137,086	13,732.7	1.69	34.78	62,799
Reactivation Rate is 1.3 cases per 1000 PY†					
TST/INH	283,095	13,742.2	1.55	39.68	Strict Dominance
TST/RIF	212,565	13,742.2	1.61	37.17	Strict Dominance
IGRA/INH	162,318	13,742.0	1.45	43.54	Strict Dominance
IGRA/RIF	139,381	13,741.9	1.53	40.29	Extended Dominance
SEQ/INH	146,788	13,742.3	1.61	37.08	75,598
SEQ/RIF	127,706	13,742.0	1.68	34.45	Extended Dominance

Base Case Results – Costs: $55,294; QALYs: 13,736.6; TB Cases: 2.58; *Base Case Results – Costs: $55,470; QALYs: 13,731.4; TB Cases: 2.59; †Base Case Results – Costs: $54,900; QALYs: 13,741.1; TB Cases: 2.56

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; PY: person years

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-6. Continued

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
Rifampin and Isoniazid are Equally Effective					
TST/INH	286,636	13,738.5	1.55	39.97	120,246
TST/RIF	212,195	13,738.3	1.49	42.43	Strict Dominance
IGRA/INH	168,965	13,738.0	1.46	43.49	Strict Dominance
IGRA/RIF	140,665	13,738.4	1.38	46.40	45,596
SEQ/INH	152,372	13,738.3	1.62	37.14	Strict Dominance
SEQ/RIF	128,849	13,737.9	1.56	39.65	Extended Dominance
Lifetime Time Horizon*					
TST/INH	300,246	20,593.9	2.18	38.79	Strict Dominance
TST/RIF	229,246	20,593.1	2.28	36.08	Strict Dominance
IGRA/INH	181,682	20,593.7	2.05	42.64	Strict Dominance
IGRA/RIF	157,324	20,594.3	2.17	39.26	29,549
SEQ/INH	166,358	20,593.6	2.28	36.11	Strict Dominance
SEQ/RIF	146,331	20,593.9	2.38	33.32	29,007
Minimum Estimated Costs†					
TST/INH	240,659	13,738.5	1.55	39.97	102,230
TST/RIF	176,908	13,738.2	1.61	37.49	Strict Dominance
IGRA/INH	126,996	13,738.0	1.46	43.49	Strict Dominance
IGRA/RIF	104,414	13,738.4	1.53	40.67	33,487
SEQ/INH	120,230	13,738.3	1.62	37.14	Strict Dominance
SEQ/RIF	101,795	13,738.2	1.69	34.36	Extended Dominance
Maximum Estimated Costs°					
TST/INH	332,779	13,738.5	1.55	39.97	138,347
TST/RIF	253,207	13,738.2	1.61	37.49	Strict Dominance
IGRA/INH	195,551	13,738.0	1.46	43.49	Strict Dominance
IGRA/RIF	167,629	13,738.4	1.53	40.67	55,971
SEQ/INH	179,072	13,738.3	1.62	37.14	Strict Dominance
SEQ/RIF	156,340	13,738.2	1.69	34.36	55,569

Base Case Results – Costs: $55,294; QALYs: 13,736.6; TB Cases: 2.58; *Base Case Results – Costs: $76,368; QALYs: 20,591.5; TB Cases: 3.57; †Base Case Results – Costs: $43,977; QALYs: 13,736.6; TB Cases: 2.58; °Base Case Results – Costs: $66,611; QALYs: 13,736.6; TB Cases: 2.58

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-7. Results of exploratory sensitivity analyses in migrants from high TB incidence countries

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
Only Screen ≤60 year olds					
TST/INH	340,999	13,706.0	3.53	36.61	Strict Dominance
TST/RIF	266,785	13,705.3	3.68	34.04	Strict Dominance
IGRA/INH	248,073	13,705.7	3.33	40.30	Strict Dominance
IGRA/RIF	210,762	13,705.9	3.48	37.61	37,584
SEQ/INH	228,570	13,705.3	3.66	34.30	Strict Dominance
SEQ/RIF	198,767	13,705.1	3.80	31.76	Extended Dominance
Only Screen ≤35 year olds					
TST/INH	265,902	13,704.7	4.58	17.82	Strict Dominance
TST/RIF	218,987	13,704.1	4.65	16.61	Strict Dominance
IGRA/INH	192,641	13,705.1	4.48	19.54	45,726
IGRA/RIF	174,331	13,704.6	4.55	18.29	Extended Dominance
SEQ/INH	181,292	13,704.3	4.64	16.75	Strict Dominance
SEQ/RIF	166,878	13,704.4	4.71	15.48	Extended Dominance
Only Screen 10-60 year olds					
TST/INH	308,686	13,705.2	3.66	34.35	Strict Dominance
TST/RIF	244,388	13,705.7	3.79	31.92	Strict Dominance
IGRA/INH	231,913	13,706.0	3.47	37.71	43,549
IGRA/RIF	197,980	13,705.2	3.60	35.32	44,152
SEQ/INH	215,256	13,705.5	3.79	31.93	Extended Dominance
SEQ/RIF	187,935	13,705.0	3.92	29.72	Extended Dominance
Only 63.5% Initiate Therapy After Arrival					
TST/INH	289,771	13,704.9	4.03	27.73	Strict Dominance
TST/RIF	237,128	13,704.7	4.15	25.56	Strict Dominance
IGRA/INH	231,450	13,705.2	3.89	30.14	65,106
IGRA/RIF	204,208	13,705.1	4.00	28.29	52,753
SEQ/INH	215,926	13,704.8	4.14	25.72	Strict Dominance
SEQ/RIF	193,620	13,704.8	4.21	24.45	Extended Dominance

Base Case Results – Costs: $119,282; QALYs: 13,703.5; TB Cases: 5.57

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; PY: person years

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-7. Continued

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
100% Adherence to Post-Arrival Follow-up					
TST/INH	448,774	13,706.3	2.47	55.76	Strict Dominance
TST/RIF	334,296	13,706.4	2.70	51.64	Strict Dominance
IGRA/INH	297,043	13,707.0	2.17	61.20	48,586
IGRA/RIF	238,472	13,706.4	2.41	56.95	39,985
SEQ/INH	268,847	13,706.0	2.72	51.37	Strict Dominance
SEQ/RIF	221,618	13,706.6	2.92	47.69	31,519
No Losses in the LTBI Cascade of Care					
TST/INH	507,187	13,707.5	1.44	74.15	Strict Dominance
TST/RIF	333,156	13,706.7	1.97	64.67	Strict Dominance
IGRA/INH	315,633	13,707.8	1.02	81.63	45,026
IGRA/RIF	229,086	13,707.3	1.60	71.36	28,778
SEQ/INH	283,325	13,707.3	1.77	68.21	42,311
SEQ/RIF	213,348	13,707.0	2.25	59.69	26,483
Reactivation Rate is 0.9 cases per 1000 PY*					
TST/INH	364,083	13,693.0	3.40	39.56	Strict Dominance
TST/RIF	282,190	13,693.1	3.56	36.75	Strict Dominance
IGRA/INH	278,115	13,693.4	3.19	43.37	53,352
IGRA/RIF	231,531	13,693.3	3.36	40.28	39,198
SEQ/INH	254,088	13,693.3	3.55	36.95	Strict Dominance
SEQ/RIF	216,552	13,692.9	3.69	34.44	Extended Dominance
Reactivation Rate is 1.3 cases per 1000 PY†					
TST/INH	345,385	13,714.5	3.39	39.06	Strict Dominance
TST/RIF	269,071	13,714.1	3.53	36.59	Strict Dominance
IGRA/INH	242,615	13,714.5	3.17	43.10	Strict Dominance
IGRA/RIF	207,273	13,714.6	3.34	40.09	30,089
SEQ/INH	224,354	13,714.1	3.54	36.41	Strict Dominance
SEQ/RIF	195,656	13,713.9	3.68	33.89	Extended Dominance

Base Case Results – Costs: $119,282; QALYs: 13,703.5; TB Cases: 5.57; *Base Case Results – Costs: $120,559; QALYs: 13,690.5; TB Cases: 5.63; †Base Case Results – Costs: $119,277; QALYs: 13,711.6; TB Cases: 5.57

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; PY: person years

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-7. Continued

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
Rifampin and Isoniazid are Equally Effective					
TST/INH	353,091	13,705.8	3.40	39.05	Strict Dominance
TST/RIF	268,060	13,706.3	3.25	41.69	53,046
IGRA/INH	257,282	13,705.7	3.18	42.89	Extended Dominance
IGRA/RIF	210,001	13,705.5	3.01	46.02	45,404
SEQ/INH	236,934	13,705.7	3.56	36.07	Extended Dominance
SEQ/RIF	198,397	13,705.9	3.42	38.65	31,860
Lifetime Time Horizon*					
TST/INH	382,528	20,406.7	4.77	38.33	Strict Dominance
TST/RIF	305,338	20,407.8	4.99	35.55	Strict Dominance
IGRA/INH	284,309	20,407.7	4.45	42.55	Strict Dominance
IGRA/RIF	245,787	20,408.3	4.69	39.41	17,427
SEQ/INH	267,705	20,407.5	5.00	35.36	Strict Dominance
SEQ/RIF	235,994	20,407.7	5.18	33.14	Extended Dominance
Minimum Estimated Costs†					
TST/INH	295,147	13,705.8	3.40	39.05	86,454
TST/RIF	225,096	13,705.6	3.55	36.23	Strict Dominance
IGRA/INH	200,264	13,705.7	3.18	42.89	47,682
IGRA/RIF	164,612	13,705.5	3.36	39.63	34,799
SEQ/INH	189,293	13,705.7	3.56	36.07	43,164
SEQ/RIF	160,175	13,705.3	3.70	33.61	Extended Dominance
Maximum Estimated Costs°					
TST/INH	411,226	13,705.8	3.40	39.05	115,497
TST/RIF	324,272	13,705.6	3.55	36.23	Strict Dominance
IGRA/INH	298,947	13,705.7	3.18	42.89	70,251
IGRA/RIF	255,097	13,705.5	3.36	39.63	55,601
SEQ/INH	278,439	13,705.7	3.56	36.07	61,610
SEQ/RIF	242,540	13,705.3	3.70	33.61	53,755

Base Case Results – Costs: $119,282; QALYs: 13,703.5; TB Cases: 5.57; *Base Case Results – Costs: $165,782; QALYs: 20,403.7; TB Cases: 7.74; † Base Case Results – Costs: $94,881; QALYs: 13,703.5; TB Cases: 5.57; ° Base Case Results – Costs: $143,682; QALYs: 13,703.5; TB Cases: 5.57

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-8. Results of exploratory sensitivity analyses in migrants from very high TB incidence countries

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
Only Screen ≤60 year olds					
TST/INH	407,219	13,672.0	5.34	36.01	Strict Dominance
TST/RIF	325,286	13,671.8	5.55	33.41	Strict Dominance
IGRA/INH	336,378	13,672.7	5.01	39.90	39,681
IGRA/RIF	283,794	13,672.4	5.26	36.97	28,826
SEQ/INH	314,688	13,671.4	5.58	33.05	Strict Dominance
SEQ/RIF	271,770	13,671.4	5.77	30.80	Extended Dominance
Only Screen ≤35 year olds					
TST/INH	320,565	13,670.4	6.92	16.98	Strict Dominance
TST/RIF	272,387	13,670.4	7.04	15.66	Strict Dominance
IGRA/INH	261,656	13,670.7	6.78	18.67	41,748
IGRA/RIF	237,244	13,670.7	6.91	17.19	29,956
SEQ/INH	249,887	13,670.3	7.04	15.65	Strict Dominance
SEQ/RIF	229,600	13,669.9	7.12	14.64	Extended Dominance
Only Screen 10-60 year olds					
TST/INH	377,198	13,671.7	5.58	33.14	Strict Dominance
TST/RIF	304,495	13,671.3	5.74	31.13	Strict Dominance
IGRA/INH	319,268	13,672.0	5.28	36.66	42,793
IGRA/RIF	271,046	13,672.0	5.49	34.21	28,276
SEQ/INH	298,962	13,671.6	5.75	31.03	Strict Dominance
SEQ/RIF	260,169	13,671.1	5.94	28.73	Extended Dominance
Only 63.5% Initiate Therapy After Arrival					
TST/INH	355,588	13,671.5	6.10	26.89	64,885
TST/RIF	296,733	13,670.7	6.26	25.00	Strict Dominance
IGRA/INH	313,125	13,671.3	5.85	29.82	52,281
IGRA/RIF	275,322	13,671.2	6.07	27.21	39,300
SEQ/INH	296,113	13,671.2	6.26	24.93	Strict Dominance
SEQ/RIF	265,154	13,670.7	6.42	23.07	Extended Dominance

Base Case Results – Costs: $178,665; QALYs: 13,668.7; TB Cases: 8.34

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; PY: person years

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-8. Continued

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
100% Adherence to Post-Arrival Follow-up					
TST/INH	522,272	13,673.3	3.76	54.96	Strict Dominance
TST/RIF	394,942	13,673.2	4.10	50.93	Strict Dominance
IGRA/INH	405,103	13,674.1	3.28	60.77	43,736
IGRA/RIF	321,390	13,674.0	3.64	56.44	28,211
SEQ/INH	370,066	13,672.9	4.13	50.54	Strict Dominance
SEQ/RIF	302,436	13,672.8	4.44	46.87	Extended Dominance
No Losses in the LTBI Cascade of Care					
TST/INH	579,739	13,674.4	2.22	73.41	Strict Dominance
TST/RIF	387,829	13,674.2	3.01	63.95	Strict Dominance
IGRA/INH	429,895	13,675.3	1.56	81.25	38,197
IGRA/RIF	306,673	13,674.6	2.43	70.90	21,708
SEQ/INH	389,771	13,674.2	2.72	67.40	Strict Dominance
SEQ/RIF	289,889	13,673.4	3.43	58.89	Extended Dominance
Reactivation Rate is 0.9 cases per 1000 PY*					
TST/INH	439,079	13,652.8	5.16	38.50	Strict Dominance
TST/RIF	346,356	13,652.5	5.39	35.82	Strict Dominance
IGRA/INH	381,904	13,653.3	4.81	42.72	46,447
IGRA/RIF	314,388	13,653.3	5.08	39.49	30,991
SEQ/INH	353,063	13,652.9	5.43	35.38	Strict Dominance
SEQ/RIF	298,580	13,652.5	5.64	32.88	Extended Dominance
Reactivation Rate is 1.3 cases per 1000 PY†					
TST/INH	409,804	13,685.8	5.14	38.28	Strict Dominance
TST/RIF	326,656	13,684.8	5.38	35.40	Strict Dominance
IGRA/INH	326,744	13,686.1	4.80	42.39	41,880
IGRA/RIF	276,827	13,686.1	5.05	39.34	28,080
SEQ/INH	306,354	13,685.5	5.39	35.25	Strict Dominance
SEQ/RIF	265,757	13,685.2	5.60	32.78	Extended Dominance

Base Case Results – Costs: $178,665; QALYs: 13,668.7; TB Cases: 8.34; *Base Case Results – Costs: $179,725; QALYs: 13,649.0; TB Cases: 8.40; †Base Case Results – Costs: $178,242; QALYs: 13,682.6; TB Cases: 8.33

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin; PY: person years

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

Table 5-8. Continued

Intervention	Costs per 1000 migrants ($)	Total QALYs per 1000 migrants	TB Cases per 1000 migrants	Reduction in TB Incidence (%)	Cost per QALY gained ($)
Rifampin and Isoniazid are Equally Effective					
TST/INH	421,783	13,672.2	5.15	38.23	Strict Dominance
TST/RIF	324,733	13,672.4	4.92	40.99	Strict Dominance
IGRA/INH	349,429	13,672.7	4.81	42.38	Strict Dominance
IGRA/RIF	281,555	13,673.0	4.56	45.32	24,273
SEQ/INH	325,391	13,672.0	5.40	35.28	Strict Dominance
SEQ/RIF	269,704	13,672.2	5.17	38.00	Extended Dominance
Lifetime Time Horizon*					
TST/INH	466,224	20,210.9	7.23	37.96	Strict Dominance
TST/RIF	380,925	20,210.4	7.56	35.14	Strict Dominance
IGRA/INH	391,404	20,211.4	6.77	41.90	Strict Dominance
IGRA/RIF	337,077	20,213.0	7.16	38.56	11,260
SEQ/INH	372,495	20,209.9	7.60	34.73	Strict Dominance
SEQ/RIF	327,903	20,211.2	7.89	32.25	Extended Dominance
Minimum Estimated Costs†					
TST/INH	351,656	13,672.2	5.15	38.23	Strict Dominance
TST/RIF	273,731	13,672.1	5.38	35.48	Strict Dominance
IGRA/INH	277,154	13,672.7	4.81	42.38	34,246
IGRA/RIF	225,939	13,672.1	5.07	39.27	24,862
SEQ/INH	261,932	13,672.0	5.40	35.28	Strict Dominance
SEQ/RIF	220,338	13,671.9	5.61	32.79	Extended Dominance
Maximum Estimated Costs°					
TST/INH	492,123	13,672.2	5.15	38.23	Strict Dominance
TST/RIF	395,585	13,672.1	5.38	35.48	Strict Dominance
IGRA/INH	406,571	13,672.7	4.81	42.38	48,497
IGRA/RIF	343,585	13,672.1	5.07	39.27	38,037
SEQ/INH	382,078	13,672.0	5.40	35.28	Strict Dominance
SEQ/RIF	330,880	13,671.9	5.61	32.79	36,886

Base Case Results – Costs: $178,665; QALYs: 13,668.7; TB Cases: 8.34; *Base Case Results – Costs: $249,392; QALYs: 20,205.2; TB Cases: 11.65; † Base Case Results – Costs: $142,066; QALYs: 13,668.7; TB Cases: 8.34; ° Base Case Results – Costs: $215,265; QALYs: 13,668.7; TB Cases: 8.34

QALY: quality adjusted life year; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon-gamma release assay; SEQ: sequential screening; INH: isoniazid; RIF: rifampin

All costs in 2016 CAD

Dominated: This intervention has higher costs and worse outcomes compared to the base case; Extended Dominance: This intervention is more effective than the base case, but has a higher cost per QALY gained compared to a more effective intervention that has a higher cost; Strict Dominance: This intervention is more expensive and has worse outcomes than another intervention.

5.7 Figures

Figure 5-1. Model Structure

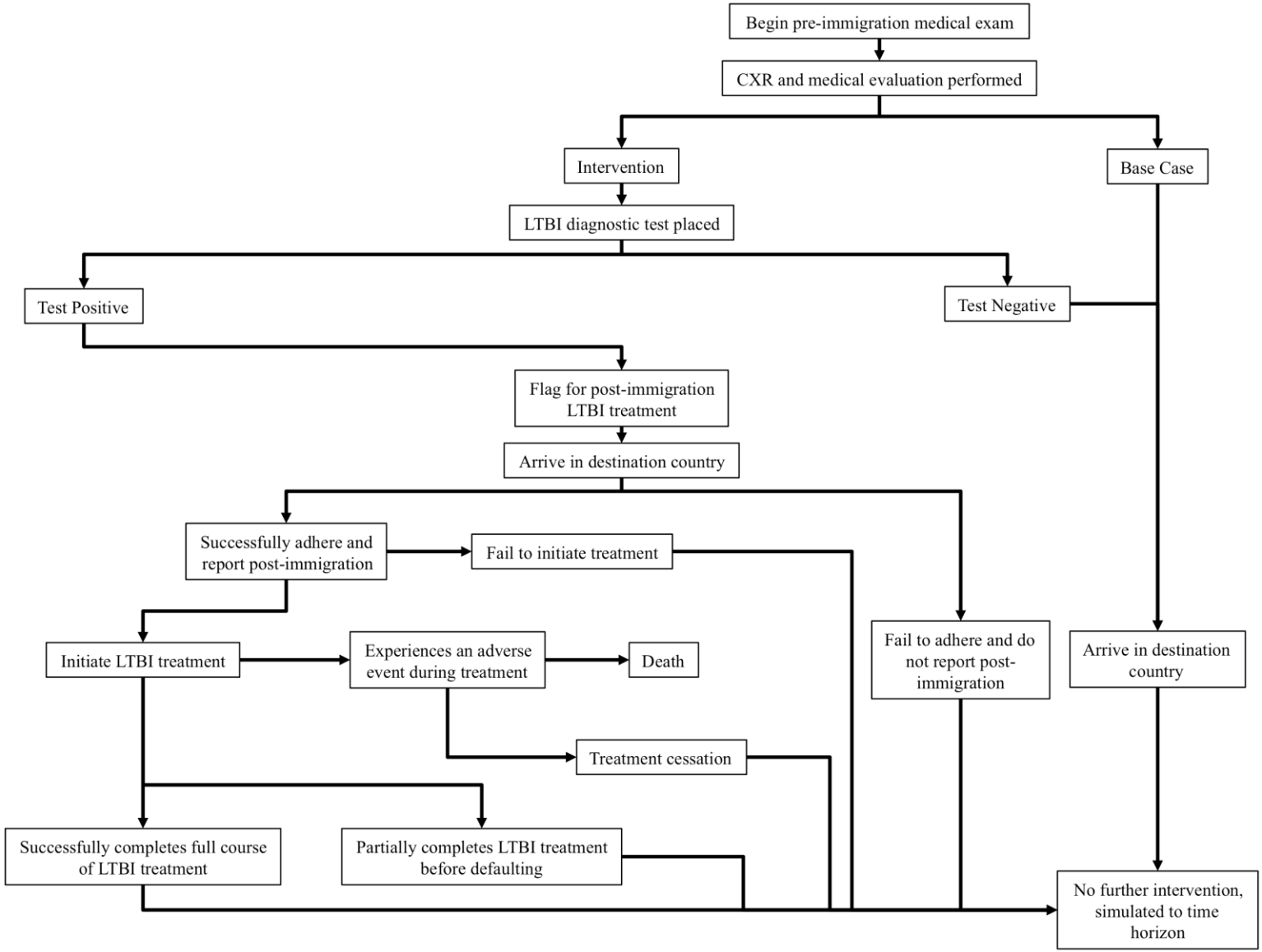


Figure 5-2. Meta-analysis of adherence with a request for post-arrival follow-up

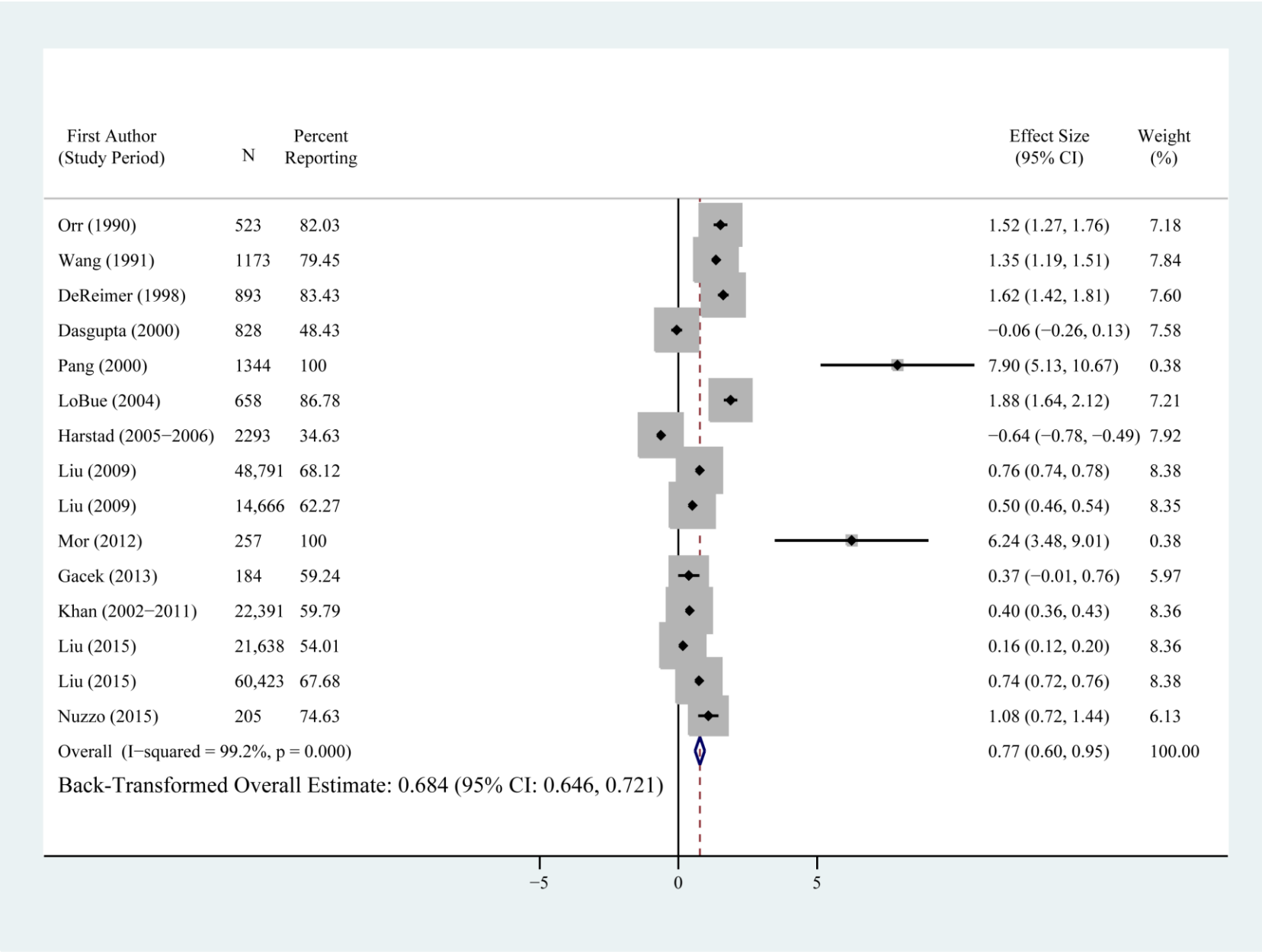


Figure 5-3. Cost-effectiveness acceptability curve in migrants from low TB incidence countries of the base case compared to the intervention that provided the largest incremental NMB. The graph demonstrates the probability an intervention is the most cost-effective option at various willingness-to-pay thresholds.

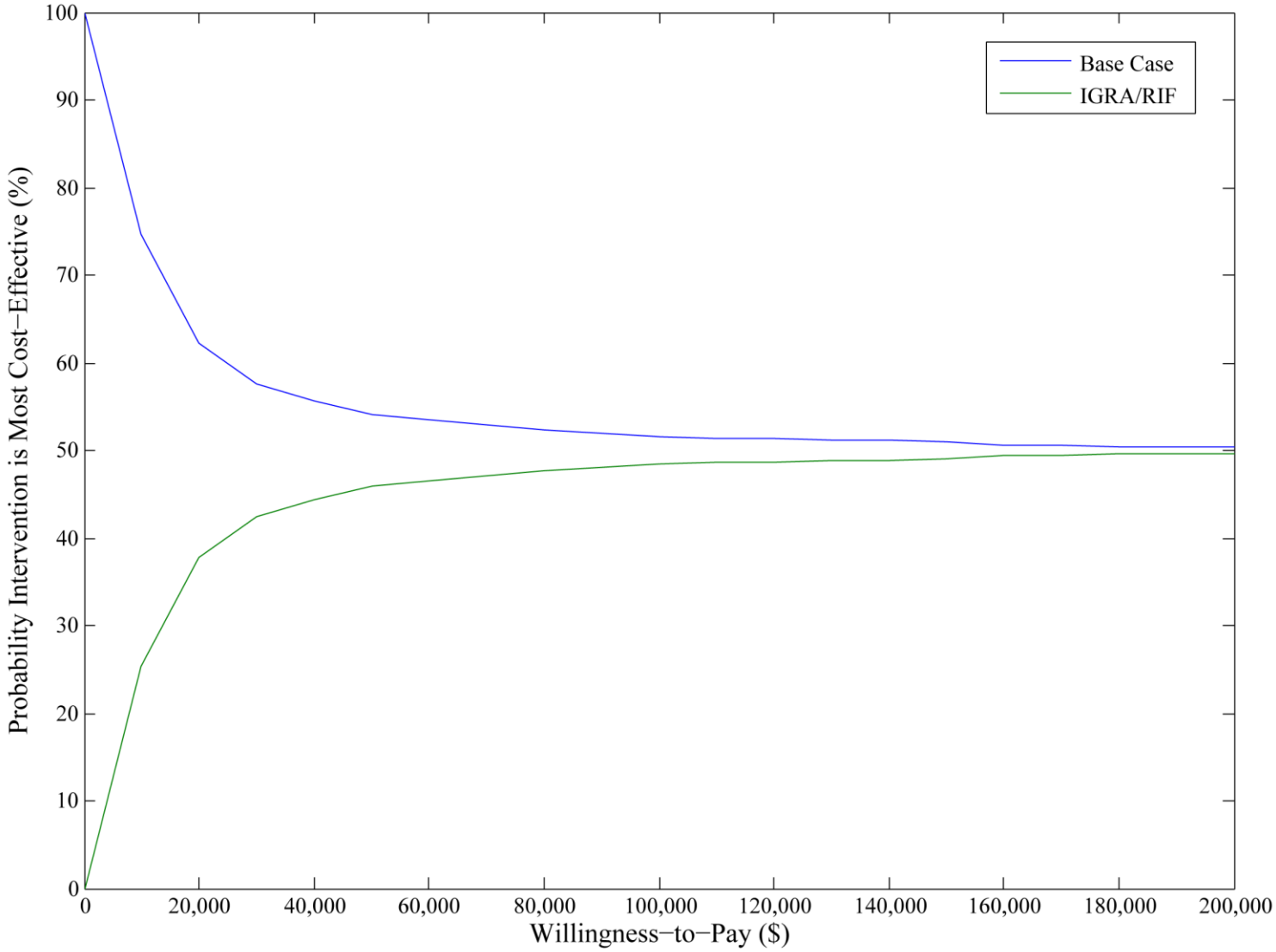


Figure 5-4. Efficiency frontier for migrants from low TB incidence countries in terms of population QALYs vs. population costs. The frontier is read from *left to right*, with interventions connected if they fall on the frontier.

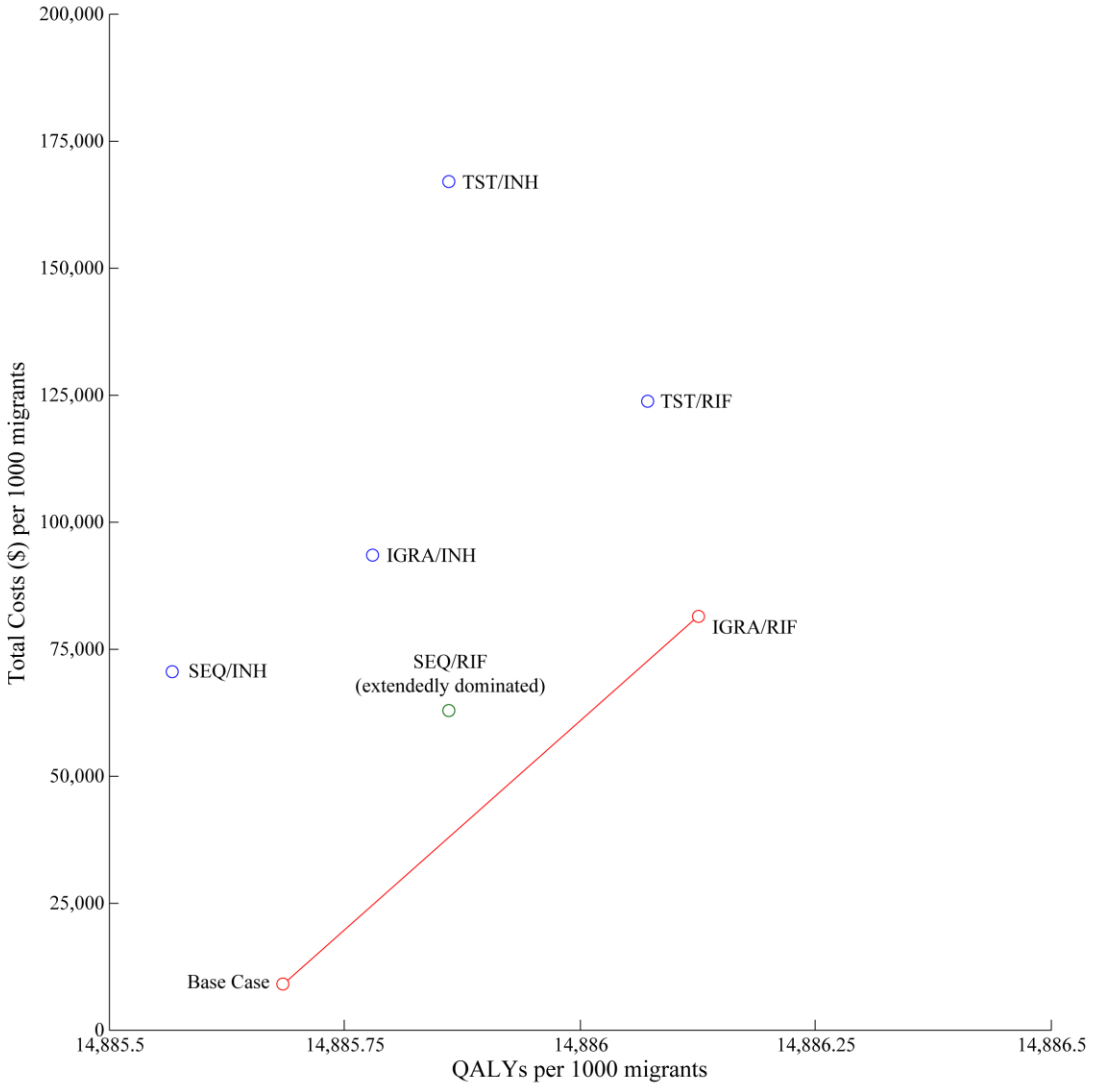


Figure 5-5. Cost-effectiveness acceptability curve in migrants from moderate TB incidence countries of the base case compared to the intervention that provided the largest incremental NMB. The graph demonstrates the probability an intervention is the most cost-effective option at various willingness-to-pay thresholds.

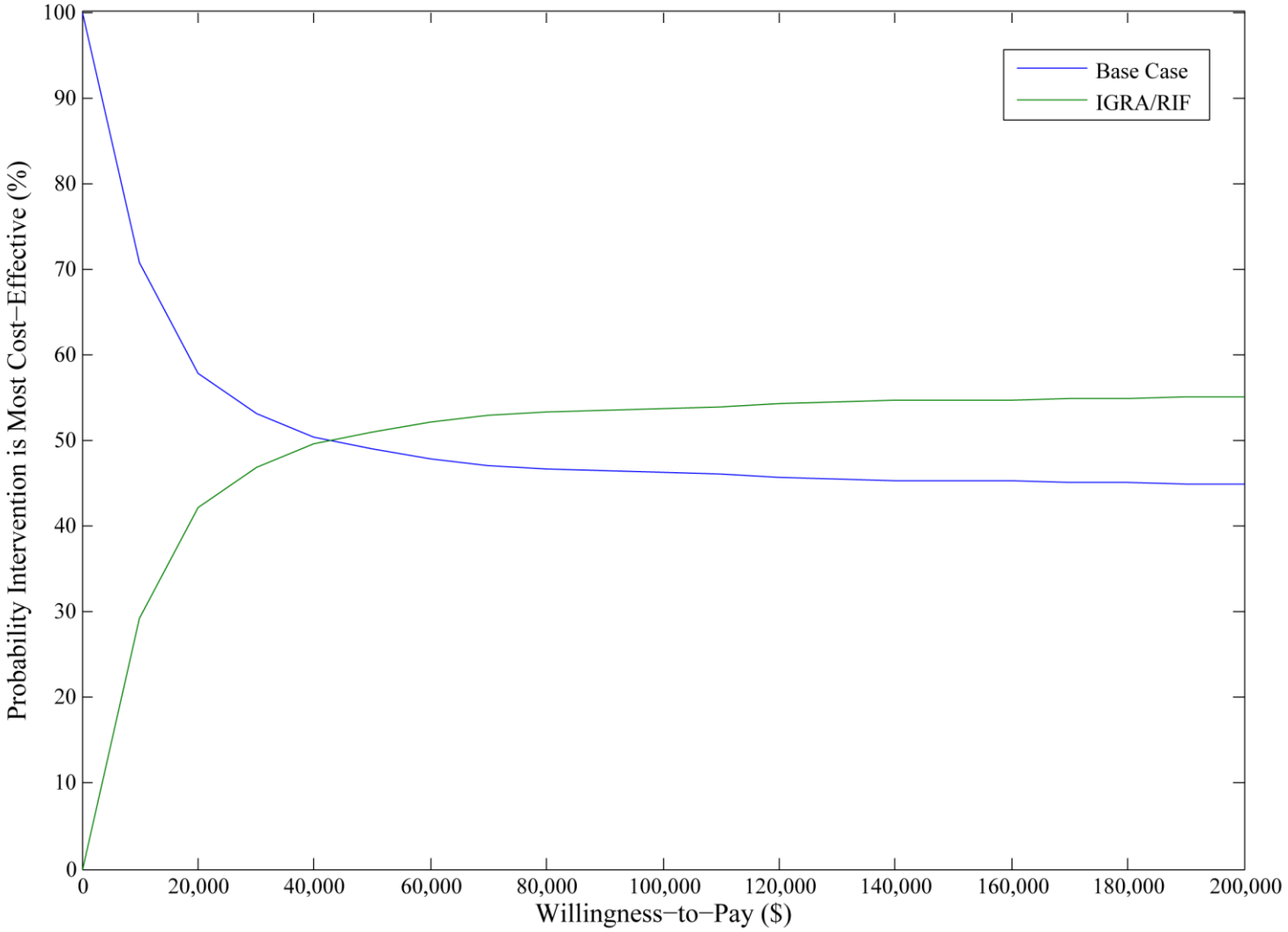


Figure 5-6. Efficiency frontier for migrants from moderate TB incidence countries in terms of population QALYs vs. population costs. The frontier is read from *left to right*, with interventions connected if they fall on the frontier.

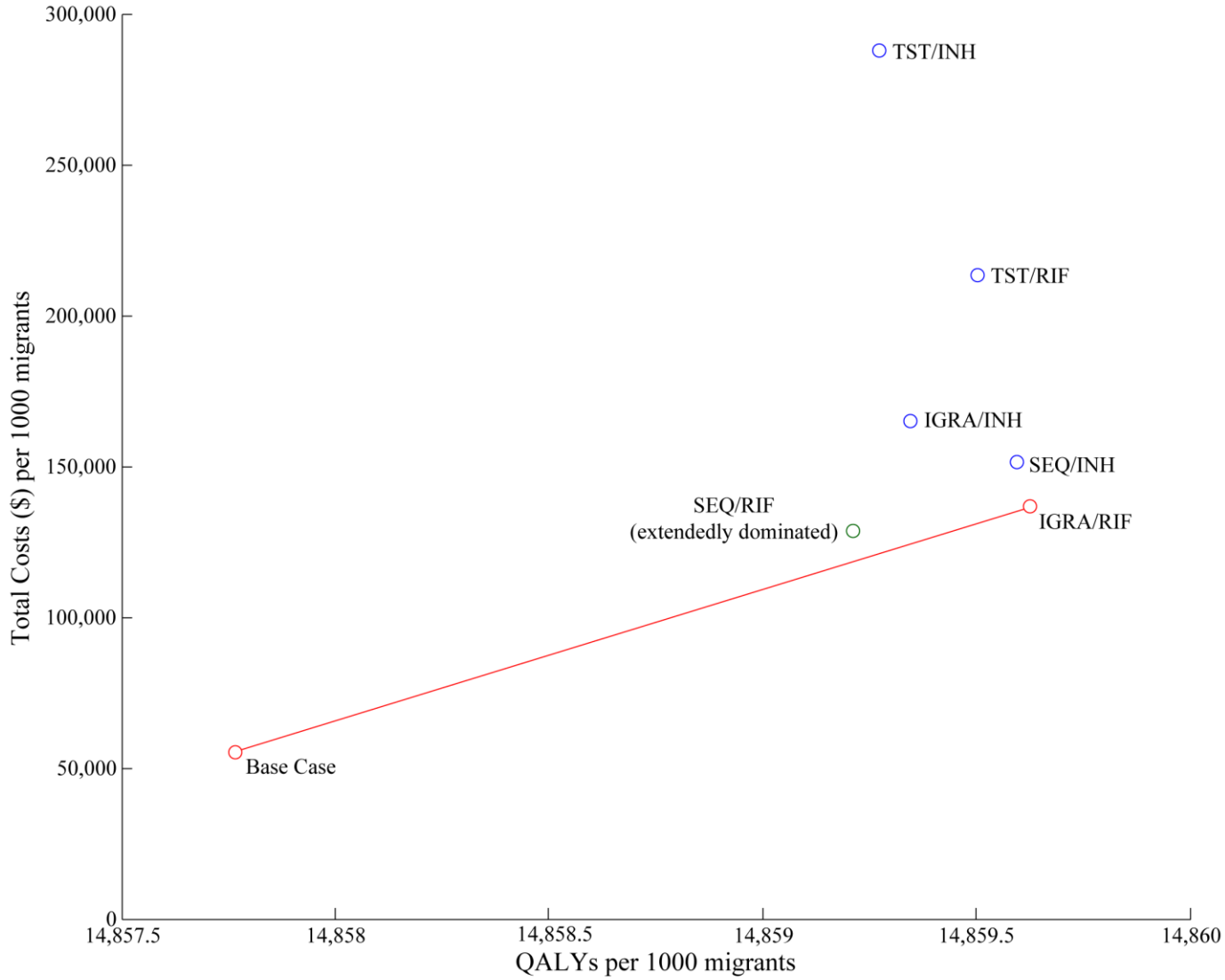


Figure 5-7. Cost-effectiveness acceptability curve in migrants from high TB incidence countries of the base case compared to the intervention that provided the largest incremental NMB. The graph demonstrates the probability an intervention is the most cost-effective option at various willingness-to-pay thresholds.

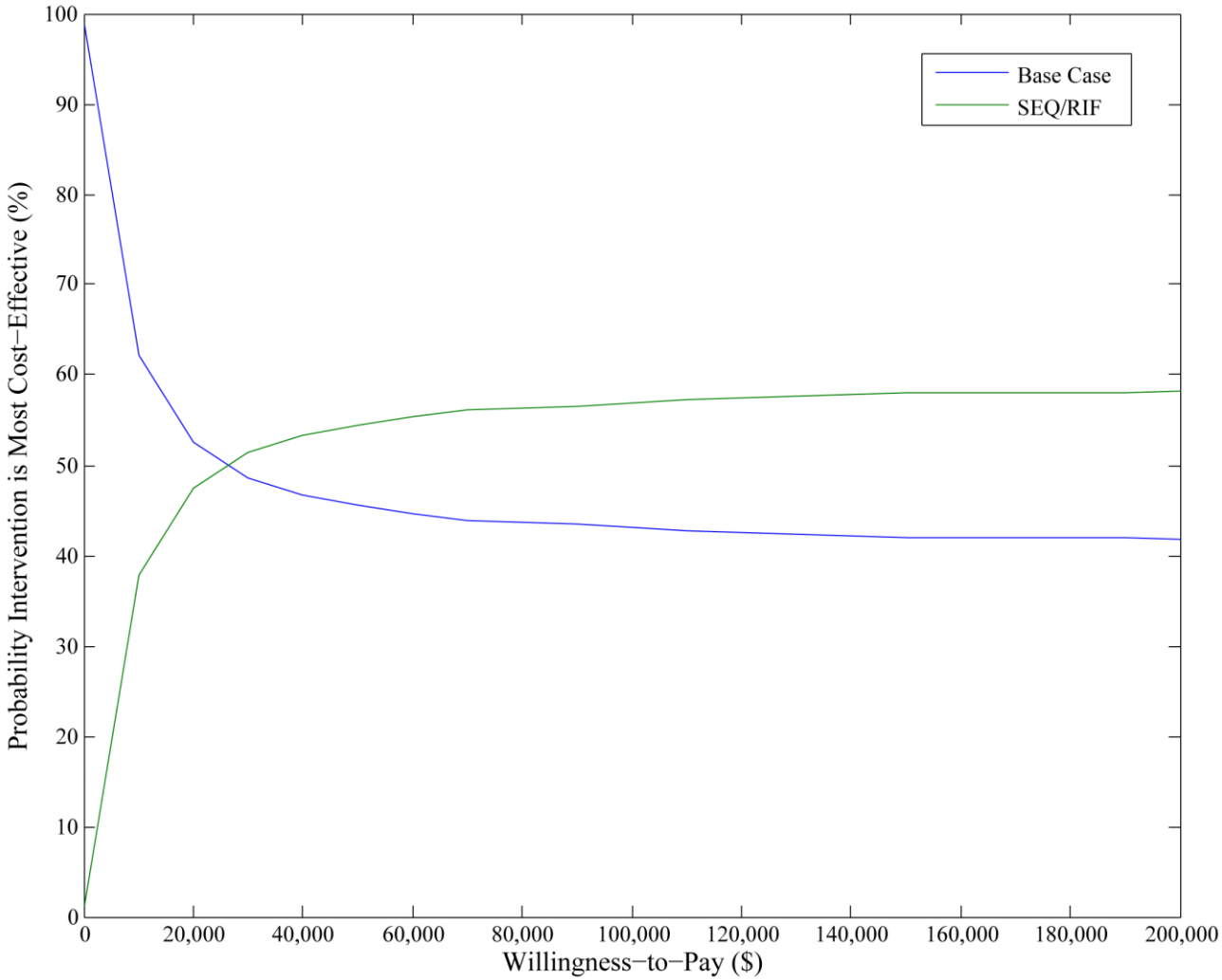


Figure 5-8. Efficiency frontier for migrants from high TB incidence countries in terms of population QALYs vs. population costs. The frontier is read from *left to right*, with interventions connected if they fall on the frontier.

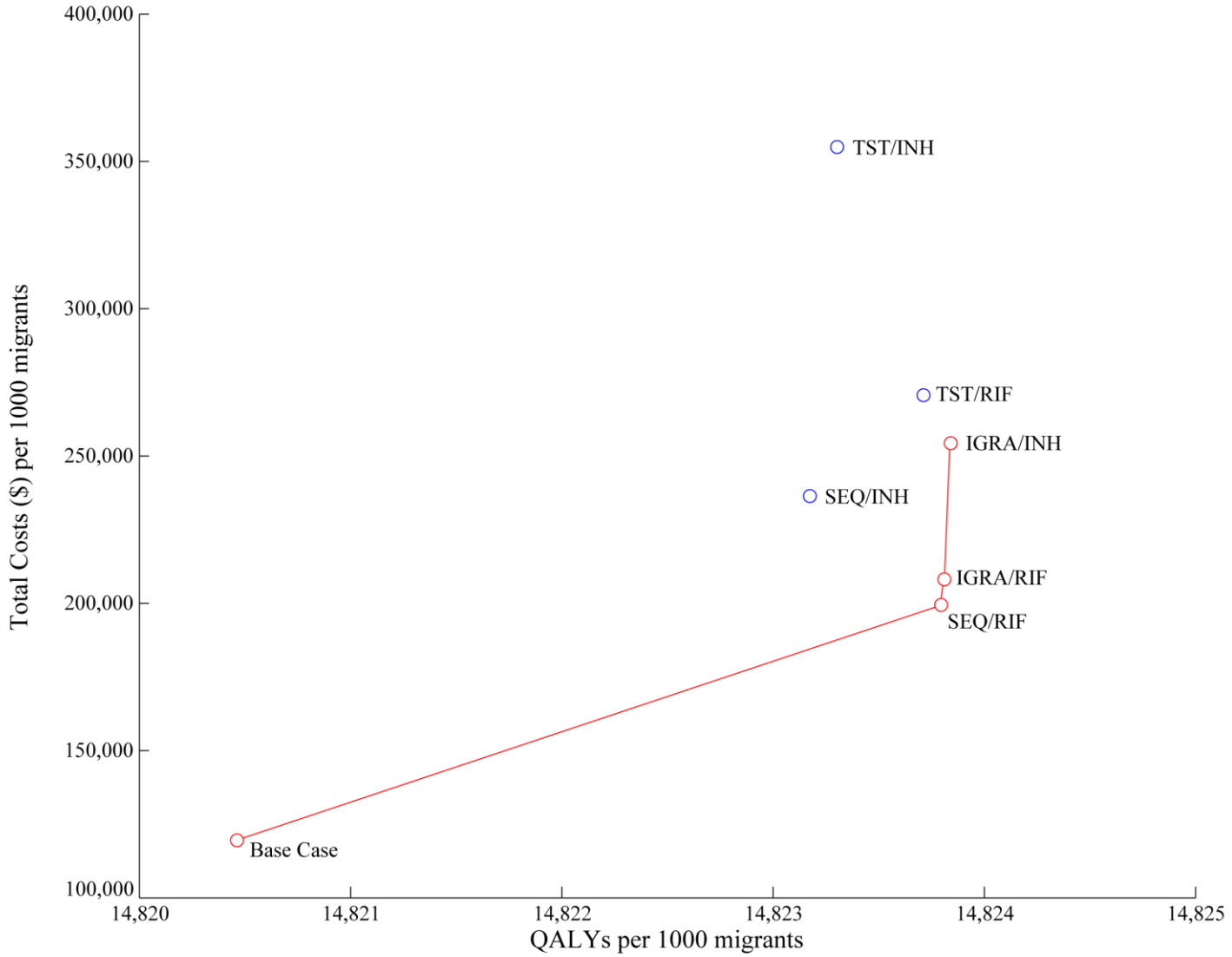


Figure 5-9. Cost-effectiveness acceptability curve in migrants from very high TB incidence countries of the base case compared to the intervention that provided the largest incremental NMB. The graph demonstrates the probability an intervention is the most cost-effective option at various willingness-to-pay thresholds.

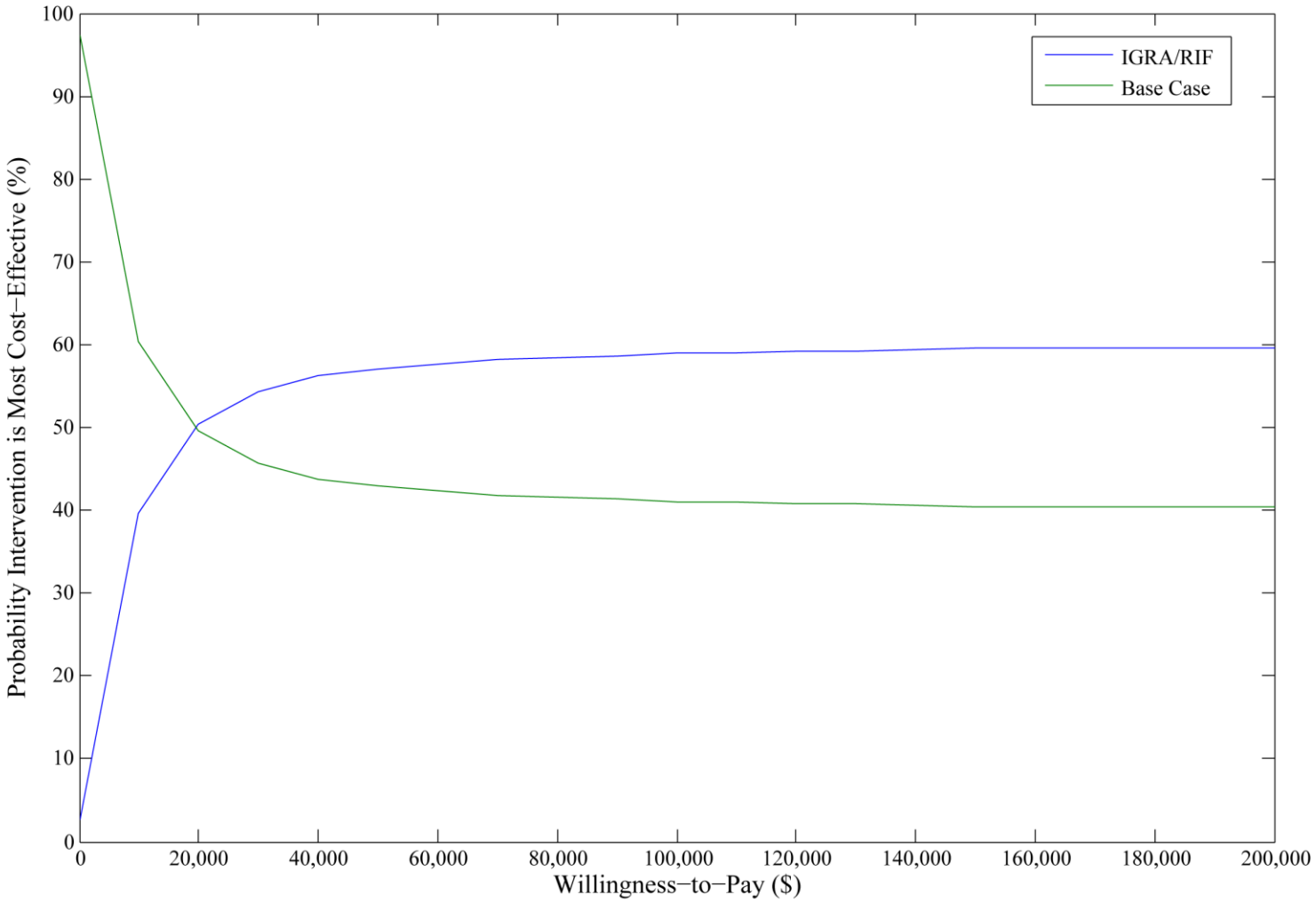
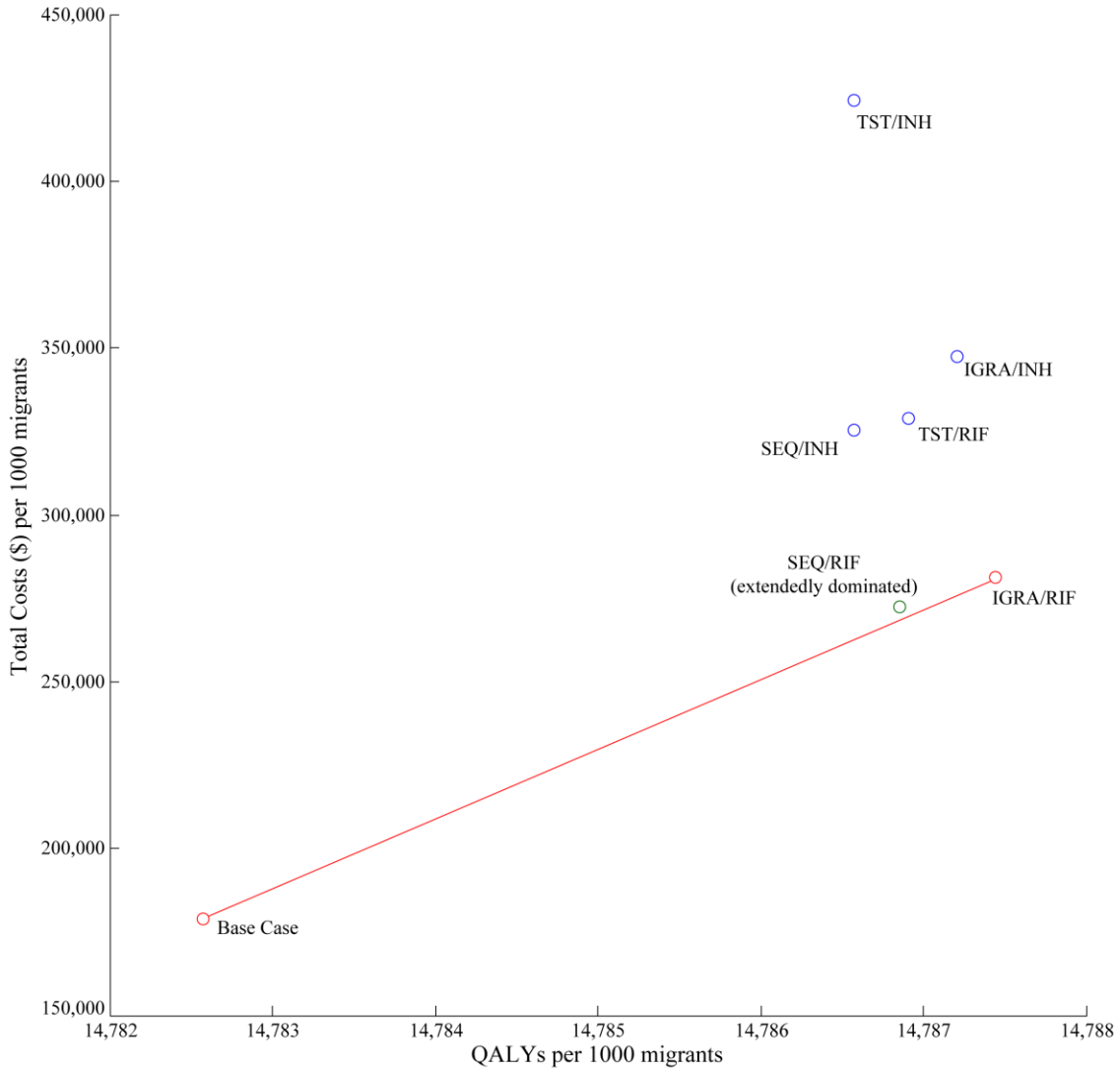


Figure 5-10. Efficiency frontier for migrants from very high TB incidence countries in terms of population QALYs vs. population costs. The frontier is read from *left to right*, with interventions connected if they fall on the frontier.



CHAPTER 6. SCREENING MIGRANTS WITH CHRONIC KIDNEY DISEASE FOR LATENT TUBERCULOSIS INFECTION: A COST-EFFECTIVENESS ANALYSIS

6.1 Background

Despite steady declines in TB incidence over the past decades, TB continues to be the leading cause of death due to infectious disease worldwide [61]. For many migrant-receiving, low TB incidence countries, the continuance of TB is driven, in part, due to undetected LTBI in migrants, which reactivates post-immigration [4,342]. In many of these countries, migrants account for more than half of the TB burden, yet routine LTBI screening is seldom employed [4,242]. Identification and effective treatment of LTBI has been shown to significantly reduce reactivation of TB [51]. While it has been demonstrated that mass LTBI screening and treatment is resource intensive [97] and as seen in Chapter 4, unlikely to be cost-effective, targeting screening to high LTBI prevalence populations at high risk of reactivation may prove both feasible and cost-effective.

WHO guidelines [164] and several health agencies including Canada, the United States, and the United Kingdom [3,346,368] have recommended targeting LTBI screening to individuals with co-morbidities that increase risk of TB. A consensus of these agency guidelines is to perform screening of individuals with CKD requiring dialysis. In this population, unadjusted rates of TB have been estimated to be up to 25-fold higher than the general population [3,134,234,369–371]. Furthermore, individuals with TB on dialysis experience mortality at significantly higher rates than the general population [372]. The drivers of these increases are uraemia-induced immune-deficiency, other co-morbid conditions that impact the immune system, and demographic factors such as age [139]. This state of impaired immunity presents a significant obstacle in diagnosing LTBI. Current diagnostic tests include the TST and IGRA, both of which rely on an adaptive immune response to TB antigens to give a positive result [373]. High rates of TST anergy [374–376] and indeterminate IGRA results [377–380] due to this immune-deficiency suggest many cases of LTBI are being missed in dialysis patients. It has been suggested that immune-deficiency in CKD patients becomes significant once estimated glomerular filtration rates (eGFR) fall below 30 to 60 ml/min per 1.73m^2 (i.e. stage 3 to stage 4 CKD) [381], but is not as severe as those with dialysis dependency. Implementation of routine LTBI screening in patients with late stage CKD (i.e. stage 4 or later) who are not yet

dialysis-dependent may still identify individuals at increased risk of TB and may likely better identify LTBI, overcoming test sensitivity shortcomings when performed at dialysis initiation.

Up to 16% of the world has CKD [139], with a significant burden in low TB incidence areas such as North America and Western Europe, and at least 2% of those with CKD require dialysis [382]. Evidence suggests that the global CKD burden will continue to increase over the coming decades, putting more individuals at increased risk of TB [383]. There is evidence to suggest that LTBI diagnostic tests can help predict risk of future TB in dialysis patients [384], yet minimal published data on the cost-effectiveness of LTBI screening in dialysis patients exists [133,218]. LTBI screening in the general population is not considered cost-effective [133]. However, focusing LTBI screening and treatment to migrants, who have a higher LTBI prevalence than the general population, may be cost-effective.

In this chapter, we use 29-years of longitudinal data of migrants to British Columbia (BC) [385] to evaluate the cost-effectiveness of LTBI screening in migrants who have been diagnosed with late stage CKD and migrants who have initiated dialysis. We stratify our analysis by age and TB incidence in the country of origin to determine which, if any, subgroup is cost-effective to screen for LTBI.

6.2 Methods

There is much uncertainty about TB risk in late stage CKD and dialysis patients. To determine this risk, individual patient data were analyzed to derive a risk prediction equation to inform key parameters for a cost-effectiveness analysis. The primary outcome of interest was active TB and, in the case of those with late stage CKD, the progression outcome was dialysis; death was also an outcome. Competing risks survival analysis was selected, as there was a high incidence of death that may affect regression parameters for our other outcomes of interest. In this analysis, we determined the adjusted risk for the outcome of interest of TB and the disease progression outcomes of death and, in the case of late stage CKD, dialysis. The cost-effectiveness analysis used these parameters, alongside values from the literature for other parameters, to determine the benefit of LTBI screening in migrants with late stage CKD or requiring dialysis.

6.2.1 Data Source

The data source spanned 1985 to 2013 inclusive, and has been described previously [385]. Briefly, we utilized a permanent data linkage between Population Data BC [386] and IRCC [387]. Population Data BC houses

individual-level, de-identified longitudinal patient data for all BC residents [386]. Included in this data are hospitalizations [388], physician visits [389], drug dispensations [390], demographics [391], and vital statistics [392]. In addition, Population Data BC links data from other sources, including the Provincial TB Registry [393], BC Provincial HIV/AIDS Surveillance Database [394], and the Patient Records and Outcome Management Information System (PROMIS) database [395]. The PROMIS database includes all patients referred to a nephrologist by their general practitioner and includes relevant data such as eGFR and dialysis utilization [395]. Data requested from IRCC included all foreign-born permanent residents who registered into the BC Medical Services Plan, the universal healthcare service in BC, during the study period, which specified, amongst others, dates of arrival and country of origin [387]. When linked, the data sources provide a comprehensive medical history of foreign-born permanent residents establishing residency in BC during the study period.

From this data source, individuals for this analysis were identified through three methods. Firstly, individuals registered in the PROMIS database (i.e. were referred to a nephrologist) that had a GFR estimate <30 mL/min per 1.73m^2 (i.e. at least stage 4 CKD) [396] or had a visit requiring dialysis (i.e. chronic or acute dialysis) were identified for inclusion. Secondly, individuals who had a physician billing code indicating dialysis were included. Thirdly, a validated method for identifying individuals with at least stage 4 CKD using administrative data was utilized [397]. In our dataset, this method identified 94% (3264 of 3472) of all individuals who were registered in the PROMIS database. Using these methods, individuals were included in our study cohort and their inclusion date was the earliest date of medical contact using any of these methods. Medical covariates of interest that may influence risk of TB were also identified. Diabetes was identified using a validated case definition from the literature [398]. HIV was identified using the BC Provincial HIV/AIDS Surveillance Database, hospital discharge records, and physician billing codes [399]. Medical immune-suppression was identified through drug dispensation and has been described previously [385]. For simplicity, HIV and medical immune-suppression were pooled. Billing codes utilized are included in **Table 6-1**.

Using this dataset, two cohort designations were created: late stage CKD (i.e. at least stage 4 CKD not requiring dialysis) and dialysis. Those who did not have dialysis as their earliest event or did not have dialysis begin within 30 days of identification were classified as late stage CKD. Individuals were classified as dialysis (both peritoneal and hemodialysis) if they ever had a dialysis date according to our data linkage (i.e. cohorts were not mutually exclusive). We excluded individuals for the following reasons: previous LTBI screening, previous LTBI

treatment, previous active TB diagnosis, and transplantation occurring prior to or <30 days after identification. These exclusions were imposed, as these individuals would likely have different management and TB risk compared to individuals without this history. A total of 6.6% of individuals classified as late stage CKD (858 of 13,016) and 11.2% classified as dialysis (201 of 1788) were excluded due to these reasons. This left a total of 12,158 and 1587 individuals who were in the late stage CKD and dialysis cohorts, respectively. **Table 6-2** displays the characteristics of the two cohorts.

6.2.2 Controlling for Tuberculosis Incidence in Country of Origin

The TB incidence in migrants originating from elevated TB incidence countries was significantly higher than those from lower TB incidence countries due to the difference in LTBI prevalence between these settings. In migrants with late stage CKD, the five-year cumulative incidence of TB in migrants from countries <100 cases per 100,000 was 0.3% and was 0.8% in migrants from countries ≥100 cases per 100,000. To fix this disparity in incident TB cases between migrants originating from countries of different TB incidences, we controlled for TB incidence by assigning an LTBI status variable by using estimated LTBI prevalence, based on IGRA positivity, from Chapter 3 [21]. To complete this, we assumed that all TB arose from LTBI (i.e. all incident TB cases in our data set were forced to have LTBI) and randomly assigned LTBI to the remaining population based on LTBI prevalence estimates. This removed the need to control for TB incidence in survival analysis. After assigning LTBI, only migrants with LTBI were at risk of TB. This resulted in the five-year cumulative incidence of TB in those with LTBI being 2.8% in migrants from countries with <100 cases per 100,000 and 2.9% in migrants from countries ≥100 cases per 100,000. This demonstrated that this method effectively controlled for TB incidence in country of origin.

6.2.3 Survival Analysis

From inclusion in the study cohort, individuals were followed until death or censoring at five years. If an individual received a transplant during follow-up, this was treated as a censoring event. The outcome of interest was TB, and, in the case of late stage CKD, the progression outcome was dialysis initiation. In this analysis we adjusted for age (<60 years or ≥60 years), diabetes at time of diagnosis (yes or no), and HIV and/or medical immune-suppression at time of diagnosis (yes or no), as these covariates affect risk of reactivation [96,400]. It was observed that the rates of the events of death and TB were much higher in the immediate 3 months after inclusion in the study

cohorts, likely due to co-prevalent TB and other health-related factors. To account for this, regression coefficients for the survival analysis for these events were subdivided into two time periods and calculated separately: months 0-3 and months 4-60. The Fine-Gray method of competing risks analysis was utilized to determine the effects of our selected covariates on outcomes of TB, death, and dialysis initiation [401]. This method creates a survival regression model employing the cumulative incidence function and sub-distribution hazard functions. Covariate coefficients are estimated using a weighted partial-likelihood function, similar to Cox proportional hazards [401]. Covariate coefficients, termed sub-distribution hazard ratios (SHR), show a direct effect in direction on the cumulative incidence of the desired outcome, but the impact is not proportional (i.e. a SHR of two does not mean this covariate increases cumulative incidence two-fold). Instead the resulting coefficients have a direct impact on the *rate* of the desired outcome, making them ideal for prognostic means, such as in economic analyses using time-to-event parameters. Results of the survival analysis are displayed in **Table 6-3**.

From our two time periods modeled, incidence of events of interest appeared to follow an exponential distribution (**Figure 6-1** and **Figure 6-2**). Two methods were utilized to determine the optimal exponential rate parameter for the two time periods. In the first method, maximum likelihood estimation (MLE) [402], which selects parameters that maximize the likelihood of the distribution fitting the observed data, was used on the baseline survival function estimated in competing risks analysis. In the second method, observed cumulative incidences of events in our dataset were used to estimate the mean time-to-event. The second method predicted observed outcomes significantly better (**Table 6-4**).

Survival analysis was completed using R (version 3.3.2) packages survival (version 2.40-1) and MASS (version 7.3-45).

6.2.4 Cost-Effectiveness Model

6.2.4.1 Overview

A DES model was developed using Simio (version 8.146.14121; Simio LLC, Sewickley, PA) and run using Simio Replication Runner. The model was examined for both internal validity (functioned as intended) and external validity to the data source used to inform it. DES was selected in order to accommodate modeling of multiple competing events in a time-to-event framework [193]. A key component of this framework is that simulated individuals are at consistent risk for possible events (e.g. for those with LTBI and late stage CKD, individuals were

at risk for TB, death, and dialysis initiation) allowing for realistic risk modeling. In this model framework, times to possible events are sampled from relevant distributions and the earliest time sampled is simulated to occur first. Once this event occurs, new times to possible events are sampled. This process occurs until death or the end of the simulation. The model took a healthcare system perspective, used a 1.5% discount rate according to CADTH guidelines [190], and had a five-year time horizon to limit extrapolation from the average follow-up duration of the data source. The main outcomes of the model were number of TB cases, number of population QALYs, and costs (in 2016 CAD). Using the model output, the reduction in overall TB incidence, the ICER for the outcome of cost per QALY gained, and the incremental NMB per person for the QALY outcome were calculated. A willingness-to-pay threshold of $100,000 per QALY gained was used to determine if an intervention was cost-effective [189,324,325,350].

Using the results of our time-to-event analysis, we examined implementing LTBI screening at two times: (1) time of dialysis initiation and (2) time of late stage CKD diagnosis (i.e. healthcare system contact with stage 4 or 5 CKD not requiring dialysis). The base case in our model was to not screen or treat for LTBI at these times. It was assumed that all individuals accepted the screening intervention when offered, but did not necessarily complete it. Two screening strategies were evaluated: the TST utilizing a 10mm cut-point for a positive test and the IGRA where a positive test was based on the manufacturer's recommendation. It was assumed no individuals had active TB at time of LTBI screening, however all individuals were simulated to receive a CXR as is standard clinical practice. Those testing positive for LTBI were recommended treatment with isoniazid. Rifampin treatment was not considered as a treatment in this chapter due to the risk of drug interactions [403,404], as patients with late stage CKD tend to have several co-morbid conditions [405,406]; this resulted in sparse data on adverse events and completion rates for rifampin in our data source and in the literature. Those who initiated treatment may complete treatment, partially complete treatment, or experience an adverse event that may lead to hospitalization and/or death. It was assumed that there was no impact of LTBI treatment on TB risk before 3 months of treatment were completed; after three months of treatment, partial protection was granted. If an individual experienced TB, it was assumed that those who did not die during treatment successfully completed it. Individuals with late stage CKD who initiate dialysis prior to the time horizon were simulated with relevant time-to-event rates reflected in **Table 6-3**. A simplified model structure is shown in **Figure 6-3**.

Analysis of model output was stratified by age <60 years and ≥60 years and TB incidence in country of origin stratified in four groups: (1) low, <30 cases per 100,000 population; (2) moderate, ≥30 and <100 cases per 100,000 persons per year; (3) high, ≥100 and <200 cases per 100,000 persons per year; (4) very high, ≥200 cases per 100,000 persons per year. Prevalence of risk modifying co-morbidities, diabetes and HIV and/or medical immune-suppression, in each analysis subgroup was based on their relevant distributions in the data source. Characteristics of the sixteen included subgroups can be found in **Table 6-5**. A minimum of 1000 replications of 100,000 individuals in each subgroup was performed.

6.2.4.2 Parameters

All parameters are listed in **Table 6-6**.

The BCCDC provided LTBI diagnostic costs, LTBI treatment costs, and active TB treatment costs (personal communication). Costs for LTBI adverse events and hospitalization were derived from the literature [119,330]. TB contact tracing costs were calculated based on the costs of contact investigations in Canada reported previously [221]. Hospitalization costs for TB were from the Canadian Institute for Health Information based on the average cost of being hospitalized for TB in BC [407].

Quality of life estimates for late stage CKD and dialysis were based on reported SF-6D values from the literature [408,409]. Adjustments for TB [331,332,410], adverse events [119,330], and hospitalization [119] were imputed based on relative impacts in relevant studies.

Completion of LTBI screening and medical evaluation came from a meta-analysis of the LTBI cascade of care [53]. LTBI diagnostic test sensitivity in dialysis was pooled from several studies evaluating diagnostic test results in patients with dialysis who had active TB or previous TB [411–416]. Diagnostic test sensitivity in late stage CKD was assumed to be the average of test sensitivity calculated in Chapter 2 and our calculated estimates for dialysis [20]. Diagnostic test specificity was derived from the literature and assumed not to change in the presence of late stage CKD or dialysis [24,34]. IGRA indeterminate rates were derived from our data source.

Initiation and completion of LTBI treatment was based on a study of end stage kidney disease patients in BC [417]. Adverse event and treatment completion rates were assumed to be equal in dialysis and late stage CKD patients and derived from our data source. Treatment effectiveness was derived from reported literature values [51]. All TB related parameters were derived from our data source.

Estimates of BCG vaccination rates were based on reported BCG vaccination schedule in the BCG World Atlas [224] and vaccine coverage was based on the average coverage rate in the preceding 36-years [316]. LTBI prevalence was based on IGRA positivity prevalence reported in Chapter 3 [21].

6.2.5 Sensitivity Analysis

Relevant probabilistic distributions were created to model parameter uncertainty. Where costs were known to fall within well-defined ranges, triangular distributions were used; in all other situations gamma distributions were used. Beta distributions were used to model probabilities. When individual data was available, relevant distributions were fit using MLE or the variance-covariance matrix of the regression coefficients [402]. Expert opinion was used when uncertainty was unknown. In the PSA we relaxed the assumption that all individuals accept screening, instead opting to reflect empirical data on screening acceptance [101]. PSA was carried out for a minimum of 2000 replications on 100,000 individuals in each subgroup. PSA results were interpreted using the average results and by constructing CEACs for each of the subgroups examined. CEACs were constructed on the basis that an intervention provided the largest NMB compared to competing interventions.

Exploratory sensitivity analyses were performed to determine the impact of select assumptions. These exploratory analyses include: reducing sensitivity and increasing indeterminate rate in late stage CKD to values used in dialysis, reducing the average cost of hospitalization to the average cost of TB hospitalization in Canada ($12,055) [407], reducing the risk of mortality after TB diagnosis (6%) [133], halving the rate of TB, exploring the impact of having a proportion of individuals refuse LTBI screening (23.3%) [101], making the cost of IGRA identical to that of TST, and increasing the discount rate to 3%. Exploratory analyses were run for 1000 replications on 100,000 individuals in each subgroup.

6.3 Results

6.3.1 LTBI Screening at Dialysis Initiation

No LTBI screening was cost-effective in migrants from low TB incidence countries (**Table 6-7**). LTBI screening with an IGRA or TST at time of dialysis initiation was highly cost-effective in migrants from moderate to very high incidence countries. In migrants who were <60 years of age, IGRA screening was dominant, while TST screening resulted in ICERs of $79,014, $59,431, and $13,096 per QALY gained in moderate, high, and very high incidence countries, respectively, compared to no screening. TST screening reduced TB incidence 19% while IGRA

reduced TB incidence 27%. In migrants ≥60 years of age, IGRA screening was still dominant and TST screening in migrants from moderate ($71,105 per QALY gained), high ($48,104 per QALY gained), and very high ($60 per QALY gained) incidence countries was also cost-effective compared to no screening. TB incidence declines were more significant in migrants ≥60 years of age, with declines in TB incidence of 23% and 33% when screening with the TST and IGRA, respectively. IGRA screening was preferred to TST screening, providing more QALYs and preventing more TB cases on average, while being significantly less expensive.

6.3.2 LTBI Screening at Late Stage CKD Diagnosis

Screening in this subgroup with an IGRA or TST reduced five-year TB incidence approximately 24% and 18%, respectively. LTBI screening remained cost-prohibitive in migrants from low TB incidence countries when applied at late stage CKD diagnosis, however in moderate to very high incidence countries, cost-effectiveness of screening varied based on age (**Table 6-8**).

In migrants <60 years of age, IGRA screening was not cost-effective in individuals from moderate ($129,953 per QALY gained) and high ($110,118 per QALY gained) incidence countries, however was cost-effective in individuals from very high incidence countries with an ICER of $86,715 per QALY gained. TST screening was not cost-effective in migrants <60 years of age, regardless of TB incidence in country of origin.

Screening migrants ≥60 years of age was significantly more cost-effective. IGRA screening was cost-effective in migrants from moderate, high, and very high TB incidence countries with ICERs of $47,554, $42,846, and $26,935, respectively. TST screening was only cost-effective in migrants from very high incidence countries ($54,257 per QALY gained), as screening migrants from moderate and high incidence countries resulted in ICERs of $122,982 and $102,141, respectively.

6.3.3 Probabilistic Sensitivity Analysis

6.3.3.1 Dialysis Initiation

Average results of the PSA are found in **Table 6-9**. The average decline in TB incidence as a result of LTBI screening was reduced approximately 50% during PSA and IGRA screening was no longer dominant in moderate and high TB incidence countries, but was still very cost-effective when considering uncertainty in screening acceptability. Screening at dialysis initiation was unlikely to be cost-effective in migrants from low TB incidence countries (<50% at a WTP threshold of $200,000 per QALY). Alternatively, IGRA screening at a WTP

threshold of $50,000 had probabilities of yielding the largest NMB of 75.9%, 78.0%, and 90% in migrants <60 years of age from moderate, high, and very high incidence countries, respectively **(Figure 6-4)**. In migrants ≥60 years of age at this threshold, probabilities were 79.0%, 83.8%, and 95.5%, respectively **(Figure 6-5)**.

6.3.3.2 Late Stage CKD Diagnosis

Table 6-10 displays the average results of the PSA. Similar to the results at dialysis initiation, TB declines were significantly reduced during PSA when considering uncertainty in screening acceptability. The ICER for IGRA screening in migrants <60 years of age from very high TB incidence countries was slightly above the WTP threshold ($100,970 per QALY gained), however this was the only decision to change during PSA. LTBI screening was unlikely to be cost-effective in migrants from low incidence countries and unlikely to be cost-effective in migrants from <60 years of age at a WTP threshold of $100,000 per QALY (**Figure 6-6**). In migrants ≥60 years of age IGRA screening was very likely to provide the largest NMB at a WTP threshold of $100,000 per QALY. IGRA screening had a probability of 57.9%, 60.2%, and 73.9% in migrants from moderate, high, and very high incidence countries, respectively, at this threshold (**Figure 6-7**).

6.3.4 Exploratory Sensitivity Analyses

The impact of changes examined in the exploratory sensitivity analysis for LTBI screening at dialysis initiation (**Table 6-11**) and at late stage CKD diagnosis (**Table 6-12**) were similar. Few of our estimates and assumptions had significant impact on the cost per QALY gained seen in our base analysis. Costs of TB hospitalization, discount rate, and LTBI screening acceptance had minimal impact on the cost per QALY gained when LTBI screening was performed at late stage CKD diagnosis and at dialysis initiation. Assuming diagnostic performance of the TST and IGRA was the same when performed at late stage CKD diagnosis as when performed at dialysis initiation increased ICERs slightly, but did not change any decisions from our base analysis. Assuming significantly fewer people died of TB when on dialysis increased ICERs, but would not change any funding decisions.

Halving the TB rate used in this analysis had significant impacts on overall ICERs when LTBI screening was done at late stage CKD diagnosis, with only IGRA screening being cost-effective in migrants ≥60 years of age from very high TB incidence countries. When this was considered in the context of LTBI screening at dialysis

initiation, IGRA screening was no longer dominant over the base case, but still cost-effective in migrants of any age from moderate to very high incidence countries.

Assuming the IGRA cost was identical to the TST reduced ICERs and resulted in IGRA screening being cost-effective when performed at late stage CKD diagnosis in migrants <60 years of age from high TB incidence countries, however this was the only decision to differ from our base case.

6.4 Discussion

The results of our analysis demonstrate that LTBI screening with an IGRA in migrants from moderate to very high TB incidence countries initiating dialysis is very cost-effective. The decision to perform LTBI screening in migrants diagnosed with late stage CKD is more complicated. Screening was only cost-effective in migrants <60 years of age from very high TB incidence countries and migrants ≥60 years of age from moderate to very high TB incidence countries. In low LTBI prevalence migrant populations, LTBI screening is not cost-effective in either group. Regardless of population, however, IGRA screening consistently dominated TST screening, with lower overall costs, fewer longitudinal TB cases, and greater gain in QALYs.

Our exploratory analysis indicates that reducing our TB rate estimate impacts ICERs and affects screening decisions in late stage CKD patients, with only migrants ≥60 years of age from very high TB incidence countries being cost-effective to screen in this scenario; no impact on decisions was seen when LTBI screening was performed upon dialysis initiation. No other scenario analyzed in our exploratory analysis had significant impact on funding decisions. PSA indicated the impact of LTBI screening on longitudinal TB incidence may be overestimated in deterministic analysis and interventions may not be as cost-effective. This is further emphasized when evaluating CEACs, which suggest no screening may in fact be preferred to IGRA screening at a WTP threshold of $100,000 per QALY in all late stage CKD populations <60 years of age.

Our study reaffirms current guidelines from several health agencies [3,346,368] on LTBI screening in new dialysis patients, however it calls into question the cost-effectiveness of doing so in low LTBI prevalence populations. The results of this chapter further suggest that certain migrants with late stage CKD should be screened for LTBI, but this represents a significantly larger population to screen than simply migrants requiring dialysis and feasibility may be brought into question. While migrant populations are at higher risk for CKD than locally-born populations [228], careful consideration for LTBI screening is necessary as the healthcare resources used for this

purpose may provide better value if used elsewhere. With limited resources for TB prevention, it is important to target LTBI screening so as to maximize returns on investment. This however must be balanced with the potential advantages of simplified screening recommendations to ensure uptake of policy.

A growing proportion of the world is developing CKD, potentially leading to increased TB rates in at-risk populations affected by this trend. A major reason for this is the worldwide diabetes epidemic, which impacted 415 million people in 2015 and is predicted to impact 642 million by 2040 [418]. Diabetes is the number one risk factor for CKD, with 80% of late stage CKD caused by diabetes or hypertension [419]. This is further supported by the high diabetes prevalence seen in our late stage CKD and dialysis cohorts. The best course of action to avert TB-related morbidity and mortality in CKD patients is to prevent upstream risk factors for CKD, which will include a key focus on preventing and appropriately managing diabetes.

Reported rates of TB in late stage CKD and dialysis populations vary greatly in the literature. An Australia wide study [235] examining the incidence of TB in those on dialysis saw rates of TB in dialysis populations over 11-times higher than rates in the general population. In comparison to our study, our rates were nearly 30 times higher than the general population, likely due to our population being strictly done in migrants who have a higher prevalence of LTBI. Despite this, overall incidence in migrants from elevated TB incidences was similar, with a longitudinal incidence of 1.8% compared to 2.0% incidence seen in our study and our data is consistent with previously reported rates in British Columbia [420]. In a study completed in India by Venkata *et al*. [138], an incidence of 4.0% was seen in patients with late stage CKD that may require maintenance dialysis. The heterogeneity seen in TB risk in these populations may be due to differences in TB prevention efforts in these jurisdictions and differences in epidemiologic drivers of TB in these populations.

This is the first comprehensive study of LTBI screening and treatment in CKD populations with an increased LTBI prevalence. Our study has several strengths. We applied appropriate competing risks methodology to determine the influence of various risk factors on progression to various health states in individuals with late stage CKD or requiring dialysis. We used patient level data to populate relevant parameters in our model, which significantly limits extrapolation and uncertainty in our estimates. We determined costs based on real healthcare utilization data to determine the burden of TB in these populations on healthcare systems. Finally, we comprehensively analyzed several heterogeneous subgroups to aid in policy-making decisions.

Two cost-effectiveness analyses have been performed that previously examined LTBI screening in hemodialysis patients. The first study completed by Kowada [218] was performed in a theoretical hemodialysis population with a LTBI prevalence of 40%, but failed to examine a base scenario where no LTBI screening was performed. The result of the analysis did indicate similar findings in that IGRA screening dominated TST screening. The second study completed by Linas and colleagues [133] examined LTBI screening in several at-risk populations, including a low LTBI prevalence end stage renal disease population from the United States with a reactivation rate of 1.85 per 1000 person years. In this study it was found that IGRA screening and TST screening had a cost of $1,240,725 and $872,612 per QALY gained, respectively (2016 CAD). These ICERs are significantly higher than those seen in our study, which may be due to background mortality rate assumptions, low risk of death due to TB, diagnostic test performance, and costs associated with TB. We examined adjusting the risk of death due to TB in our exploratory analysis, however this did not explain the difference.

This chapter has limitations in generalizability and referral bias, however where possible, sensitivity analysis was performed to determine their impact. Firstly, this study is based on migrant populations in BC, which may have different epidemiological characteristics than migrant populations in other parts of Canada and the world. Furthermore, for individuals to be listed in PROMIS, they must first be referred to a nephrologist. This suggests a certain proportion of our study population may not reflect the “average” CKD patient, as these individuals may in fact be sicker with a higher co-morbidity burden. Costs for this study were BC-specific and Canadian data indicates that lengths and costs of TB hospitalizations in BC are amongst the highest in Canada, which can skew our results to favoring intervention. Many of the TB cases from our data source occurred soon after late stage CKD diagnosis or dialysis initiation, implying that many TB cases were simultaneously diagnosed; this may limit the number of preventable TB cases longer-term. We attempted to account for this by allowing migrants to be continually at risk of TB during LTBI treatment and not granting treatment benefit until 3 months of treatment were completed. Finally, economic modeling requires careful balance of complexity and simplicity. We accounted for several risk-modifying covariates, however there are several more that could potentially influence longitudinal TB risk, such as abnormal CXR, socioeconomic status, and immigration class. We believe our choices in covariates maximize generalizability to the clinic, while maintaining the level of detail required for a representative model.

6.5 Conclusions

IGRA screening in migrants from moderate to very high TB incidence countries of all ages at time of dialysis initiation and in migrants ≥60 years of age who have late stage CKD is very cost-effective. Healthcare agencies should consider LTBI screening policies for elderly migrant populations with late stage CKD that originate from countries of elevated TB incidence, while reconsidering policies dictating LTBI screening in low LTBI prevalence populations initiating dialysis.

6.6 Tables

Table 6-1. Billing codes to identify individuals with late stage CKD and dialysis not indexed in PROMIS

Classification Type	Record Source and Method	Billing Codes
Late Stage CKD	DAD and MSP. Two DAD records within three years or two MSP billing records within three years.	ICD-9: 584, 585, 586 ICD-10: N17, N18, N19
Dialysis	MSP. Two or more billing fee item codes separated by at least 90 days.	MSP Billing Fee Item Code: 323, 324, 350, 351, 352, 355, 356, 358, 359, 361, 7598, 7599, 33723, 33750, 33751, 33752, 33708, 33756, 33758, 33759, 33761, 77390, 77380
Diabetes	DAD and MSP. One DAD record or two or more MSP records within two years.	ICD-9: 250 ICD10: E10, E11, E12, E13, E14
HIV	DAD and MSP. One DAD record or two or more MSP records within two years.	ICD-9: 042, 043, 044 ICD-10: B20, B21, B22, B23, B24

DAD: Hospital discharge abstract database; MSP: Medical Services Plan physician billing; ICD: International Classification of Diseases; CKD: Chronic Kidney Disease; HIV: Human Immunodeficiency Virus

When a disease required two or more events to be identified, the earlier of the two events was considered diagnosis date.

Table 6-2. Characteristics of dataset used for calibration

Parameter	Late Stage CKD	Dialysis
N	12,158	1587
Total Follow-up Time (Years)	38,275	4597
Mean Follow-up Time in Years (SD)	3.15 (1.85)	2.90 (1.82)
Median Follow-up Time in Years (Q1-Q3)	3.61 (1.41-5.00)	2.92 (1.18-5.00)
Total TB Cases (%)	81 (0.67%)	32 (2.02%)
Mean Time to TB in Years (SD)	1.53 (1.58)	1.50 (1.33)
Median Time to TB in Years (Q1-Q3)	0.90 (0.08-2.97)	0.92 (0.41-2.58)
TB Rate per 1000 Person Years	2.12	7.08
Total Deaths (%)	2639 (21.7%)	475 (29.9%)
Mean Time to Death (Years)	1.32 (1.46)	1.65 (1.43)
Number in Dialysis State at End of Follow-up (%)	803 (6.6%)	-
Mean Time to Dialysis in Years (SD)	1.79 (1.37)	-
Mean Age (SD)	64.26 (17.63)	60.34 (16.80)
Number of Males (%)	6623 (54.5%)	925 (58.3%)
Age ≥60 (%)	7881 (64.8%)	901 (56.8%)
Diabetes (%)	4694 (38.6%)	794 (50.0%)
HIV or Medical Immune-Suppression (%)	368 (3.02%)	45 (2.84%)
Low Incidence (%)	1605 (13.2%)	132 (8.3%)
Moderate Incidence (%)	2215 (18.2%)	316 (19.9%)
High Incidence (%)	3917 (32.2%)	491 (30.9%)
Very High Incidence (%)	4421 (36.4%)	648 (40.8%)
Estimated LTBI Prevalence	22.4%	25.9%
Estimated TB Rate per 1000 Person Years | LTBI	9.47	28.8

Dataset was censored at 5 years.

Q1-Q3: Quartile 1 to Quartile 3; TB: tuberculosis; HIV: human immunodeficiency virus; LTBI: latent tuberculosis infection; CKD: chronic kidney disease

Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000

Table 6-3. Time-to-event parameters

Parameter	Mean Time Estimate in Years[a]	SHR for Age[b] (PSA Distribution)[e]	SHR for Diabetes[c] (PSA Distribution)[e]	SHR for Immune-Compromised[d] (PSA Distribution)[e]
Month 1-3, CKD with LTBI				
Time to TB	22.762	1.3612 Normal(0.308,0.415)	0.3782 Normal(-0.972,0.471)	1.1421 Normal(0.133,1.019)
Time to Death	4.387	1.8918 Normal(0.638,0.163)	0.7875 Normal(-0.239,0.142)	1.6552 Normal(0.504,0.310)
Month 4-60, CKD with LTBI				
Time to TB	538.925	2.0806 Normal(0.733,0.408)	1.0831 Normal(0.080,0.337)	0.9512 Normal(-0.050,1.014)
Time to Death	147.685	4.976 Normal(1.605,0.193)	1.221 Normal(0.200,0.120)	2.269 Normal(0.819,0.257)
Month 1-60, CKD with LTBI				
Time to Dialysis	51.966	0.5457 Normal(-0.606,0.135)	2.0082 Normal(0.697,0.134)	0.4263 Normal(-0.853,0.581)
Month 1-3, CKD no LTBI				
Time to Death	4.863	2.2309 Normal(0.802,0.091)	0.7867 Normal(-0.240,0.077)	1.3763 Normal(0.319,0.183)
Month 4-60, CKD no LTBI				
Time to Death	152.951	6.386 Normal(1.854,0.107)	1.094 Normal(0.090,0.061)	1.291 Normal(0.255,0.161)
Month 1-60, CKD no LTBI				
Time to Dialysis	71.519	0.5742 Normal(-0.555,0.082)	2.3433 Normal(0.852,0.082)	0.7933 Normal(-0.232,0.253)
Month 1-3, Dialysis with LTBI				
Time to TB	11.326	0.2001 Normal(-1.609,1.118)	1 (NA)	1 (NA)
Time to Death	11.786	2.506 Normal(0.919,0.520)	1.89 Normal(0.637,0.466)	1 (NA)
Month 4-60, Dialysis with LTBI				
Time to TB	65.797	0.5937 Normal(-0.521,0.399)	1.742 Normal(0.555,0.404)	1.3612 Normal(0.308,1.024)
Time to Death	77.148	4.3557 Normal(1.471,0.304)	2.2345 Normal(0.804,0.237)	0.8126 Normal(-0.208,0.589)
Month 1-3, Dialysis no LTBI				
Time to Death	11.560	2.6515 Normal(0.975,0.307)	1.9606 Normal(0.673,0.267)	0.8923 Normal(-0.114,0.717)
Month 4-60, Dialysis no LTBI				
Time to Death	51.724	4.267 Normal(1.451,0.167)	1.427 Normal(0.355,0.127)	0.905 Normal(-0.010,0.359)
After TB Cure, CKD				
Time to Death	73.681	1.011 Normal(0.011,1.348)	2.885 Normal(1.060,1.167)	7.116 Normal(1.962,1.392)
After TB Cure, Dialysis				
Time to Death	60.674	1 (NA)	1.112 Normal(0.106,1.414)	1 (NA)

All effect estimates are from Fine-Gray competing risks regression. LTBI: Latent Tuberculosis Infection; TB: Tuberculosis; CKD: Chronic Kidney Disease; SHR: Sub-distribution Hazard Ratio
[a]Based on BC TB Data and modeled with an exponential distribution; [b]If age over 60; [c]If diagnosed with diabetes; [d]If on immunosuppressants or diagnosed with HIV; [e]Results are exponentiated

Table 6-4. Model fit comparison of outcomes of interest using MLE of baseline survival and manual fitting to data

Estimation Method	Tuberculosis (% Deviation from Actual)	Death (% Deviation from Actual)	Dialysis (% Deviation from Actual)
CKD			
Actual	81	2639	803
MLE	101 (24.7%)	3110 (17.8%)	921 (14.7%)
Manual Fit to Data	90 (11.1%)	2775 (5.1%)	813 (1.2%)
Dialysis			
Actual	32	475	-
MLE	40 (25%)	542 (14.1%)	-
Manual Fit to Data	35 (9.4%)	465 (2.1%)	-

MLE: Maximum Likelihood Estimation

Table 6-5. Characteristics of included subgroups

Cohort	Age (at time of intervention)	TB Incidence in Country of Origin	Prevalence of Diabetes (at time of intervention)	Prevalence of HIV and/or medical immune-suppression (at time of intervention)
Late Stage CKD	≥60 years	Low	30.6%	2.8%
Late Stage CKD	≥60 years	Moderate	51.6%	4.7%
Late Stage CKD	≥60 years	High	45.2%	1.7%
Late Stage CKD	≥60 years	Very High	54.4%	3.9%
Late Stage CKD	<60 years	Low	11.3%	4.1%
Late Stage CKD	<60 years	Moderate	24.6%	3.0%
Late Stage CKD	<60 years	High	18.1%	2.9%
Late Stage CKD	<60 years	Very High	27.2%	2.4%
Dialysis	≥60 years	Low	36.7%	1.7%
Dialysis	≥60 years	Moderate	66.5%	2.4%
Dialysis	≥60 years	High	58.8%	2.2%
Dialysis	≥60 years	Very High	69.8%	4.9%
Dialysis	<60 years	Low	23.6%	0%
Dialysis	<60 years	Moderate	43.4%	3.3%
Dialysis	<60 years	High	28.1%	1.1%
Dialysis	<60 years	Very High	32.4%	2.8%

Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000
CKD: Chronic Kidney Disease; TB: Tuberculosis; HIV: Human Immunodeficiency Virus

Table 6-6. Model parameters and values used for sensitivity analysis

Parameter	Estimate	Range for PSA	Reference
General Costs			
Death due to TB or LTBI AE	$15,500	Gamma(29,560)	Imputed from [338]
CXR	$42	-	BCCDC, [330,337]
Cost per X-Ray	$35		
Nurse Costs	$7		
LTBI Costs			
Full INH Treatment	$992	Triangular, 804-1179	BCCDC, [330,337]
Drug Costs	$181		
Nurse and Clinician Costs	$741		
Follow-up CXR	$42		
Routine Tests	$28		
Partial INH	$462	Triangular, 174-804	BCCDC, [330,337]
Complete TST	$31	Triangular, 24-38	BCCDC, [330,337]
TST Cost	$11		
Nurse Costs (Two Visits)	$20		
Incomplete TST	$21	Triangular, 17-25	BCCDC, [330,337]
IGRA	$54	Triangular, 31-62	BCCDC, [330,337]
Kit and Technician Cost	$47		
Nurse Costs	$7		
LTBI Adverse Event	$732	Triangular, 549-916	[330]
LTBI Hospitalization	$6641	Triangular, 5305-9985	[119]
TB Costs			
Tuberculosis without Hospitalization	CKD: $8631 Dialysis: $14,535		
Tuberculosis with Hospitalization	CKD: $40,111 Dialysis: $46,015		
Drug, Workup, Follow-up Costs	$1620	Gamma(119,14)	BCCDC, [221,330]
Contact Tracing (per Contact)	$369	Gamma(56.4,6.6)	[221,421]
Cost per Hospitalization	$15,740	Gamma(29,552)	[407]

All costs are in 2016 CAD.
PSA: Probabilistic Sensitivity Analysis; INH: Isoniazid; RIF: Rifampin; BCCDC: British Columbia Centre for Disease Control; TST: Tuberculin Skin Test; IGRA: Interferon-Gamma Release Assay; CXR: Chest X-Ray; LTBI: Latent Tuberculosis Infection; TB: Tuberculosis; AE: Adverse Event; CKD: Chronic Kidney Disease

Table 6-6. Continued

Parameter	Estimate	Range for PSA	Reference
QALYs			
Chronic Kidney Disease	0.66	Beta(9.63,4.96)	[408,409]
Dialysis	0.62	Beta(8.02,4.92)	[408,409]
LTBI Adjustment	1	-	Implied from [331]
Adverse Event Adjustment	0.8	Triangular, ±25%	[119,330]
TB Adjustment	0.75	Triangular, ±25%	[331–333,410]
Hospitalization	0.4	Triangular, ±25%	Adjusted from [119]
Dead	0	-	Standard
Screening Parameters			
Accept Screening	1	Beta(227,69)	[101]
TST Sensitivity (CKD)	0.651	Beta(34.46,18.47)	Mean of Dialysis and Chapter 2, [20]
TST Sensitivity (Dialysis)	0.519	Beta(40,37)	[411,412,416]
TST Specificity (No BCG)	0.974	Beta(770,21)	[24,34]
TST Specificity (BCG)	0.602	Beta(239,158)	[24,34]
IGRA Sensitivity (CKD)	0.780	Beta(48.54,13.69)	Mean of Dialysis and Chapter 2, [20]
IGRA Sensitivity (Dialysis)	0.670	Beta(61,30)	[412–415]
IGRA Specificity	0.957	Beta(900,40)	[24,34]
IGRA Indeterminate (CKD) ¶	0.041	Beta(4,93)	In House TB Data, [414,422–424]
IGRA Indeterminate (Dialysis) ¶	0.067	Beta(143,2003)	In House TB Data, [414,422–424]
Complete TST†	0.913	Beta(44.23,4.22)	[53]
Complete Medical Evaluation	0.880	Beta(32.91,4.49)	[53]
Population Characteristics			
LTBI Prevalence: Very High Incidence	0.336	Beta(50.59,99.97)	Chapter 3, [21]
LTBI Prevalence: High Incidence	0.203	Beta(336.99,1323.04)	Chapter 3, [21]
LTBI Prevalence Moderate Incidence	0.159	Beta(68.26,361.05)	Chapter 3, [21]
LTBI Prevalence Low Incidence	0.029	Beta(1.50,50.12)	Chapter 3, [21]

¶Treated as a negative result if it occurred twice in a row; was equally likely to occur in those with and without LTBI
†Assuming TST was accepted
Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000
QALY: Quality Adjusted Life Year; PSA: Probabilistic Sensitivity Analysis; INH: Isoniazid; RIF: Rifampin; TST: Tuberculin Skin Test; IGRA: Interferon-Gamma Release Assay; CXR: Chest X-Ray; LTBI: Latent Tuberculosis Infection; TB: Tuberculosis; CKD: Chronic Kidney Disease; BCG: Bacillus Calmette-Guérin

Table 6-6. Continued

Parameter	Estimate	Range for PSA	Reference
Treatment Parameters			
Initiate	0.735	Beta(97,35)	[417]
Complete INH	0.767	Beta(69,21)	In House TB Data, [417,425]
AE INH	0.089	Beta(8,82)	In House TB Data, [417]
Hospitalization | AE	0.033	Beta(1,29)	[417,426]
Death INH	0.000023	Beta(1,43333)	[340]
LTBI Risk Reduction INH	0.93	Normal(-2.597,0.461)§	[51]
Partial Risk Reduction INH	0.5	Normal(-0.679,0.300)§	Imputed from [51]
Duration of LTBI AE Impact	7 days	Gamma(0.7,10)	Expert Opinion, [119]
LTBI Hospitalization Duration	7 days	Gamma(1.96,7)	Expert Opinion, [426]
TB Parameters			
All Cause Death | TB (CKD)	0.25	Beta(8,24)	In House TB Data, [372]
All Cause Death | TB (Dialysis)	0.313	Beta(20,44)	In House TB Data, [372]
Proportion Hospitalized | TB			
CKD	0.578	Beta(48,35)	In House TB Data, [427]
Dialysis	0.617	Beta(29,18)	
Number of Contacts per CKD TB Case	19	Gamma(0.84,22.37)	In House TB Data, [221]
Number of Contacts per Dialysis TB Case	35	Gamma(0.50,70.27)	In House TB Data, [221]
Number of Hospitalizations | Hospitalized			
CKD	2	Gamma(3.10,0.65)	In House TB Data, [427]
Dialysis	2	Gamma(3.41,0.59)	
Length of TB Hospitalization (days)			
CKD	35	Gamma(0.87, 40.58)	In House TB Data, [427]
Dialysis	39	Gamma(1.06, 36.43)	
Model Parameters			
BCG Vaccination (<30 cases)	0.605	Beta(45137,29502)	[224]
BCG Vaccination (≥30 cases)	0.998	Beta(185381,384)	[224]
BCG Vaccination Uptake	0.837	-	[316]
Discount Rate	0.015	-	[190]
Time Horizon	5 years	-	-

§Results from Normal distribution are exponentiated

PSA: Probabilistic Sensitivity Analysis; INH: Isoniazid; RIF: Rifampin; AE: Adverse Event; LTBI: Latent Tuberculosis Infection; TB: Tuberculosis; CKD: Chronic Kidney Disease; BCG: Bacillus Calmette-Guérin

Table 6-7. Results of LTBI screening at dialysis initiation

Intervention	Cost per Person ($)	QALYs per Person	TB Cases (per 1000 persons)	TB Incidence Reduction (%)	Cost per QALY Gained ($)	Incremental Net Monetary Benefit ($)
Age <60, Low TB Incidence						
Base Case	93.22	2.79916	2.70	-	-	-
IGRA/INH	165.02	2.79956	1.97	27.04	179,322	-31.76
TST/INH	236.80	2.79946	2.18	19.34	469,978	-113.03
Age <60, Moderate TB Incidence						
Base Case	558.43	2.77204	16.19	-	-	-
IGRA/INH	554.66	2.77459	11.73	27.55	Dominant	259.25
TST/INH	695.31	2.77377	13.03	19.55	79,014	36.35
Age <60, High TB Incidence						
Base Case	665.25	2.79032	19.28	-	-	-
IGRA/INH	653.29	2.79333	14.07	27.01	Dominant	312.25
TST/INH	788.57	2.79240	15.58	19.19	59,431	84.18
Age <60, Very High TB Incidence						
Base Case	1128.83	2.78068	32.72	-	-	-
IGRA/INH	1043.94	2.78584	23.80	27.25	Dominant	600.51
TST/INH	1176.58	2.78433	26.38	19.36	13,096	316.87
Age ≥60, Low TB Incidence						
Base Case	66.05	2.30411	1.88	-	-	-
IGRA/INH	140.41	2.30450	1.27	32.34	190,181	-35.26
TST/INH	209.44	2.30432	1.45	23.07	678,316	-122.25
Age ≥60, Moderate TB Incidence						
Base Case	490.47	2.23394	13.93	-	-	-
IGRA/INH	473.51	2.23653	9.32	33.09	Dominant	275.96
TST/INH	613.37	2.23567	10.64	23.62	71,015	50.16
Age ≥60, High TB Incidence						
Base Case	584.97	2.25025	16.62	-	-	-
IGRA/INH	554.63	2.25336	11.13	32.99	Dominant	341.25
TST/INH	691.47	2.25247	12.72	23.43	48,104	114.90
Age ≥60, Very High TB Incidence						
Base Case	1085.22	2.21854	30.82	-	-	-
IGRA/INH	938.04	2.22441	20.61	33.13	Dominant	734.50
TST/INH	1085.46	2.22261	23.56	23.54	60	407.23

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test; INH: isoniazid; QALY: quality adjusted life year
Dominant: this intervention has lower costs and better outcomes than the base case.
Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000

Table 6-8. Results of LTBI screening at late stage CKD diagnosis

Intervention	Cost per Person ($)	QALYs per Person	TB Cases (per 1000 persons)	TB Incidence Reduction (%)	Cost per QALY Gained ($)	Incremental Net Monetary Benefit ($)
Age <60, Low TB Incidence						
Base Case	19.03	2.99234	0.65	-	-	-
IGRA/INH	111.54	2.99253	0.50	23.07	491,731	-73.70
TST/INH	177.86	2.99247	0.53	18.02	1,221,979	-145.83
Age <60, Moderate TB Incidence						
Base Case	105.97	2.98834	3.60	-	-	-
IGRA/INH	237.05	2.98935	2.71	24.69	129,953	-30.21
TST/INH	340.81	2.98905	2.93	18.79	328,704	-163.40
Age <60, High TB Incidence						
Base Case	133.89	2.98611	4.57	-	-	-
IGRA/INH	279.62	2.98744	3.48	23.83	110,118	-13.39
TST/INH	372.26	2.98706	3.74	18.12	251,498	-143.59
Age <60, Very High TB Incidence						
Base Case	224.19	2.98232	7.63	-	-	-
IGRA/INH	407.13	2.98443	5.70	25.23	86,715	28.02
TST/INH	467.77	2.98391	6.16	19.23	153,115	-84.50
Age ≥60, Low TB Incidence						
Base Case	30.76	2.55349	1.00	-	-	-
IGRA/INH	119.45	2.55383	0.78	22.45	263,378	-55.02
TST/INH	183.15	2.55370	0.83	17.13	719,334	-131.21
Age ≥60, Moderate TB Incidence						
Base Case	188.66	2.51217	6.12	-	-	-
IGRA/INH	297.32	2.51445	4.66	23.72	47,554	119.84
TST/INH	400.45	2.51389	5.00	18.22	122,982	-39.58
Age ≥60, High TB Incidence						
Base Case	230.92	2.53062	7.48	-	-	-
IGRA/INH	349.59	2.53339	5.72	23.58	42,846	158.31
TST/INH	443.24	2.53270	6.13	18.07	102,141	-4.45
Age ≥60, Very High TB Incidence						
Base Case	402.59	2.50768	13.04	-	-	-
IGRA/INH	538.98	2.51275	9.92	23.90	26,935	369.99
TST/INH	605.91	2.51143	10.67	18.21	54,257	171.41

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test; INH: isoniazid; QALY: quality adjusted life year
Dominant: this intervention has lower costs and better outcomes than the base case.
Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000

Table 6-9. Average results of PSA of LTBI screening at dialysis initiation

Intervention	Cost per Person ($)	QALYs per Person	TB Cases (per 1000 persons)	TB Incidence Reduction (%)	Cost per QALY Gained ($)	Incremental Net Monetary Benefit ($)
Age <60, Low TB Incidence						
Base Case	99.50	2.55650	2.83	-	-	-
IGRA/INH	155.18	2.55676	2.41	15.03	216,436	-29.95
TST/INH	213.29	2.55665	2.53	10.57	755,952	-98.74
Age <60, Moderate TB Incidence						
Base Case	593.39	2.52874	16.84	-	-	-
IGRA/INH	611.49	2.53032	14.21	15.61	11,440	140.16
TST/INH	715.58	2.52986	14.96	11.18	108,961	-10.05
Age <60, High TB Incidence						
Base Case	695.01	2.54710	19.74	-	-	-
IGRA/INH	714.20	2.54886	16.73	15.25	10,906	156.83
TST/INH	812.63	2.54835	17.60	10.86	94,754	6.51
Age <60, Very High TB Incidence						
Base Case	1191.79	2.53705	33.83	-	-	-
IGRA/INH	1174.12	2.54012	28.61	15.44	Dominant	324.05
TST/INH	1265.12	2.53920	30.12	10.95	34,143	141.43
Age ≥60, Low TB Incidence						
Base Case	78.41	2.09561	2.17	-	-	-
IGRA/INH	134.06	2.09586	1.79	17.73	215,568	-29.83
TST/INH	190.37	2.09573	1.90	12.47	920,295	-99.79
Age ≥60, Moderate TB Incidence						
Base Case	553.07	2.02792	15.30	-	-	-
IGRA/INH	560.51	2.02981	12.52	18.13	3,954	180.67
TST/INH	664.93	2.02923	13.33	12.89	85,411	19.11
Age ≥60, High TB Incidence						
Base Case	661.68	2.04276	18.32	-	-	-
IGRA/INH	662.29	2.04501	14.99	18.14	269	224.10
TST/INH	762.61	2.04434	15.95	12.94	64,175	56.34
Age ≥60, Very High TB Incidence						
Base Case	1230.66	2.01013	34.07	-	-	-
IGRA/INH	1165.66	2.01433	27.82	18.33	Dominant	485.11
TST/INH	1267.68	2.01309	29.63	13.03	12,481	259.55

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test; INH: isoniazid; QALY: quality adjusted life years
Dominant: this intervention has lower costs and better outcomes than the base case.
Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000

Table 6-10. Average results of PSA of LTBI screening at late stage CKD diagnosis

Intervention	Cost per Person ($)	QALYs per Person	TB Cases (per 1000 persons)	TB Incidence Reduction (%)	Cost per QALY Gained ($)	Incremental Net Monetary Benefit ($)
Age <60, Low TB Incidence						
Base Case	20.57	2.97975	0.69	-	-	-
IGRA/INH	88.74	2.97990	0.60	12.38	446,061	-52.89
TST/INH	143.49	2.97985	0.62	9.52	1,163,751	-112.36
Age <60, Moderate TB Incidence						
Base Case	112.63	2.97384	3.73	-	-	-
IGRA/INH	214.41	2.97455	3.23	13.49	144,140	-31.17
TST/INH	296.63	2.97436	3.34	10.44	358,087	-132.61
Age <60, High TB Incidence						
Base Case	141.90	2.97231	4.71	-	-	-
IGRA/INH	255.83	2.97321	4.10	12.98	127,233	-24.38
TST/INH	329.34	2.97296	4.24	9.97	289,676	-122.73
Age <60, Very High TB Incidence						
Base Case	238.16	2.96688	7.87	-	-	-
IGRA/INH	385.81	2.96834	6.79	13.74	100,970	-1.42
TST/INH	433.66	2.96795	7.05	10.42	183,557	-88.99
Age ≥60, Low TB Incidence						
Base Case	35.72	2.54005	1.13	-	-	-
IGRA/INH	100.93	2.54033	0.99	12.63	234,412	-37.39
TST/INH	153.64	2.54024	1.02	9.61	617,042	-98.81
Age ≥60, Moderate TB Incidence						
Base Case	214.01	2.49415	6.73	-	-	-
IGRA/INH	299.89	2.49585	5.85	13.02	50,588	83.89
TST/INH	381.50	2.49536	6.06	9.90	138,074	-46.18
Age ≥60, High TB Incidence						
Base Case	259.02	2.51355	8.17	-	-	-
IGRA/INH	354.80	2.51558	7.11	12.94	47,064	107.73
TST/INH	429.01	2.51504	7.36	9.80	113,702	-20.49
Age ≥60, Very High TB Incidence						
Base Case	456.42	2.48729	14.34	-	-	-
IGRA/INH	570.54	2.49098	12.45	13.19	30,860	255.68
TST/INH	622.96	2.49006	12.90	10.03	60,081	110.65

QALY: quality adjusted life year; TB: tuberculosis; IGRA: interferon-gamma release assay; INH: isoniazid; TST: tuberculin skin test
Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000

Table 6-11. Results of exploratory sensitivity analysis of LTBI screening at dialysis initiation in cost per QALY gained

Intervention	Base Case	3% Discount Rate	Hospitalization Cost of $12,055	Halved TB Rate	76.7% Accept Screening	IGRA Cost is Equivalent to TST	Only 6% Die With TB
Age <60, Low TB Incidence							
IGRA/INH	179,322	188,946	187,497	326,520	183,187	118,118	280,232
TST/INH	469,978	491,217	478,096	870,892	686,536	469,978	805,755
Age <60, Moderate TB Incidence							
IGRA/INH	Dominant	372	5,851	55,241	Dominant	Dominant	2,918
TST/INH	79,014	84,361	86,667	222,081	78,578	79,014	118,162
Age <60, High TB Incidence							
IGRA/INH	Dominant	Dominant	3,310	50,224	Dominant	Dominant	Dominant
TST/INH	59,431	63,855	66,935	178,783	60,443	59,431	93,401
Age <60, Very High TB Incidence							
IGRA/INH	Dominant	Dominant	Dominant	23,669	Dominant	Dominant	Dominant
TST/INH	13,096	15,539	20,371	84,195	13,112	13,096	23,704
Age ≥60, Low TB Incidence							
IGRA/INH	190,181	201,477	197,672	487,976	233,210	127,823	297,213
TST/INH	678,316	716,219	707,823	1,210,116	782,254	678,316	992,359
Age ≥60, Moderate TB Incidence							
IGRA/INH	Dominant	Dominant	880	45,111	Dominant	Dominant	Dominant
TST/INH	71,015	76,037	79,002	174,430	67,733	71,015	136,847
Age ≥60, High TB Incidence							
IGRA/INH	Dominant	Dominant	Dominant	37,366	Dominant	Dominant	Dominant
TST/INH	48,104	51,927	55,430	161,687	47,738	48,104	97,091
Age ≥60, Very High TB Incidence							
IGRA/INH	Dominant	Dominant	Dominant	8,610	Dominant	Dominant	Dominant
TST/INH	60	1,936	7,495	60,804	12	60	8,342

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test; INH: isoniazid
Dominant: this intervention has lower costs and better outcomes than the base case.
Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000

Table 6-12. Results of exploratory sensitivity analysis of LTBI screening at late stage CKD diagnosis in cost per QALY gained

Intervention	Base Case	3% Discount Rate	Hospitalization Cost of $12,055	Halved TB Rate	76.7% Accept Screening	IGRA Cost is Equivalent to TST	Tests Equivalent to Dialysis*
Age <60, Low TB Incidence							
IGRA/INH	491,731	516,870	492,391	1,488,372	581,898	373,988	586,996
TST/INH	1,221,979	1,291,770	1,182,972	15,017,123	1,449,954	1,221,979	1,925,303
Age <60, Moderate TB Incidence							
IGRA/INH	129,953	136,294	133,549	299,349	132,087	106,696	149,817
TST/INH	328,704	344,019	331,437	778,971	303,266	328,704	429,164
Age <60, High TB Incidence							
IGRA/INH	110,118	115,402	113,398	242,002	113,590	92,222	125,333
TST/INH	251,498	263,609	253,904	539,712	251,443	251,498	313,553
Age <60, Very High TB Incidence							
IGRA/INH	86,715	91,413	90,450	203,666	84,423	75,554	93,536
TST/INH	153,115	161,009	157,188	342,686	155,758	153,115	182,425
Age ≥60, Low TB Incidence							
IGRA/INH	263,378	273,183	254,692	386,072	223,426	194,281	232,638
TST/INH	719,334	760,588	704,859	942,666	561,380	719,334	815,770
Age ≥60, Moderate TB Incidence							
IGRA/INH	47,554	50,129	49,964	112,785	46,309	37,111	55,242
TST/INH	122,982	128,622	125,245	262,355	125,199	122,982	149,820
Age ≥60, High TB Incidence							
IGRA/INH	42,846	45,220	45,456	109,343	42,281	34,218	48,920
TST/INH	102,141	107,228	104,783	236,027	97,966	102,141	119,283
Age ≥60, Very High TB Incidence							
IGRA/INH	26,935	28,650	29,413	77,352	27,636	22,241	30,077
TST/INH	54,257	57,024	56,806	132,206	53,483	54,257	64,358

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test; INH: isoniazid
Very High Incidence: ≥200 cases per 100,000; High Incidence: ≥100 and <200 cases per 100,000; Moderate Incidence: ≥30 and <100 cases per 100,000; Low Incidence: <30 cases per 100,000

6.7 Figures

Figure 6-1. Proportion of individuals with late stage CKD in each health state over the follow-up time of the data source who (A) have LTBI or (B) do not have LTBI

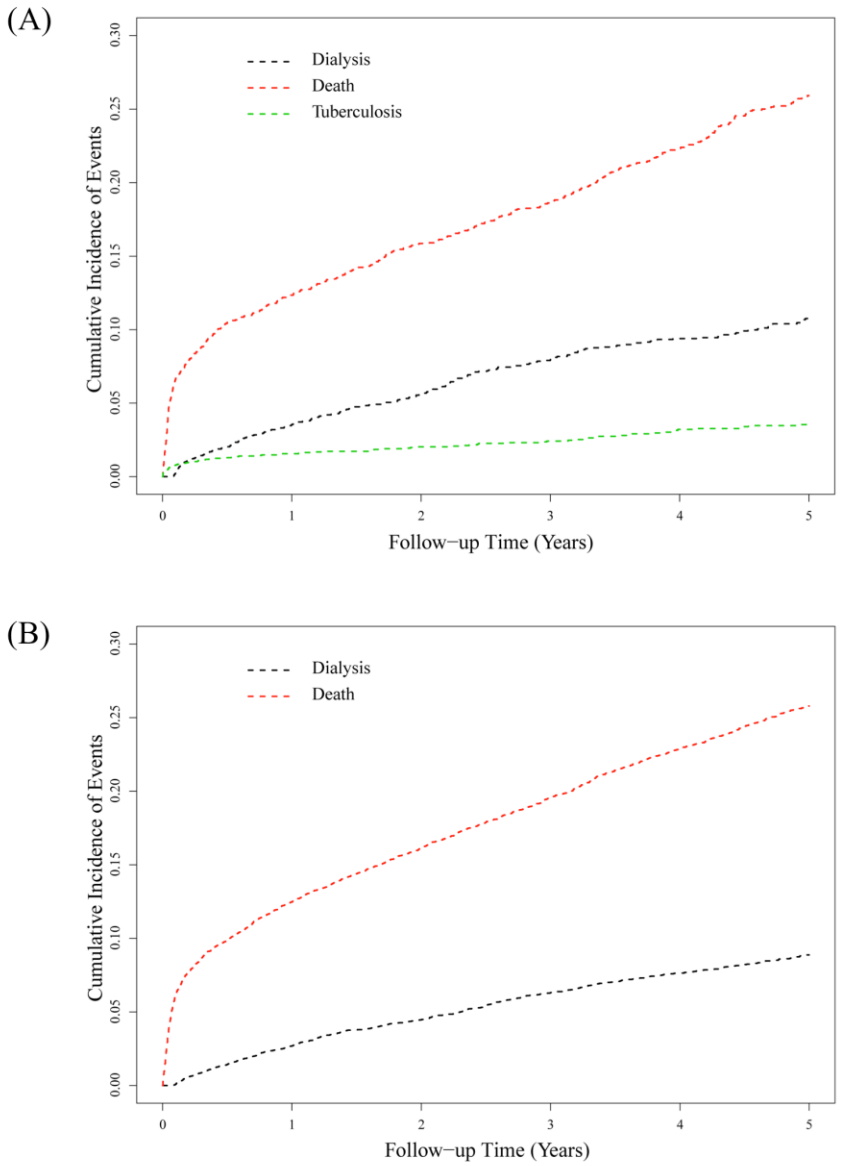


Figure 6-2. Proportion of individuals initiating dialysis in each health state over the follow-up time of the data source who (A) have LTBI or (B) do not have LTBI

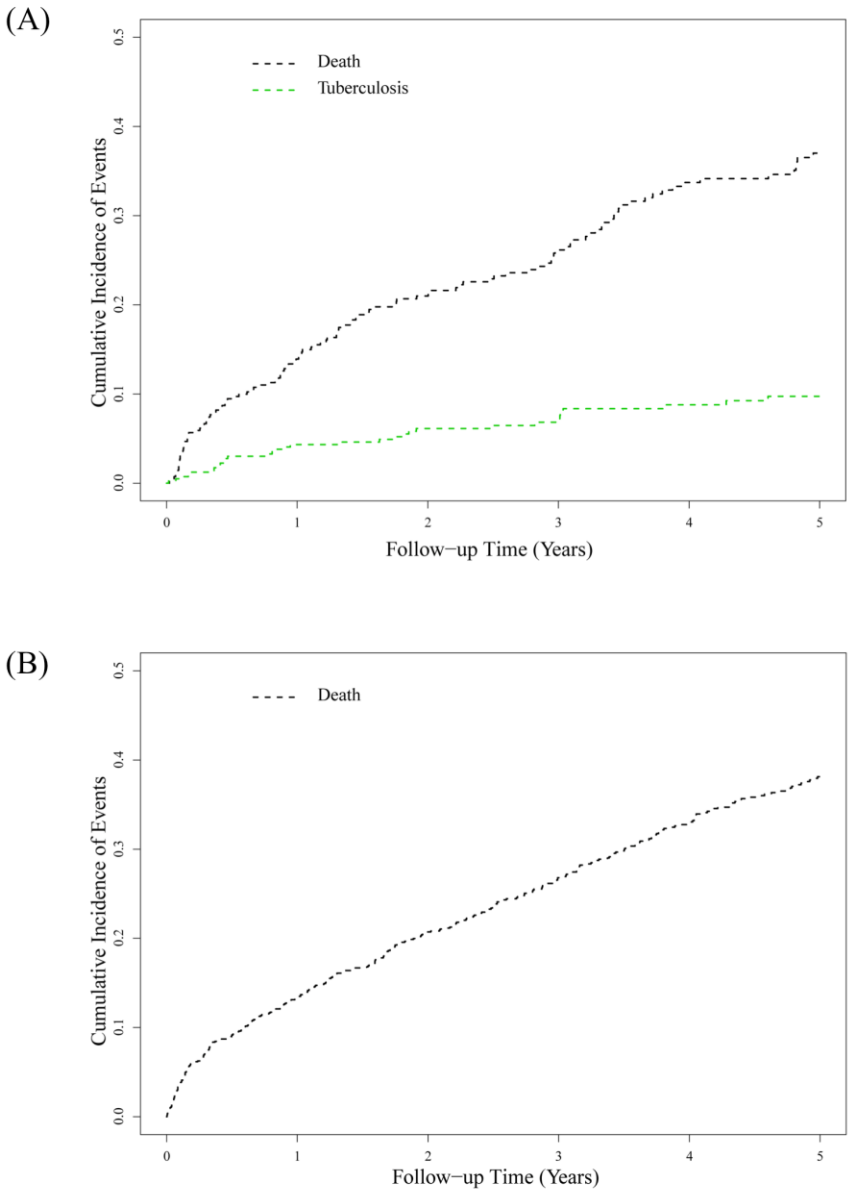
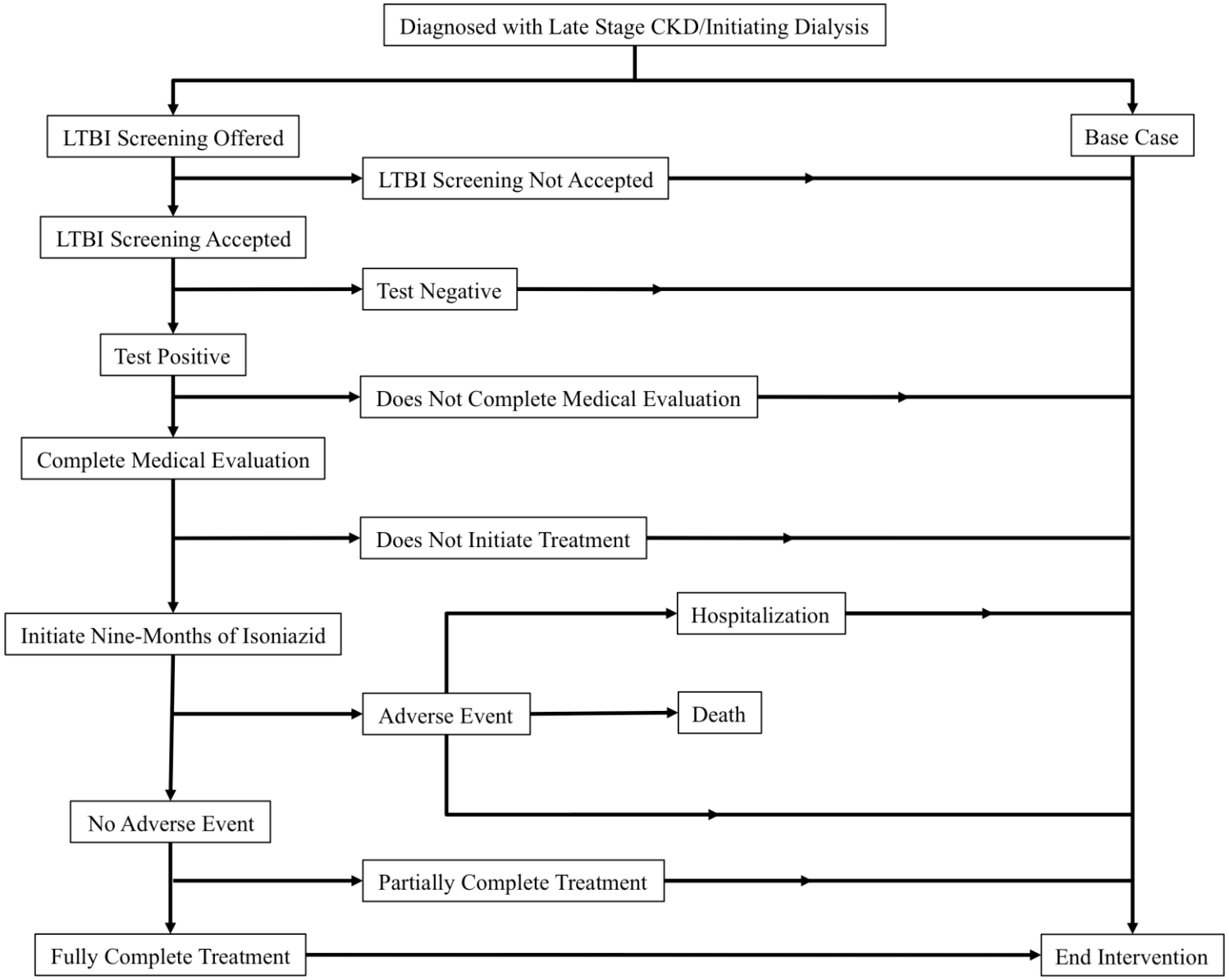


Figure 6-3. Model structure and health state transitions. (A) Model structure and typical pathway of screening and treatment for LTBI in simulated patients; (B) Possible health state transitions

(A)



(B)

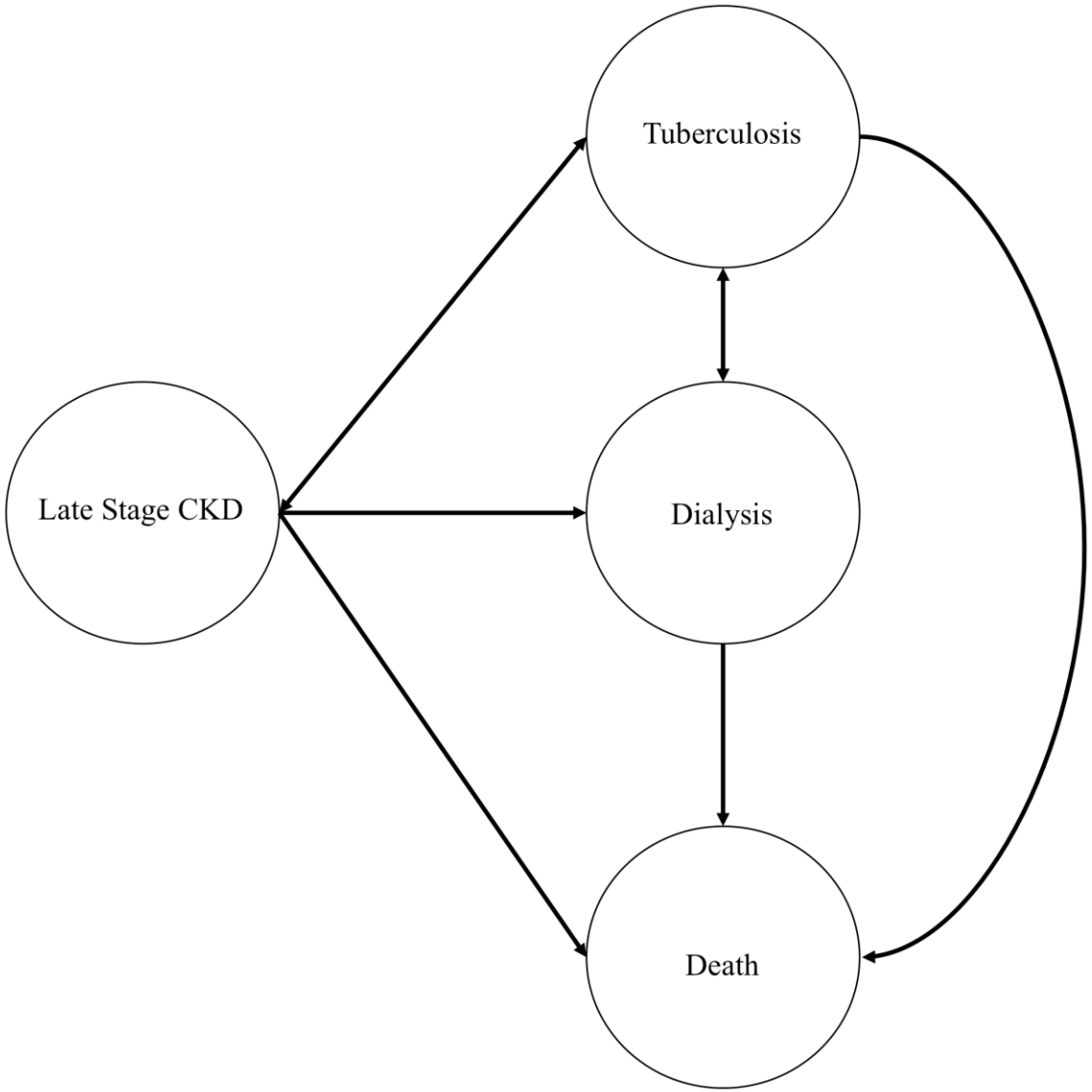
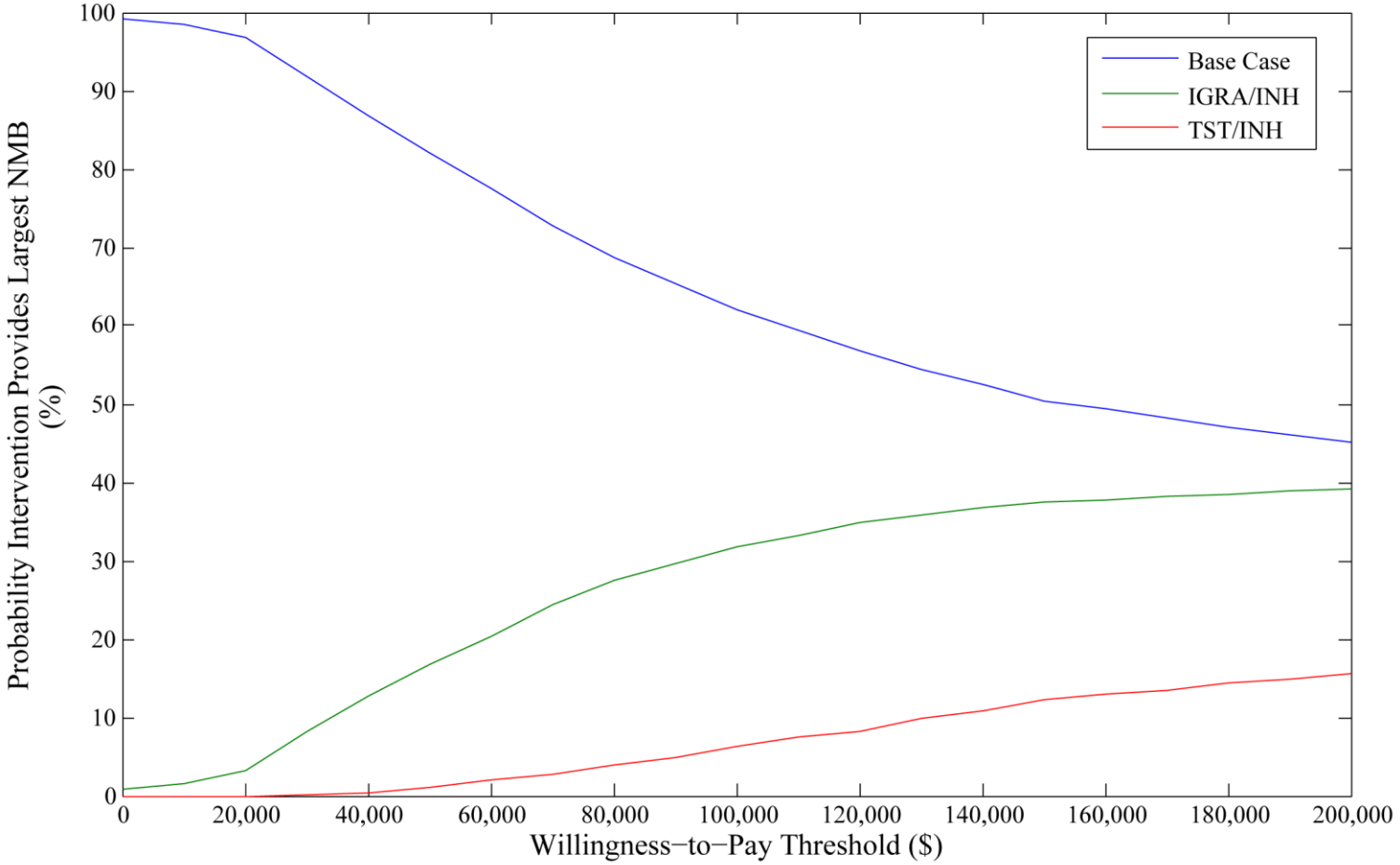
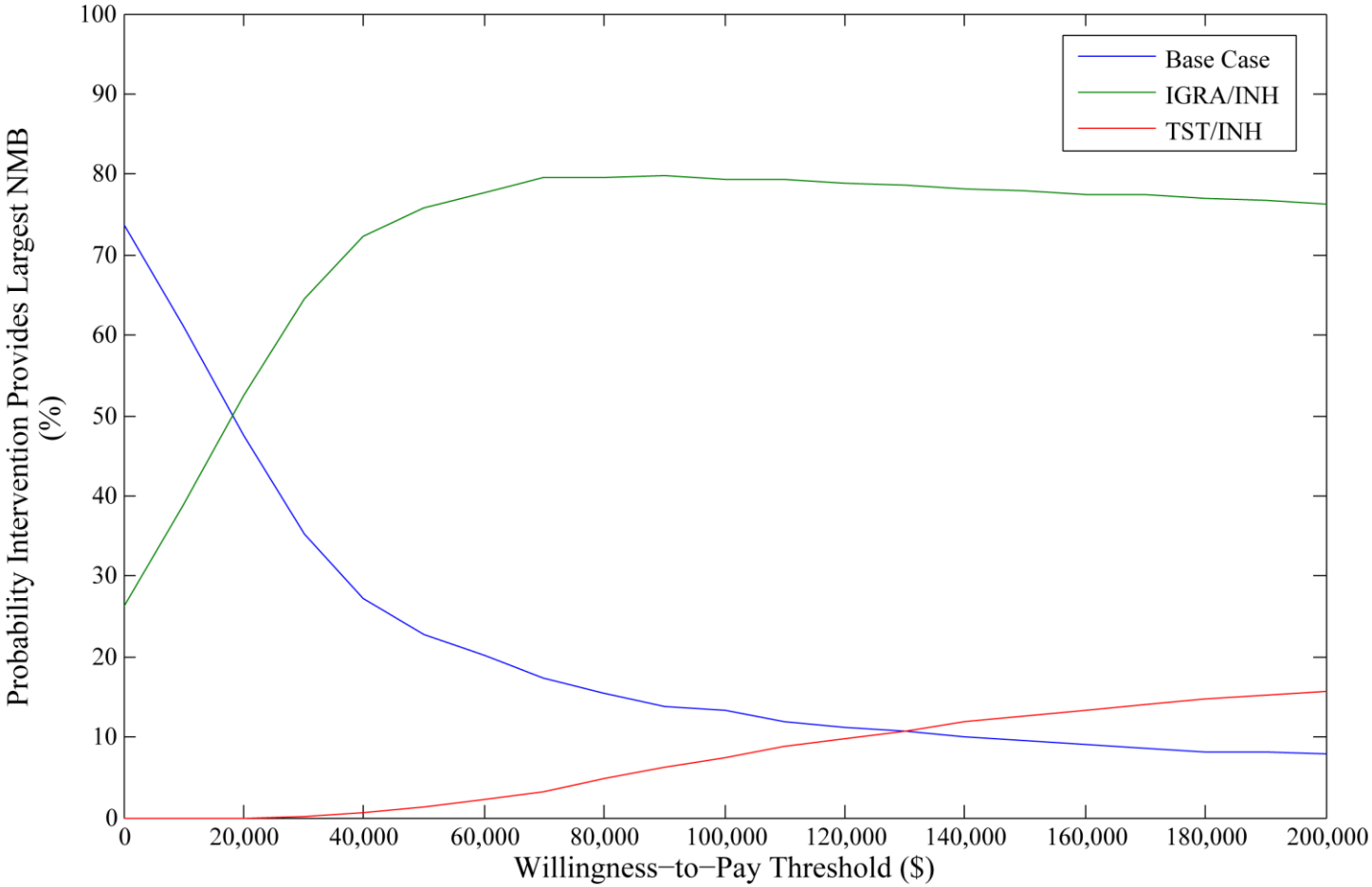


Figure 6-4. Cost-effectiveness acceptability curves for migrants <60 years of age at dialysis initiation for LTBI screening. The plots display the probability an intervention has the largest net monetary benefit at various willingness-to-pay thresholds in migrants from (A) low incidence countries, (B) moderate incidence countries, (C) high incidence countries, and (D) very high incidence countries.

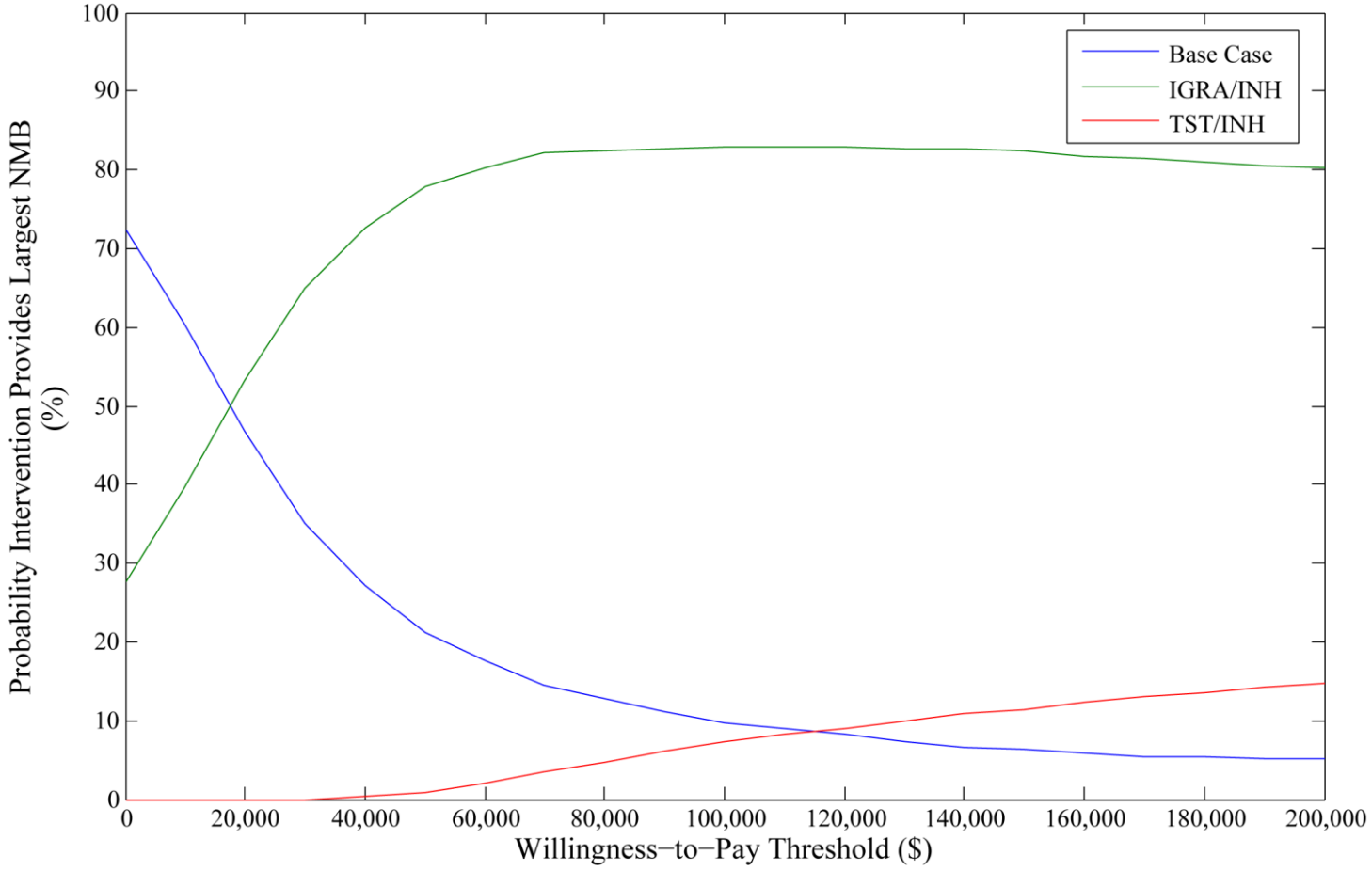
(A)



(B)


Base Case
IGRA/INH
TST/INH
Probability Intervention Provides Largest NMB (%)
Willingness−to−Pay Threshold ($)
0
10
20
30
40
50
60
70
80
90
100
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000

(C)


Base Case
IGRA/INH
TST/INH
Probability Intervention Provides Largest NMB (%)
Willingness−to−Pay Threshold ($)
0
10
20
30
40
50
60
70
80
90
100
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000

(D)

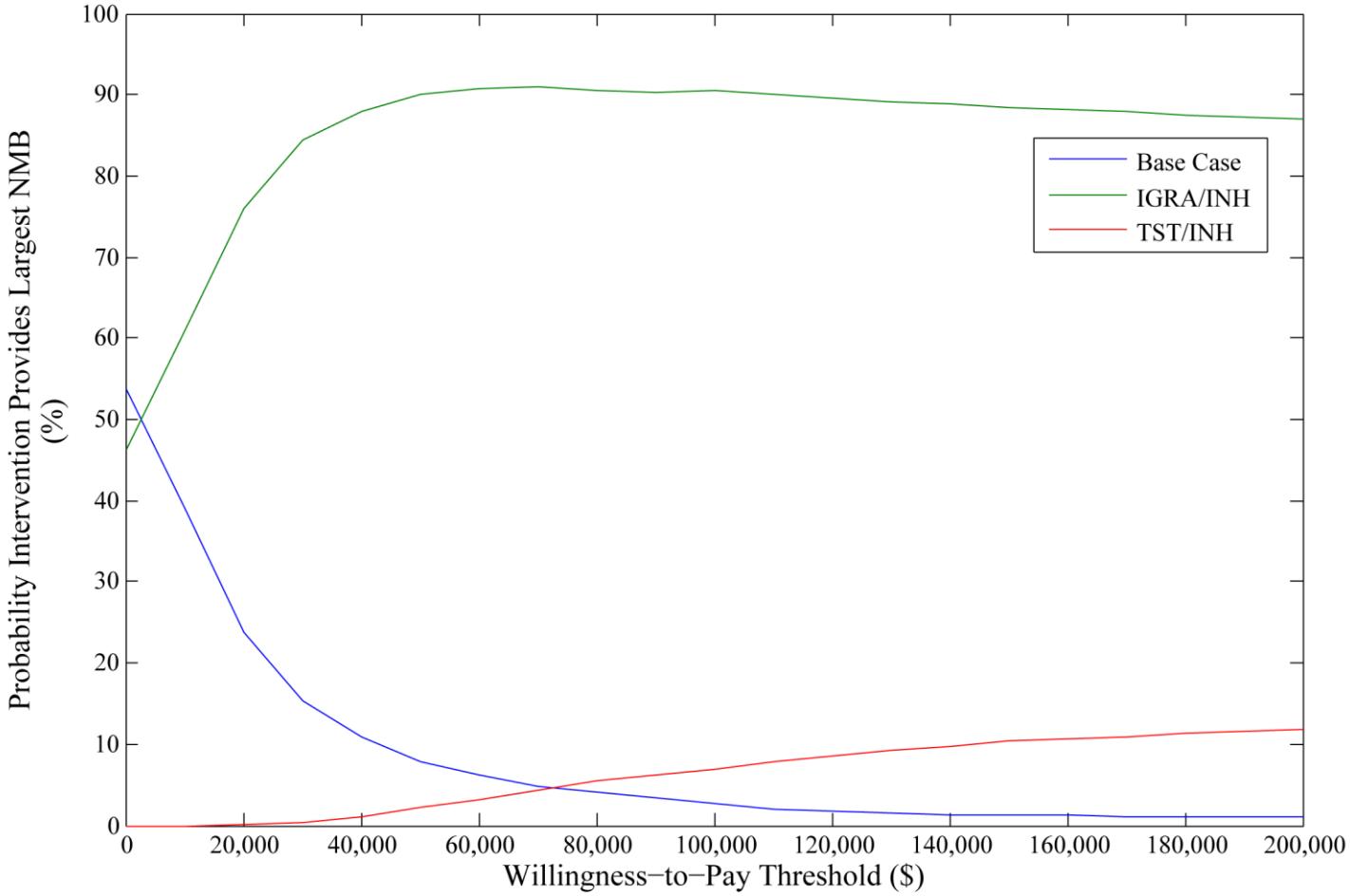
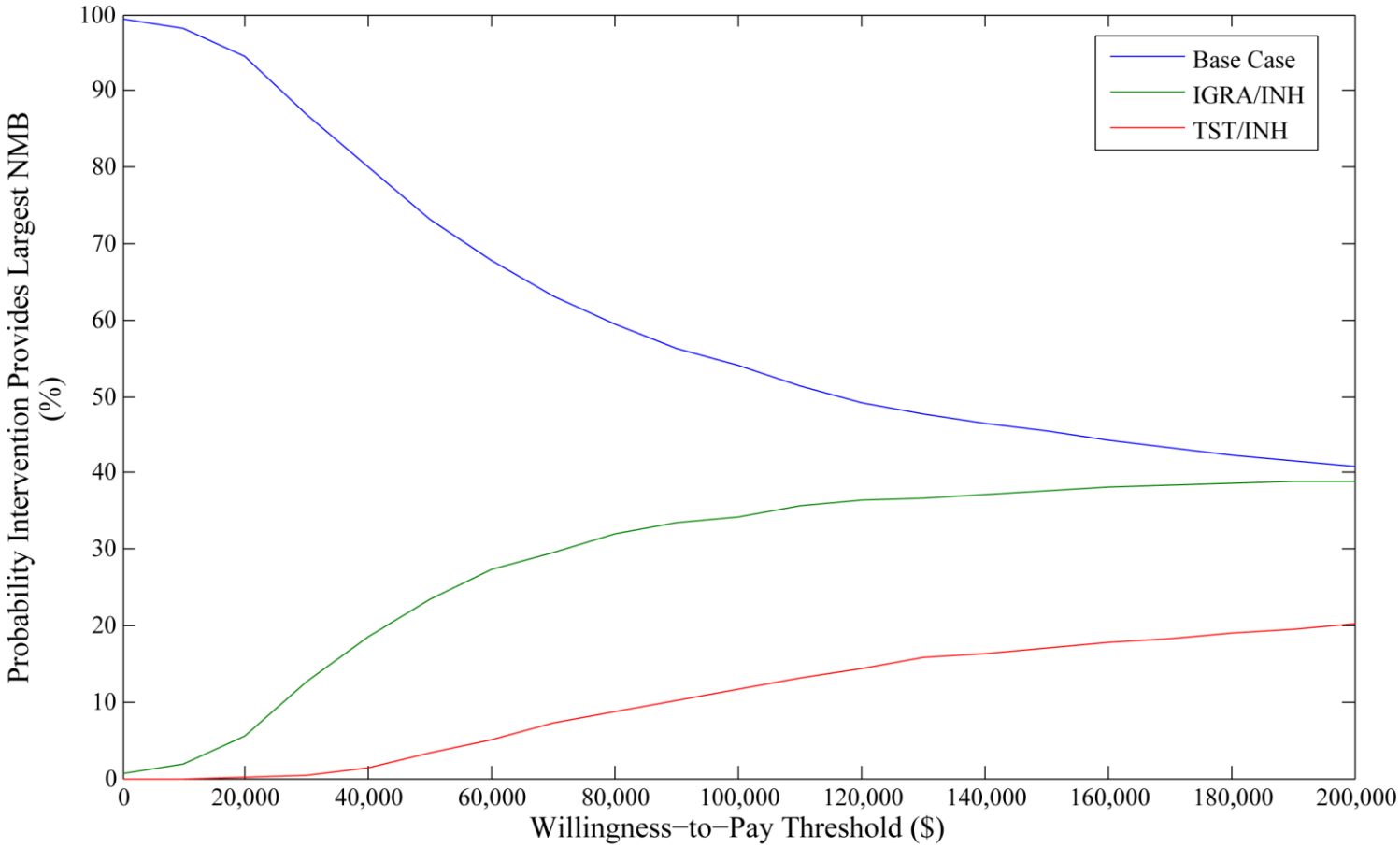
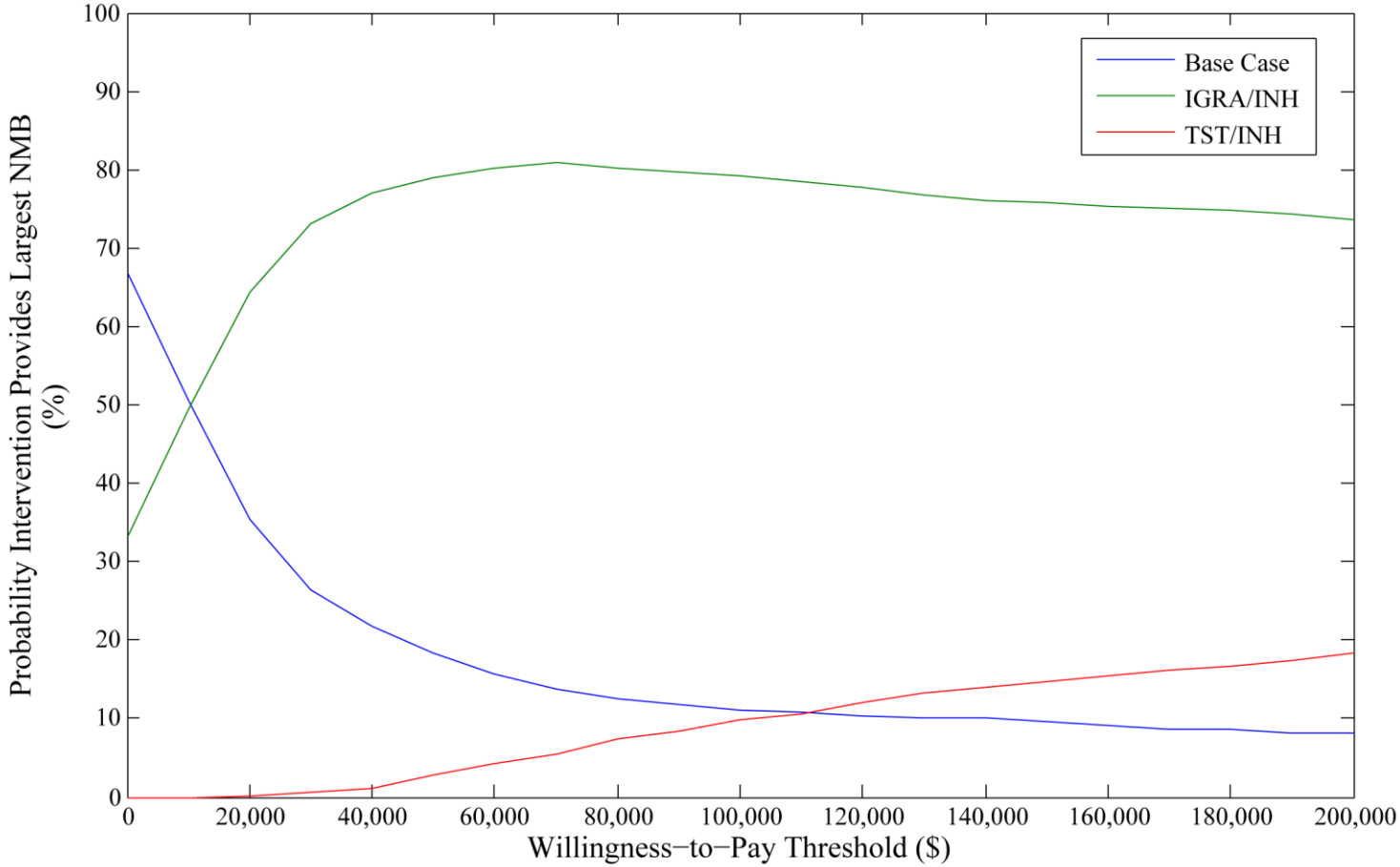

Probability Intervention Provides Largest NMB (%)
100
90
80
70
60
50
40
30
20
10
0
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000
Willingness−to−Pay Threshold ($)
Base Case
IGRA/INH
TST/INH

Figure 6-5. Cost-effectiveness acceptability curves for migrants ≥60 years of age at dialysis initiation for LTBI screening. The plots display the probability an intervention has the largest net monetary benefit at various willingness-to-pay thresholds in migrants from (A) low incidence countries, (B) moderate incidence countries, (C) high incidence countries, and (D) very high incidence countries.

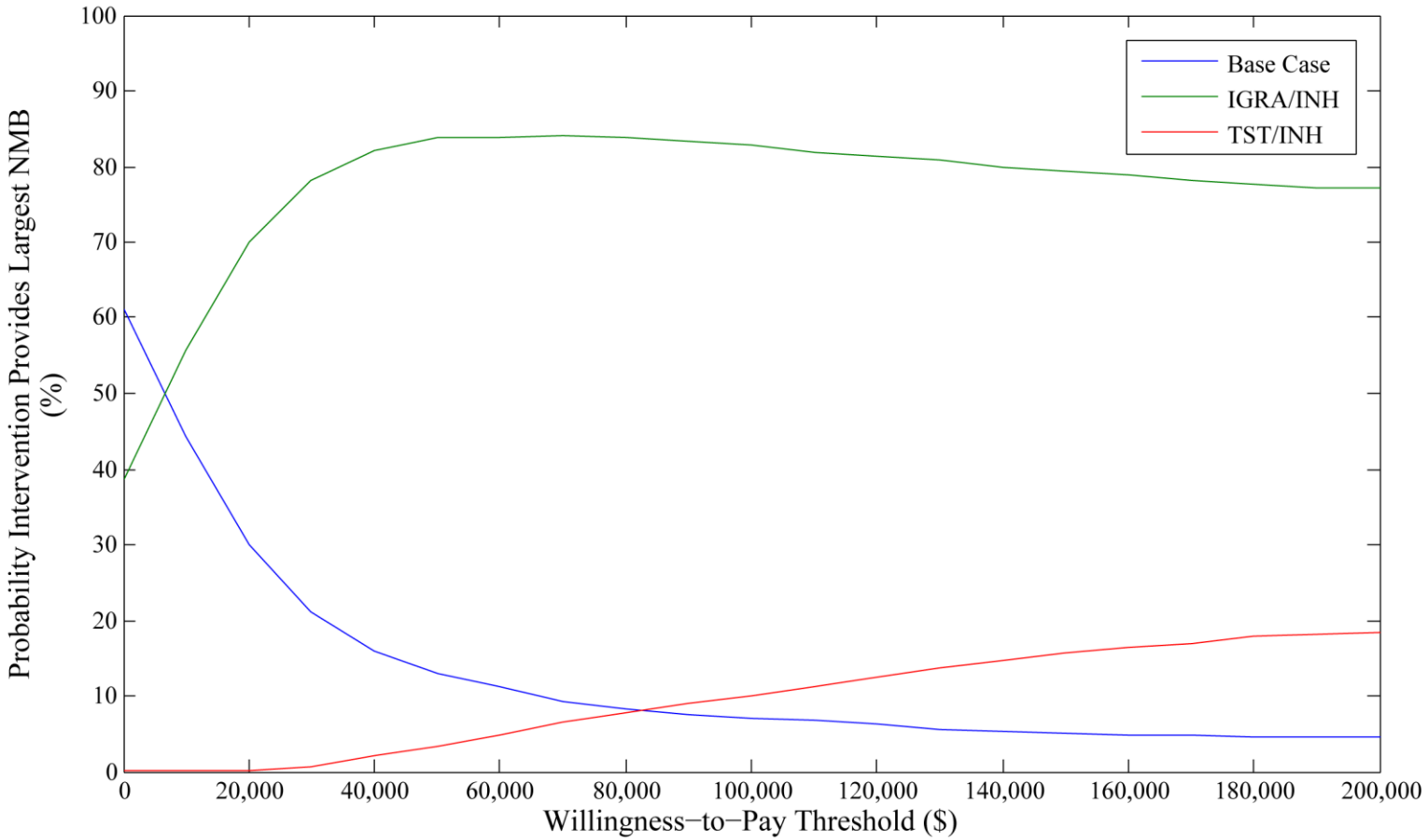
(A)



(B)


Base Case
IGRA/INH
TST/INH
Probability Intervention Provides Largest NMB (%)
Willingness−to−Pay Threshold ($)
0
10
20
30
40
50
60
70
80
90
100
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000

(C)


Probability Intervention Provides Largest NMB (%)
100
90
80
70
60
50
40
30
20
10
0
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000
Willingness−to−Pay Threshold ($)
Base Case
IGRA/INH
TST/INH

(D)

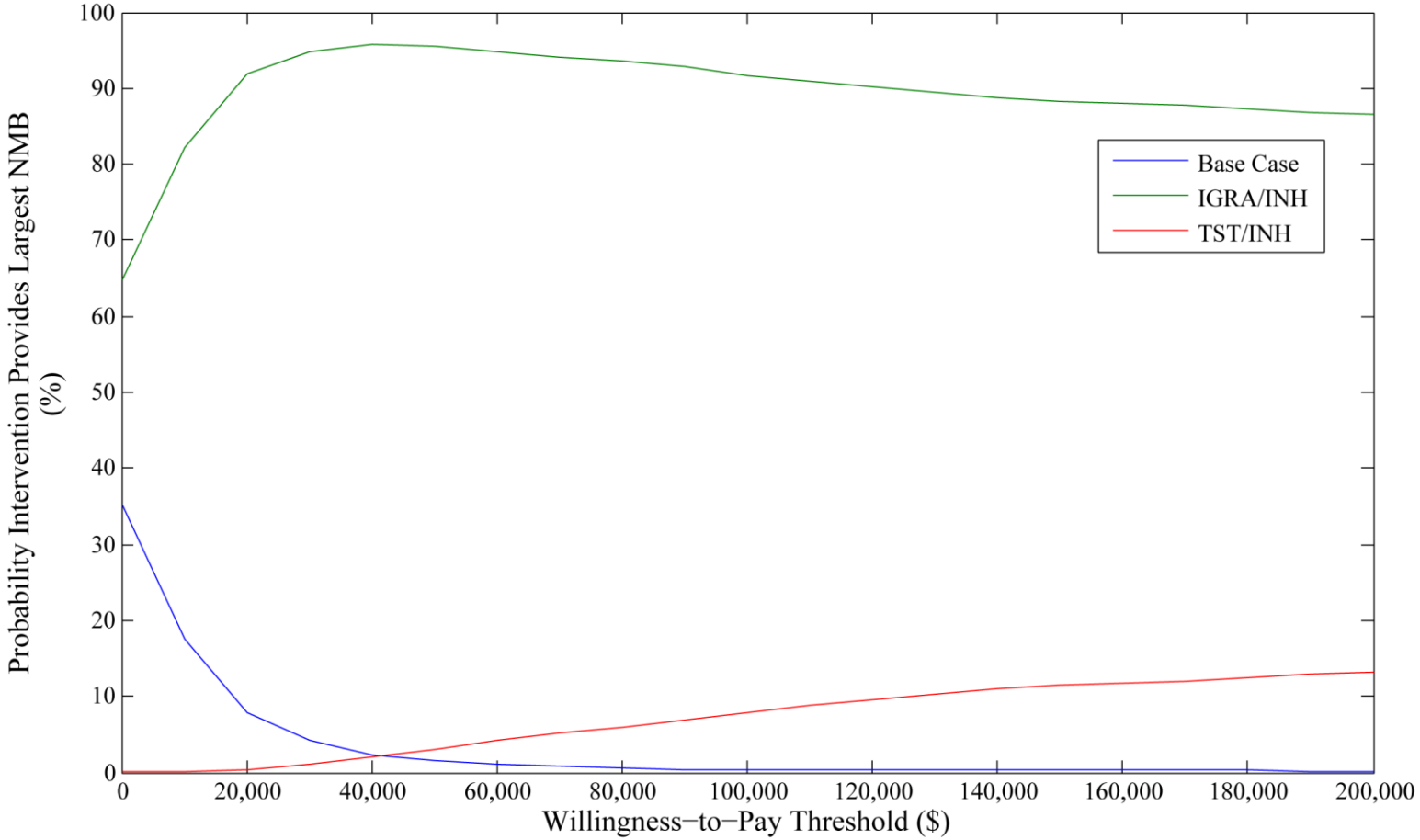
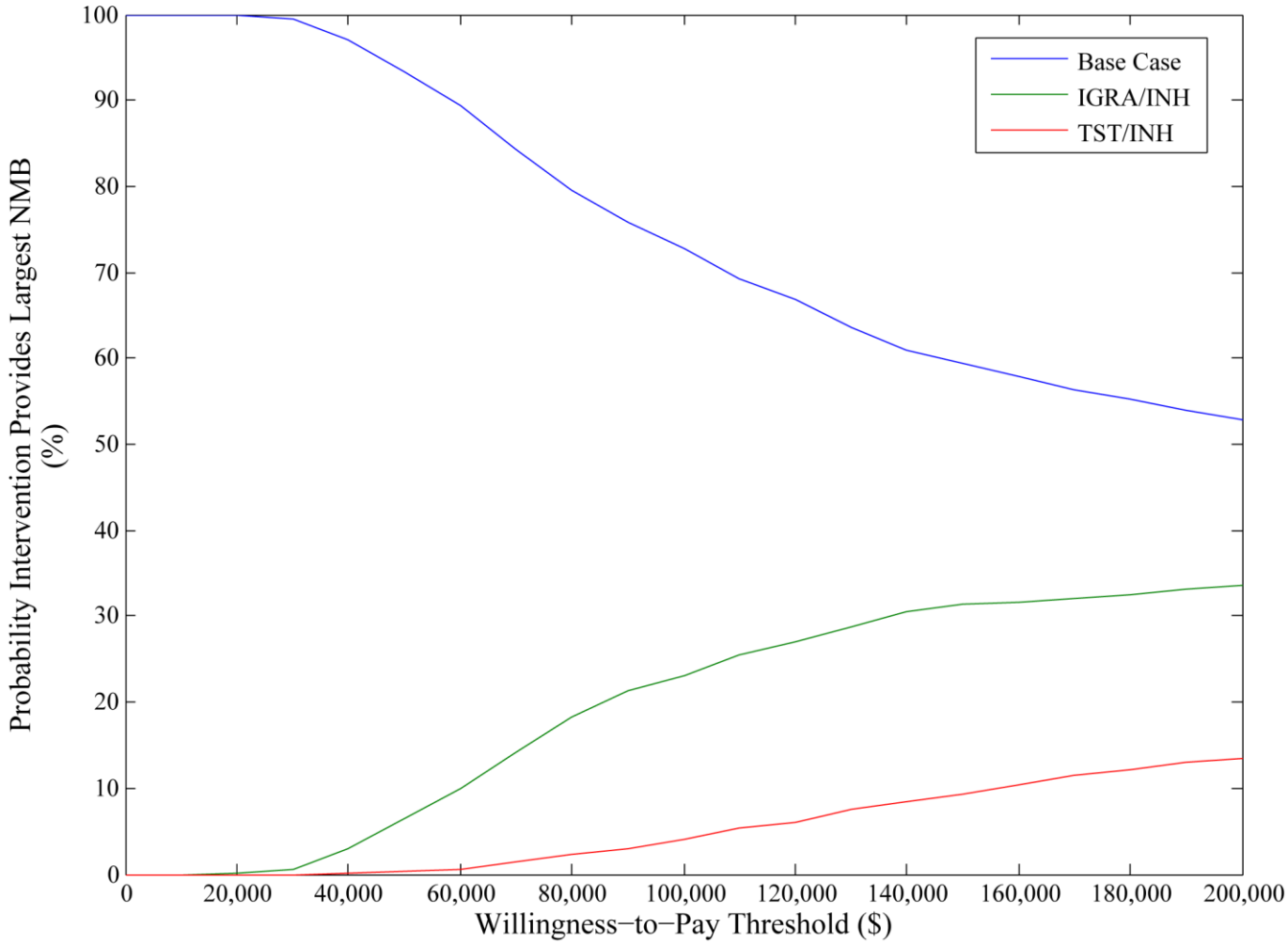
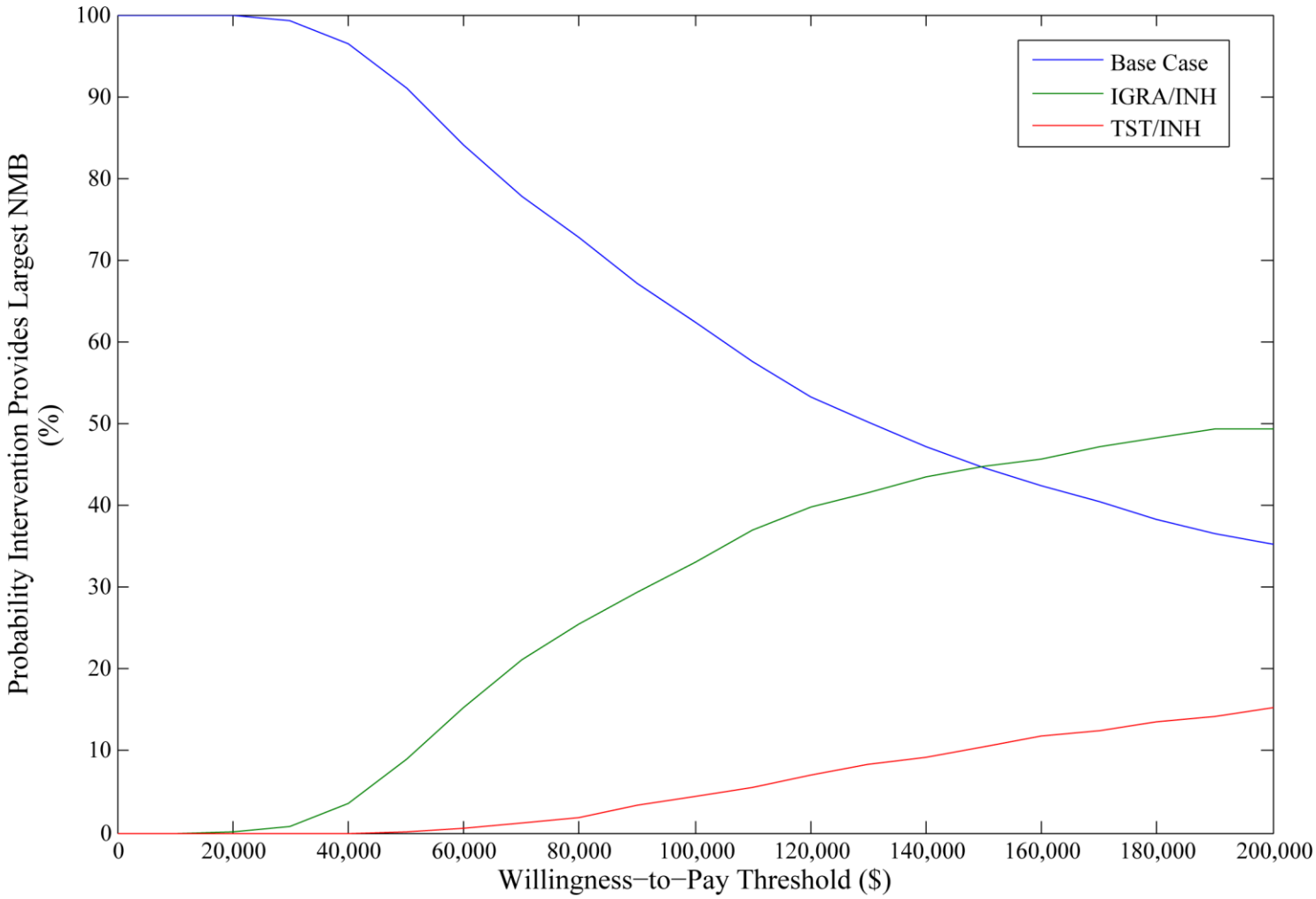

Probability Intervention Provides Largest NMB (%)
100
90
80
70
60
50
40
30
20
10
0
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000
Willingness−to−Pay Threshold ($)
Base Case
IGRA/INH
TST/INH

Figure 6-6. Cost-effectiveness acceptability curves for migrants <60 years of age at late stage CKD diagnosis for LTBI screening. The plots display the probability an intervention has the largest net monetary benefit at various willingness-to-pay thresholds in migrants from (A) low incidence countries, (B) moderate incidence countries, (C) high incidence countries, and (D) very high incidence countries.

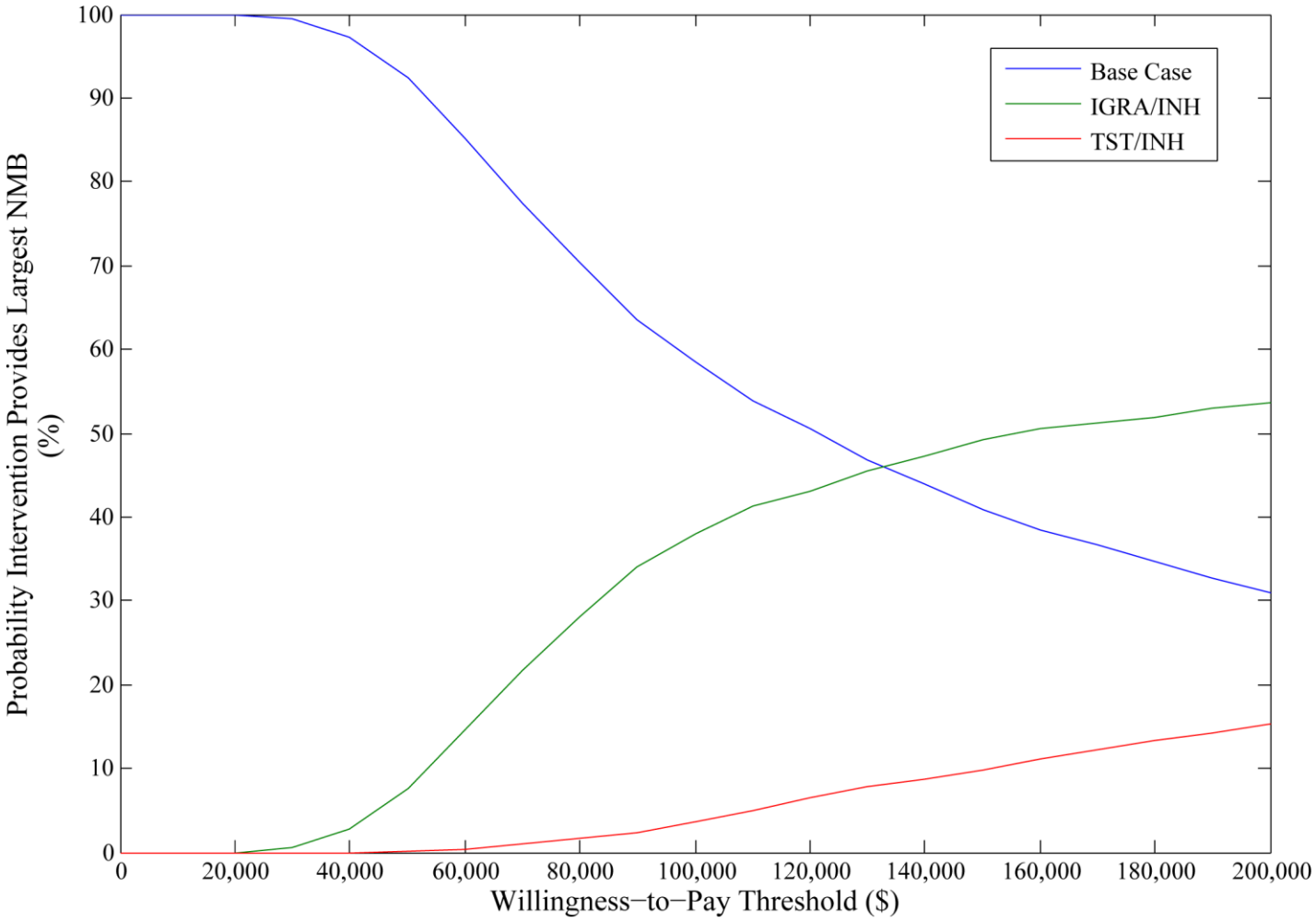
(A)



(B)


Base Case
IGRA/INH
TST/INH
Probability Intervention Provides Largest NMB (%)
Willingness−to−Pay Threshold ($)
0
10
20
30
40
50
60
70
80
90
100
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000

(C)


Base Case
IGRA/INH
TST/INH
Probability Intervention Provides Largest NMB (%)
Willingness−to−Pay Threshold ($)
0
10
20
30
40
50
60
70
80
90
100
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000

(D)

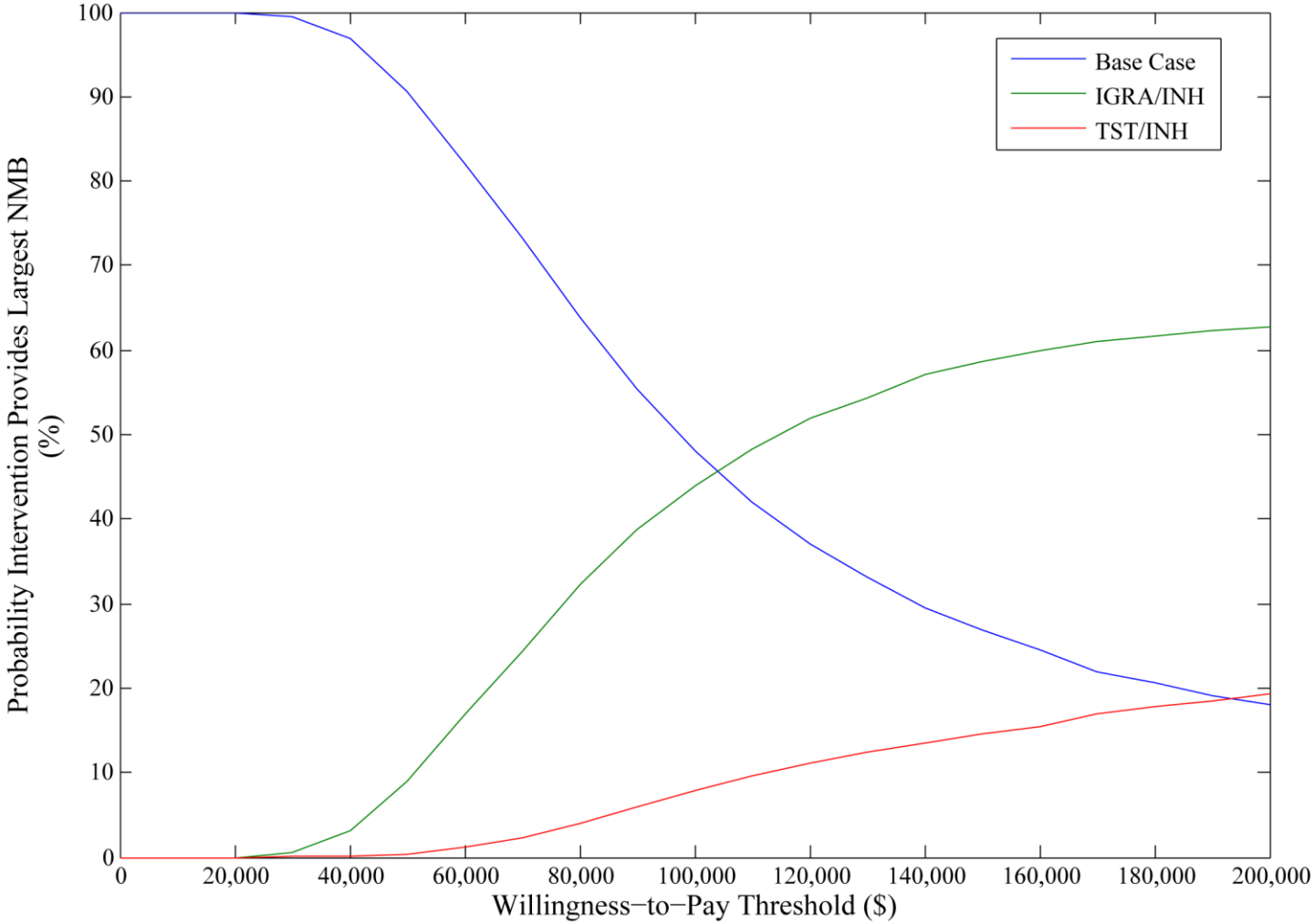
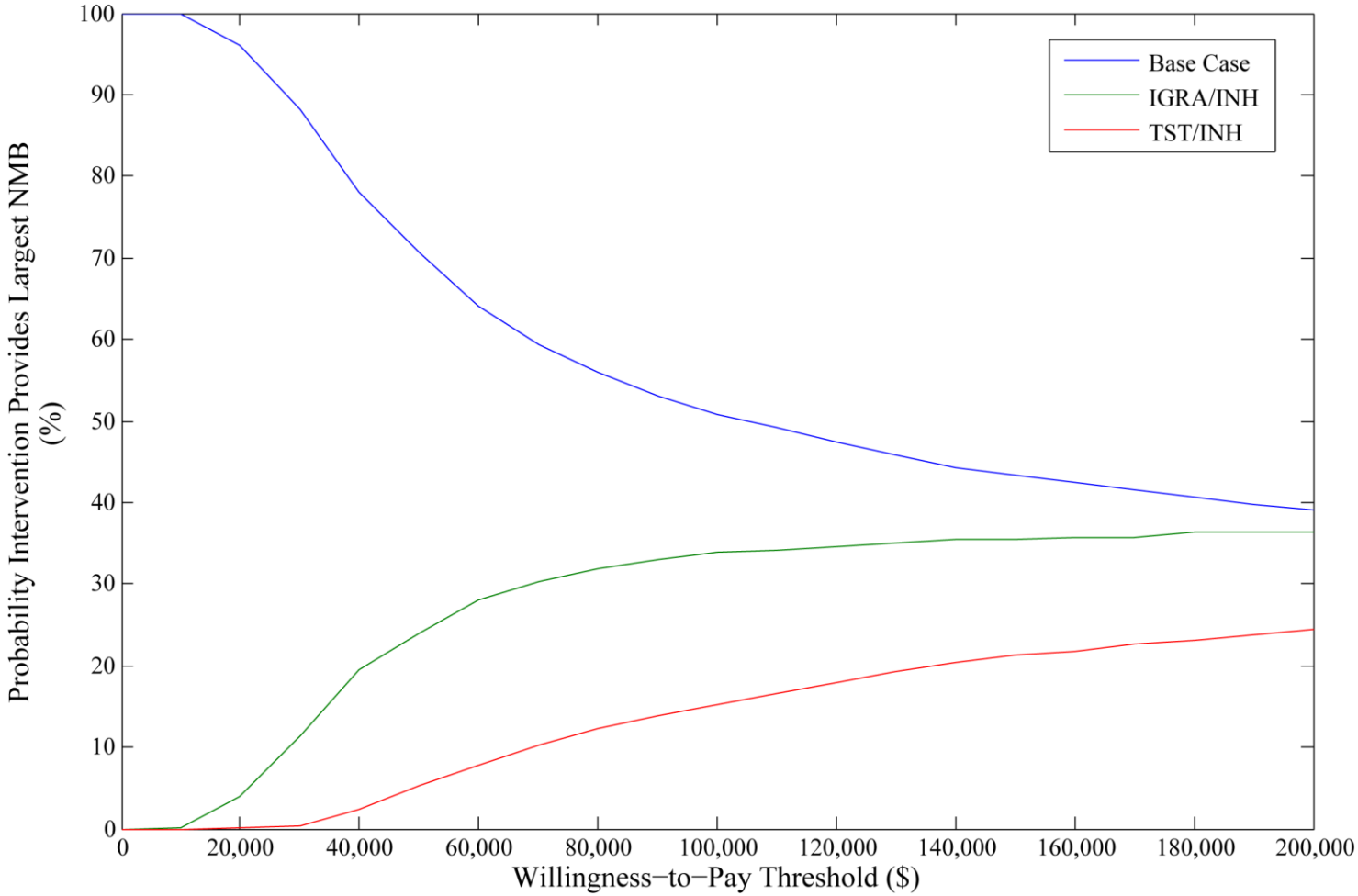
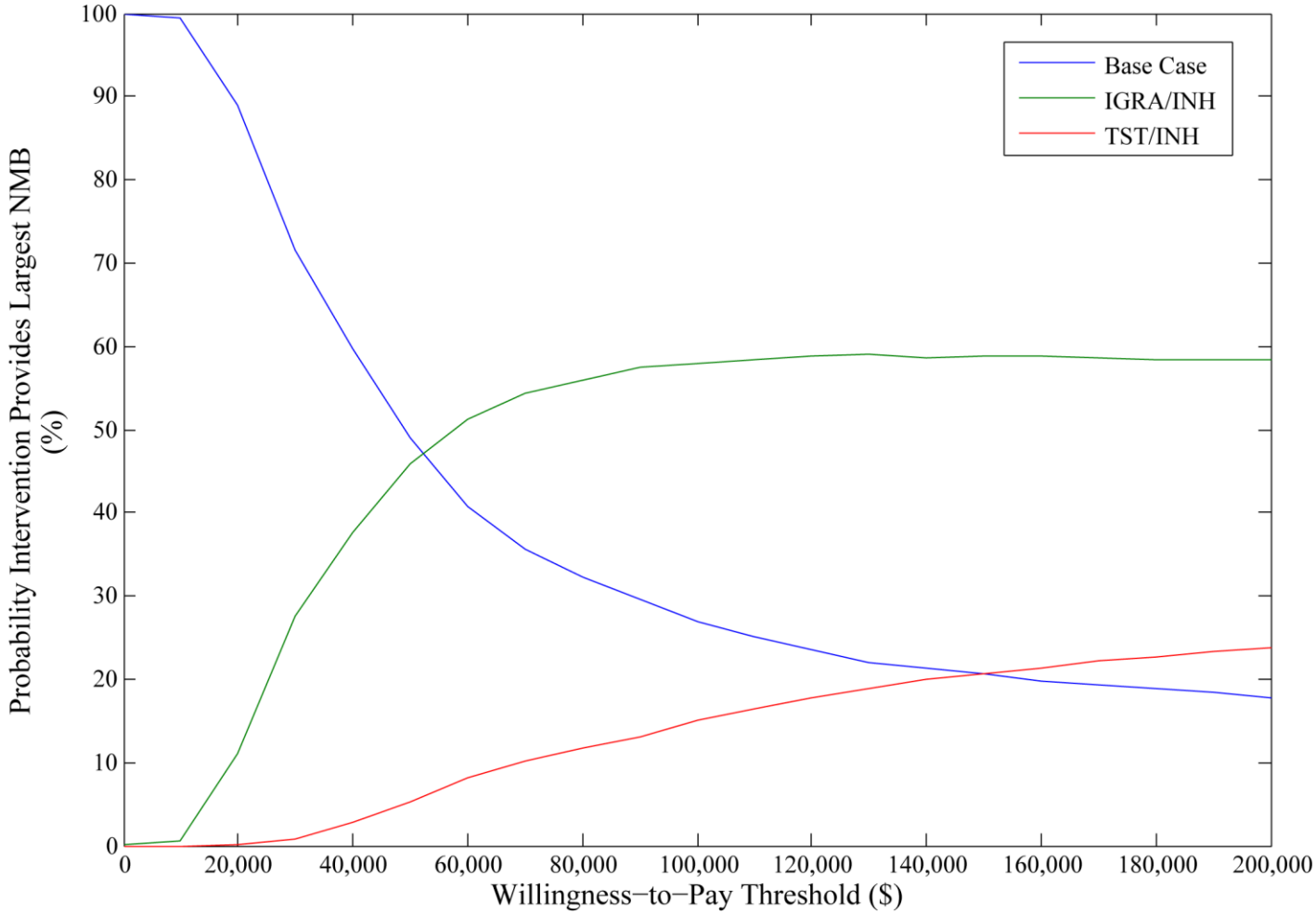

Base Case
IGRA/INH
TST/INH
Probability Intervention Provides Largest NMB (%)
Willingness−to−Pay Threshold ($)
0
10
20
30
40
50
60
70
80
90
100
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000

Figure 6-7. Cost-effectiveness acceptability curves for migrants ≥60 years of age at late stage CKD diagnosis for LTBI screening. The plots display the probability an intervention has the largest net monetary benefit at various willingness-to-pay thresholds in migrants from (A) low incidence countries, (B) moderate incidence countries, (C) high incidence countries, and (D) very high incidence countries.

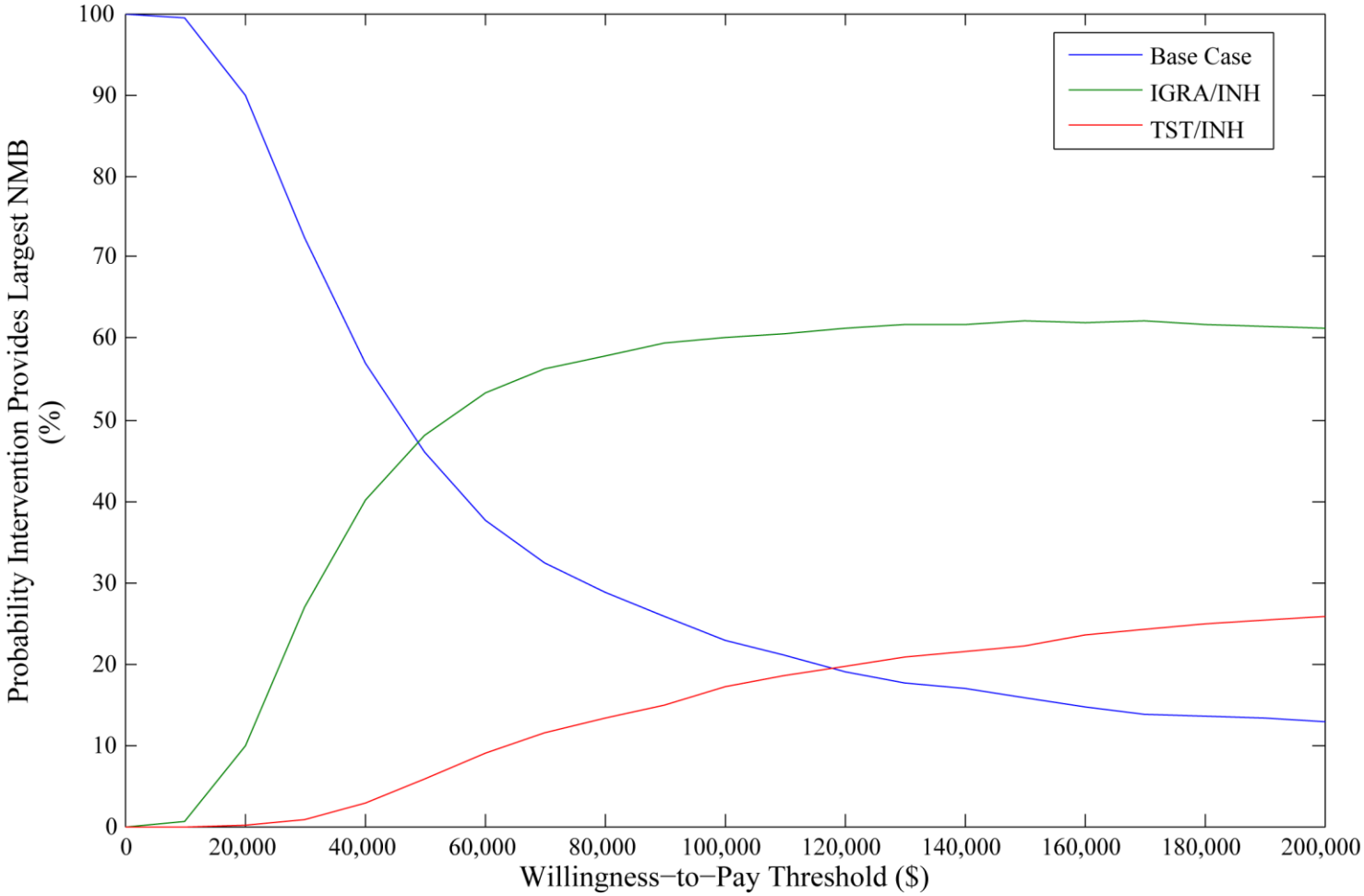
(A)



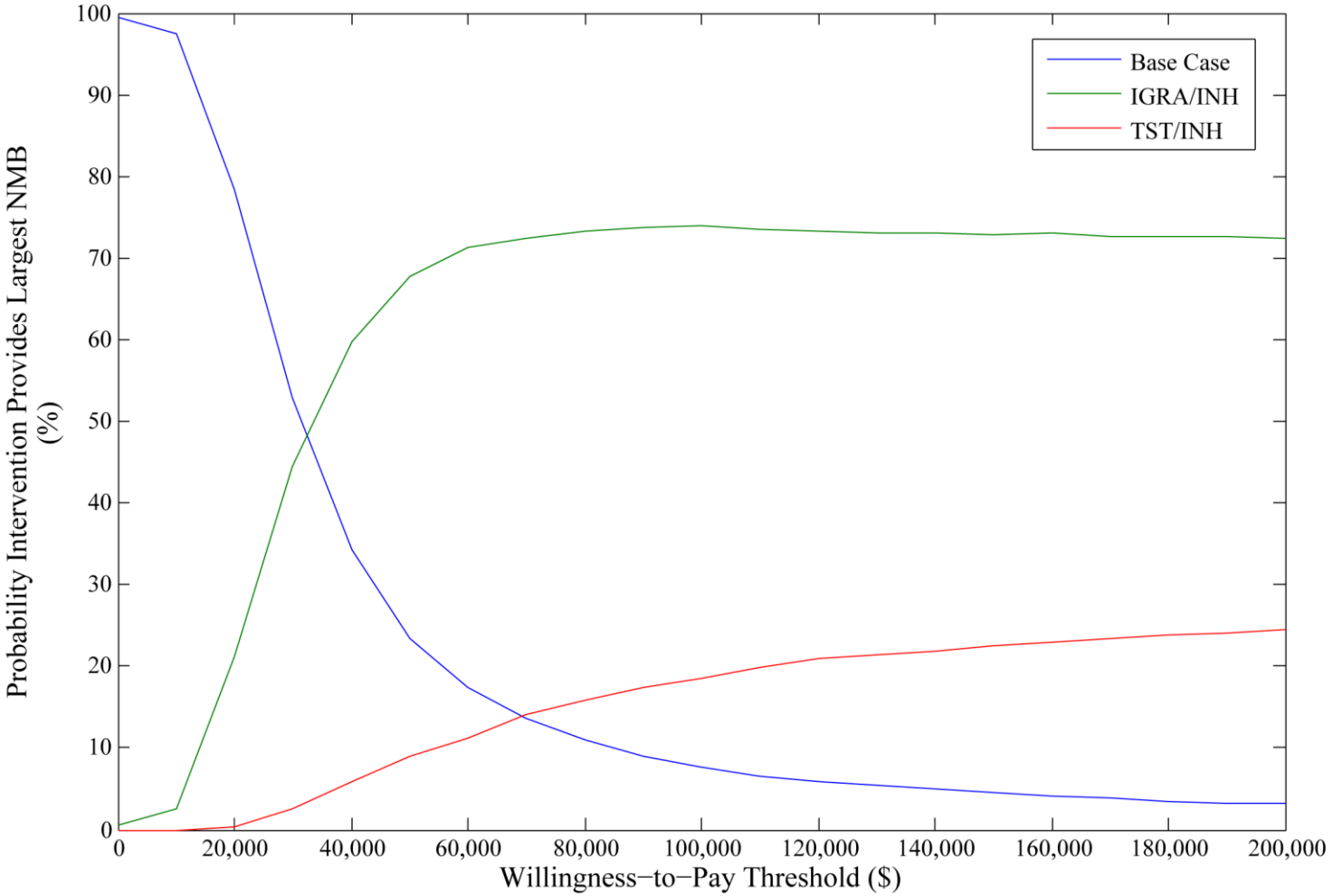
(B)


Probability Intervention Provides Largest NMB (%)
100
90
80
70
60
50
40
30
20
10
0
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000
Willingness−to−Pay Threshold ($)
Base Case
IGRA/INH
TST/INH

(C)


Probability Intervention Provides Largest NMB (%)
100
90
80
70
60
50
40
30
20
10
0
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000
Willingness−to−Pay Threshold ($)
Base Case
IGRA/INH
TST/INH

(D)


Probability Intervention Provides Largest NMB (%)
100
90
80
70
60
50
40
30
20
10
0
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000
Willingness−to−Pay Threshold ($)
Base Case
IGRA/INH
TST/INH

CHAPTER 7. DISCUSSION AND CONCLUSIONS

7.1 Overall Summary of Findings

Prior to the undertaking of this thesis, the cost-effectiveness of LTBI screening in migrants had only been evaluated in broad, non-specific populations resulting in heterogeneity in conclusions between evaluations. These differing results and a recent analysis quantifying attrition in domestic LTBI screening programs meant that LTBI screening in migrants had to be comprehensively evaluated from a fresh perspective. Moreover, the updated Canadian TB Standards [3] highlighted several groups at increased risk of TB, such as people with CKD, with diabetes, with HIV, and on medical immune-suppressants who should be considered for LTBI screening. This represents an enormous population, one that would be difficult to screen using current healthcare resources. We postulated that reducing attrition in LTBI screening programs and/or targeting LTBI screening to migrant populations with high LTBI prevalence and high-risk for TB may result in evidence to support cost-effective screening programs. Targeting LTBI screening to new migrants to Canada who have been flagged for post-arrival follow-up due to CXR abnormalities was very cost-effective, while broadly applying LTBI screening to all new migrants was cost-prohibitive. Additionally, targeting screening to specific migrants from countries with TB incidences ≥30 cases per 100,000 with late stage CKD or requiring dialysis, was cost-effective or cost saving. Finally, performing mass LTBI screening prior to immigration in migrants from countries with TB incidences ≥30 cases per 100,000 to attenuate losses typically seen in post-arrival LTBI screening programs, resulted in a cost-effective method of reducing the TB burden.

We determined in Chapter 2 the sensitivity of the TST and IGRA for detecting LTBI using active TB as a proxy measure, resulting in an estimate of sensitivity for the TST of 78.18% and for the IGRA of 88.89%. We further determined that migrants screened with an IGRA, as opposed to TST, were less likely to be test positive and less likely to be treated for LTBI, however had no significant difference in longitudinal TB, suggesting that IGRA screening would reduce the number of migrants treated for LTBI without worsening long-term outcomes, likely due to more focused treatment on those with true LTBI as opposed to TST positivity confounded by BCG-vaccination. We further explored diagnostic test performance in chapter 3, where we determined the prevalence of TST and

IGRA positivity in migrants from low, moderate, high, and very high TB incidence countries. We found that migrants tested with the TST had an overall higher prevalence of test positivity, with 19.9%, 38.5%, 32.7%, and 41.6% testing positive in low, moderate, high, and very high TB incidence countries, respectively. In comparison, migrants from these same incidences had an IGRA-positivity prevalence of 2.9%, 15.9%, 20.3%, and 33.6%, respectively.

Using the results from chapter 2 and 3, we determined that it was very cost-effective to target LTBI screening to new migrants flagged for post-arrival medical surveillance due to CXR abnormalities or a history of TB. This supports current practice. A move to post-arrival screening with an IGRA and subsequent treatment with rifampin was dominant over the current strategy of TST screening and isoniazid treatment. Furthermore, even if the current strategy was not to screen for LTBI in this population, the high prevalence of LTBI and increased risk of TB yielded an ICER of $11,921 per QALY gained and $8829 per TB case prevented for IGRA screening and rifampin treatment. In our analysis of universal post-arrival LTBI screening in new migrants to Canada we determined that there was no screening option that was cost-effective, even if we limited this universal screening to migrants from countries with the highest TB incidences. The best value option was screening migrants from countries with a TB incidence ≥30 per 100,000 population with an IGRA and treating with rifampin for an ICER of $138,484 per QALY gained.

We further analyzed LTBI screening pre-immigration as a flag for post-arrival follow-up and treatment. This avoided ethical dilemmas associated with coercive pre-immigration LTBI treatment, while taking advantage of already implemented routine pre-immigration medical exams. We assumed that gaps in the LTBI cascade of care associated with screening and medical evaluations could be narrowed. LTBI screening in migrants from countries with a TB incidence <30 cases per 100,000 population was not cost-effective. To contrast, performing LTBI screening in migrants from moderate to very high incidence countries was very cost-effective and if performed using IGRA screening pre-immigration and rifampin treatment post-arrival would reduce 25-year TB incidence by approximately 40% in the screened population and had ICERs of $48,993, $49,035, and $33,696 per QALY gained in migrants from moderate, high, and very high TB incidence countries, respectively.

Focusing on LTBI screening years after migration, we examined LTBI screening in migrants with CKD. From a pool of several co-morbidities that affect TB reactivation this was selected due to the growing worldwide prevalence of CKD and the syndemic risk with TB in especially high burden areas [139]. We found that screening

could be cost-effective in subgroups of migrants with CKD. When analyzing migrants <60 years of age with late stage CKD, we found that screening was only cost-effective in migrants from very high TB incidence countries with an IGRA followed by isoniazid treatment with an ICER of $86,715 per QALY gained. If we applied screening in those ≥60 years of age with late stage CKD, screening became cost-effective in migrants from moderate, high, and very high TB incidence countries with costs per QALY gained of $47,554, $42,846, and $26,935, respectively. Screening in migrants who had to initiate dialysis was much more cost-effective. Regardless of age, screening with an IGRA and treating with isoniazid was dominant when compared to no screening in migrants from moderate to very high incidence countries; no screening was cost-effective in migrants from low TB incidence countries.

7.2 Implications and Impact

This work has significant implications for TB policy and prevention worldwide. We have challenged the current paradigm surrounding TB prevention in migrants. Current recommendations on migrant TB prevention have focused on LTBI screening immediately post-immigration. The results presented in this thesis suggest this will be cost-prohibitive. We have shown that mass LTBI screening is not cost-effective and even efforts to focus LTBI screening to migrants from areas with the highest LTBI prevalence still fall well above commonly accepted WTP thresholds. We demonstrated that currently implemented pre-immigration medical exams could be utilized to perform LTBI screening cost-effectively in migrants from countries with a TB incidence ≥30 per 100,000 population. This thesis proposes a mind-shift from preventing TB post-landing to preventing TB pre-immigration through widespread pre-landing LTBI screening in prospective new migrants to low TB incidence countries.

We have further demonstrated the TST is an ineffective tool to identify LTBI in migrant populations. While IGRA usage may be increasing, TST use is still very common due to its practicality, characterization, and cost. Our work throughout has shown that the TST has poorer sensitivity and specificity for active TB than the IGRA, identifies more migrants for LTBI treatment than the IGRA, performs significantly poorer than the IGRA in immunocompromised populations, and is associated with larger longitudinal costs to the healthcare system than the IGRA, despite being a more inexpensive test than the IGRA. This thesis proposes a change in screening from the TST-based LTBI screening to IGRA-based LTBI screening in all migrants based on the reduced long-term costs, better long-term outcomes, and better diagnostic characteristics in migrant populations.

Additionally, this thesis identifies rifampin as the preferred LTBI treatment option in migrants in the absence of contraindications. We have shown that even using a conservative estimate of rifampin effectiveness (80%) that is significantly lower than isoniazid effectiveness (93%), rifampin treatment is nearly always more cost-effective than isoniazid treatment. Current treatment guidelines in Canada, the United States, and the United Kingdom [3,346,368] recommend isoniazid as the primary choice for LTBI therapy due to the uncertainty around rifampin effectiveness. However this thesis has shown even a significant reduction in the treatment effectiveness of rifampin is not enough for isoniazid treatment to be more cost-effective than rifampin due to the well-established reduced rates of treatment emergent adverse events and improved rates of treatment completion. Considering the low rates of treatment recommendation, initiation, and completion in migrants when typically recommended isoniazid treatment [53] and the significant long-term benefit of LTBI treatment in high prevalence migrant populations, policy makers should consider rifampin a first-line drug choice for LTBI treatment moving forward.

This thesis has further highlighted the impact gaps in the LTBI cascade of care have on longitudinal TB when applied to the scenario of post-arrival LTBI screening of migrants. In Canada, post-arrival medical surveillance is passive and as few as 60% adhere within the 30-day specified follow-up window post-immigration. This sizable gap is responsible for up to an additional 15% of TB cases in new migrants referred for surveillance. Compared to treatment non-adherence (responsible for up to an additional 4% of TB cases), closing this gap should be the top priority of healthcare systems employing a passive post-arrival surveillance system like Canada. At the present, significant focus is placed on improving LTBI treatment adherence, however consideration of upstream gaps may have much more impact on long-term outcomes.

Finally, this thesis has highlighted that LTBI screening and treatment is highly cost-effective in migrant populations with an elevated prevalence of LTBI at increased risk of TB. While it has long been established that LTBI screening in HIV populations is cost-effective, paucity of data in other populations at elevated risk of TB led to great uncertainty about screening elsewhere. This thesis demonstrates that targeted screening at healthcare system contact in the context of migrants from countries of elevated TB incidence with late stage CKD or requiring dialysis is extremely cost-effective. LTBI screening is the norm in many jurisdictions at dialysis initiation, but this thesis has two important implications about this practice. Firstly, LTBI screening in those with CKD or requiring dialysis is not cost-effective in migrants from low TB incidence countries and thus not cost-effective in many locally born populations in low incidence countries; use of resources for screening this population must be reconsidered.

Secondly, LTBI screening was cost-effective in older populations with late stage CKD who are at one-third the risk of TB compared to those requiring dialysis. This implies that LTBI screening in similar populations, such as those on immune-suppressing medications or those with cancers of the head and neck [3], are likely to also be cost-effective. This would suggest that currently practiced LTBI screening prior to therapy with TNF-α inhibitors is likely to be of value to healthcare systems only when applied to populations with an increased prevalence of LTBI, even though it has not been comprehensively evaluated.

7.3 Strengths and Limitations

This thesis is backed by several key strengths in its methodologies. Firstly, a comprehensive systematic review and meta-analysis was completed to inform diagnostic test sensitivity and approximate LTBI prevalence in the cost-effectiveness analyses performed in this thesis. We further refined LTBI prevalence estimates in Chapter 3 and 4 using country-of-origin-specific TB incidence data from Ontario, Canada. Utilizing the wealth of available data surrounding LTBI diagnostics in migrants and utilizing these results to optimize LTBI prevalence estimates strengthens how well the analyses reflect the real world. Secondly, we analyzed the internal validity of the model structure for each cost-effectiveness model developed in Chapters 4, 5, and 6, through several stepwise experiments to ensure model output matched the expected results. These included: assigning deterministic timing parameters to ensure events occurred at the desired times, assigning specific costs/QALYs to individuals to ensure costs/QALYs were accrued correctly, forcing all individuals to develop TB to ensure TB incidence was calculated correctly, and forcing all individuals down specific patient pathways to ensure there was no error in coding. Each model was further analyzed for external validity against the data source used to ensure that the parameters pulled from this source yielded similar outcomes when run in our model. Thirdly, each cost-effectiveness analysis carefully considered the impact the LTBI cascade of care would have on interventions analyzed. Previous cost-effectiveness analyses performed in migrants had minimized the extent of attrition at each step or failed to consider attrition at all and thus overestimated the benefits of LTBI interventions. Fourthly, this thesis used patient-level administrative data to create a DES model for LTBI screening in migrants with late stage CKD or who were initiating dialysis. The use of patient-level data allows increased flexibility and complexity in what is modeled, improved accuracy of parameter estimates, and a better understanding of the uncertainty of model results. Furthermore, this makes the results of this analysis directly applicable to the population targeted by the intervention and can allow policy makers

of other jurisdictions to judge how generalizable the results are to their own target populations. Finally, this thesis provides a comprehensive evaluation of LTBI screening at each step of the typical immigration process most migrants traverse. Through this, policy makers can evaluate relative costs and population impact of interventions at each step to determine what intervention to use, when to use it, and how it should be implemented.

While this thesis has several strengths, the results must be interpreted while considering its limitations. A mentioned strength is our use of literature data and real world TB incidence data from Ontario, Canada to estimate LTBI prevalence, however while this is the 'gold-standard' method, the results must be interpreted in the context of imperfect diagnostic tests and limited follow-up time of large migrant cohorts. Key limitations of all model-based evaluations are the simplifying assumptions required to ensure a model is easily understandable while being complex enough to sufficiently answer the question of interest. In the economic evaluations presented in this thesis, neither drug resistance nor active transmission to the greater population was considered. Drug resistance was not considered due to the difficulty in estimating the prevalence of MDR-TB, the difficulty in estimating the impact improperly treating isoniazid-resistant LTBI would have on long-term outcomes, and the costs associated with drug resistance. Adding these nuances to models would be possible, but would increase model complexity significantly. Nevertheless, even if this limitation were corrected, it would only strengthen the results, which largely support rifampin treatment. Active transmission to the greater population was not considered due to the increased complexity required to consider transmission dynamics. In already complicated models, this change would increase model run times to impractical lengths. Instead, we made a simplifying assumption in chapters 4 and 5 of limited transmission to the population modeled and in chapter 6 that no active transmission occurred. These assumptions are unlikely to significantly impact results due to the limited reported transmission of TB from migrant populations to locally born populations [4,428]. In addition to these limitations, a mean population reactivation rate was assumed in the models presented in chapters 4 and 5 of this thesis. This assumption did not allow a nuanced evaluation of where the risks of LTBI treatment outweigh the benefits. Even in individuals from elevated TB incidence countries, those with a significantly lower risk of progression than the population average we assumed may not be cost-effective to screen. A further limitation of this thesis is that LTBI diagnostic performance is based on surrogate measures, such as active TB (for sensitivity) and low likelihood of TB exposure (for specificity). The immune state of individuals with active TB is different than for those without active TB (and therefore those with LTBI), however it is impossible to determine how much this impacts test results. Exploring uncertainty via PSA is an important step in

evaluating deterministic results in context, however having a gold standard for LTBI diagnosis would be extremely beneficial to LTBI economic analyses. The models presented in this thesis assume a healthcare system perspective where the costs and impact to individual patients and others outside the healthcare system is not considered. This was chosen due to the different TB programmes in place in Canada and worldwide, making some of the societal costs and impacts considered (e.g. DOT, transportation costs) likely to be very program specific. Even so, as TB impacts more than just the healthcare system and individual, a societal perspective is more representative of TB and should be considered moving forward. Finally, long-term longitudinal studies of TB outcomes are scarce due to the difficulty in ensuring adequate follow-up. As a result, extrapolation to five, ten, and twenty-five year time horizons had to be made in the chapters containing economic analyses. These extrapolations could impact our results as TB incidence is highest in the first few years post-exposure however there is evidence to suggest reactivation of LTBI in migrants is consistent over time [244,366]. Nevertheless, as the full benefit of LTBI screening is unlikely to be realized over short time horizons, these extrapolations were necessary.

7.4 Knowledge Translation and Implementation

In Canada it is current practice to follow-up with new migrants flagged for medical surveillance post-arrival. However this passive system results in only 60% of migrants adhering within 30 days of arrival. This thesis has shown that ensuring adherence to post-arrival follow-up can reduce TB incidence in this subgroup by over 10%. This information can be applied to rationalize increased efforts to follow-up with new migrants and provide LTBI screening and treatment where appropriate. This can be done through monetary incentives to follow-up, use of culturally appropriate interventions, ensuring healthcare coverage upon arrival, or mandating post-arrival follow-up. Gaps at all steps in the LTBI cascade of care mean that fewer than 20% of migrants complete an adequate course of LTBI therapy. Our research in chapters 4 and 5 highlight the effect attrition in the cascade has and the benefits closing specific gaps can have on longitudinal TB incidence. Failure to implement changes will impede TB prevention efforts in Canada and lead to morbidity and mortality that can otherwise be avoided.

The current practice for new dialysis patients in BC is to screen with an IGRA prior to initiation in an effort to identify LTBI and provide treatment. Our research in chapter 6 highlights the importance of this practice, but also identifies individuals from low TB incidence countries are not a cost-effective group to screen. We also highlight the value of LTBI screening in migrants from moderate to very high TB incidence countries ≥60 years of age who have

late stage CKD not requiring dialysis. We have shown that the median time to TB is exceptionally short in both migrants diagnosed with late stage CKD and initiating dialysis, suggesting that upstream screening is prudent to perform. Implementing a screening program for those with late stage CKD is cost-effective, can reduce TB incidence, and avert unnecessary TB-related morbidity and mortality. Prioritizing this screening to individuals with late stage CKD who also have diabetes and are therefore at increased risk of eventually requiring dialysis may be an important first step, requiring buy-in of patients and healthcare workers alike.

The End TB Strategy proposed by the WHO aims to reduce the TB burden globally by 90% to approximately 100 cases per million persons per year worldwide [74]. In low TB incidence countries like Canada, the goal is elimination, hoping to reach TB incidences of 10 cases per million by 2035 and 1 case per million by 2050 [70]. The research presented in this thesis provides strategies for low TB incidence countries to not only significantly impact TB incidence domestically, but also help provide valuable infrastructure in lower income, TB endemic regions. Providing routine IGRA screening during pre-immigration medical exams will require infrastructure not currently present in many low-income, high incidence countries that represent significant proportions of new migrants annually to migrant receiving countries. Support for this infrastructure by high-income countries can have bilateral benefit, providing access and training to healthcare professionals in these countries, which may aid in TB prevention and elimination efforts locally. Previous introduction of mandatory pre-immigration CXR to detect TB has had a significant impact on TB infrastructure in these regions [365]. This provides a framework for the impact and a blueprint for the planning, implementation, and execution of routine LTBI screening in these settings. To achieve the goals of the End TB Strategy, investment from high-income countries in TB infrastructure in low-income, TB endemic settings is necessary. Implementation of routine pre-immigration LTBI screening is a mutually beneficial option for many migrant-receiving countries.

7.5 Future Directions

This research provides a solid foundation for making decisions regarding migrant LTBI screening, yet much can still be done to better understand LTBI diagnostics and how best to direct healthcare dollars allocated to TB prevention. LTBI diagnostic test sensitivity and specificity are currently determined using proxy measures, of which a proxy of active TB for test sensitivity was used in chapter 2. Further research should focus on identifying new diagnostics that can more appropriately identify TB infection. Promising research has been performed already

with the advent of the new diagnostic test C-Tb. C-Tb combines the specificity of IGRAs with the convenience and practicality of a TST, using ESAT-6 and CFP10 antigens [429,430]. Clinical trials have shown it to be acceptable, well tolerated, have a high specificity, and a positive response associated with increased risk of TB [429–431]. Test sensitivity still requires careful investigation as concordance with IGRA and TST varied significantly between phase II and phase III trials, suggesting that it may not be as sensitive as either of these tests for LTBI [429–431]. Nevertheless, it may be a useful test where IGRA is not practical. In addition, research suggests that certain biomarkers may become elevated in individuals with LTBI; the expression of these biomarkers may indicate individuals at risk of progression [432,433]. New diagnostic tests that can identify these biomarkers may potentially prove much more valuable than the currently available TST and IGRA, which lack an ability to predict who will progress to active disease and when.

Building upon our work completed in chapter 3, an updated meta-analysis of predictors of IGRA positivity and long-term TB outcomes in migrants would prove valuable to identify further subgroups to target for LTBI screening. At the time of writing, there was a dearth of longitudinal outcomes in migrants tested with an IGRA due to its relatively recent arrival as an LTBI screening platform compared with the century old TST. Furthermore, an update on current rates of test positivity for both TST and IGRA can elicit more accurate estimates of LTBI prevalence in migrants from various TB incidences. Complicating this update, however, may be the rapid creation of new generation IGRAs that have different diagnostic performances than previous generations. In this thesis, we pooled the diagnostic results of all IGRA platforms to ensure that there was enough data to determine an estimate; in the future, there may be a wealth of data on a specific generation of IGRA that will allow a more robust estimate of test performance.

This thesis has provided solid evidence for LTBI screening decisions both pre- and immediately post-immigration, however further research is necessary due to two issues. We have shown that in the nearly 98% of prospective migrants not screened post-arrival, TB incidence in country of origin is not sufficient to make LTBI screening cost-effective. In addition, while we have shown that pre-immigration LTBI screening is very cost-effective in moderate to very high TB incidence countries, if fully funded by the healthcare system it may not be feasible due to the additional costs associated with screening hundreds of thousands of prospective migrants. Further to this point, blanket screening recommendations based on population averages, while benefiting the population as a whole, may unnecessarily expose certain individuals to LTBI treatment when individual risks outweigh the benefits.

These issues require research into identifying demographic and medical risk factors associated with TB and their magnitude of effect on TB risk. In the case of post-immigration LTBI screening, this will maximize the immediate impact of screening and focusing this intervention in high-risk groups may be cost-effective. In the case of pre-immigration screening, this will reduce the impact pre-immigration LTBI screening has, but may make the number of prospective migrants screened more feasible from a cost perspective and will likely focus screening to those at highest risk of TB, improving the benefit-to-risk tradeoff made when prescribing LTBI treatment. There is evidence to suggest that socioeconomic status and immigration class are risk factors for TB [96,434] and may be two areas worth exploring in more detail to help make post-immigration LTBI screening cost-effective and pre-immigration LTBI screening equitable and feasible.

Finally, we have demonstrated that in migrants from moderate to very high TB incidence countries, it is cost-effective to screen for LTBI at the time of dialysis initiation and in migrants ≥60 years of age at the time of late stage CKD diagnosis. While this research is the first to analyze this question in the context of migrants, it also requires further follow-up research in regards to other medical co-morbidities that increase risk of TB. One of the largest screening conundrums surrounds diabetes. There are currently no routine LTBI screening programs for individuals diagnosed with diabetes and the WHO does not support mass screening in this population [164]. However, given that it is a significant risk factor for other co-morbidities, such as CKD, there may be benefit in determining if there are subgroups with diabetes in which screening is cost-effective. Furthermore, the results of our analysis suggest that it may be cost-effective to screen populations with a similar TB risk profile to those with late stage CKD, which includes those on immune-suppressing medications and those with cancers of the head or neck. While several co-morbidities may be cost-effective to screen, however, it will be necessary to perform a comprehensive analysis to determine where and how LTBI screening should be prioritized. An important next step is to complete an economic evaluation of LTBI screening upon diagnosis of several different co-morbidities. Efficiency frontiers can be created to determine the population costs and benefits of LTBI screening for the selected co-morbidities, allowing for healthcare resource prioritization in the future.

7.6 Final Conclusions

This thesis assessed the performance of LTBI diagnostic tests in migrants from countries of various TB incidences and applied these findings to determine the cost-effectiveness of migrant LTBI screening at different

steps in the migration process. IGRA screening was shown to be more specific than the TST for detecting LTBI and resulted in fewer individuals being prescribed LTBI treatment with no increase in longitudinal TB incidence, suggesting the increased cost of IGRA screening in the short term may reap significant long term benefits. Moreover, due to the higher specificity, the IGRA had a lower positive test prevalence than the TST at each of the TB incidences evaluated, resulting in fewer individuals being considered for LTBI treatment and therefore not at risk for treatment-emergent adverse events.

LTBI screening could be made cost-effective if targeted to migrants with an increased risk of TB or by improving the number of migrants who eventually complete LTBI treatment. In Canada, applying post-arrival IGRA screening to migrants with abnormal CXR or previous TB and offering rifampin treatment to those testing positive was very cost-effective. However, universal screening was not cost-effective, even if targeted to migrants from the highest TB incidence countries largely due to inadequacies seen in domestic LTBI programs due to losses in the cascade of care. Applying IGRA screening pre-immigration in order to reduce losses typically seen in these domestic LTBI programs, however, proved to be very cost-effective when applied to migrants from countries with a TB incidence ≥30 cases per 100,000 population.

Performing LTBI screening in migrants from countries with a TB incidence ≥30 cases per 100,000 population who have been diagnosed with renal co-morbidity that significantly increases their risk of TB was cost-effective. IGRA screening and isoniazid treatment in migrants ≥60 years of age at time of late stage CKD diagnosis or screening and treatment of migrants of any age at time of dialysis initiation was highly cost-effective in those form these TB incidences. LTBI screening with an IGRA was only cost-effective in migrants <60 years of age at time of late stage CKD diagnosis if they were from countries with a TB incidence ≥200 cases per 100,000 population.

Finally, building upon the conclusions of this thesis, future research should be geared to determining cost-effectiveness of LTBI screening in elevated LTBI prevalence populations diagnosed with a co-morbidity increasing risk of TB. Completing these analyses will allow a comprehensive efficiency frontier to be created, which can be used to help inform feasible allocation of healthcare dollars to the populations that may benefit the most from LTBI screening.

REFERENCES

1. Lienhardt C, Glaziou P, Uplekar M, Lönnroth K, Getahun H, Raviglione M. Global tuberculosis control: lessons learnt and future prospects. *Nat Rev Microbiol* 2012;10(6):407–416.
2. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc Sci Med* 2009;68(12):2240–2246.
3. Public Health Agency of Canada. *Canadian Tuberculosis Standards 7th Edition*. Ottawa (ON): Government of Canada; 2014. Available: http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tb-canada-7/index-eng.php [accessed 1 Nov 2017].
4. Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. *BMC Med* 2016;14:48.
5. WHO. *Global tuberculosis report 2016*. Geneva: World Health Organization; 2017. Available: http://www.who.int/tb/publications/global_report/en/ [accessed 1 Nov 2017].
6. WHO. *Global tuberculosis report 2017*. Geneva: World Health Organization; 2017. Available: http://www.who.int/tb/publications/global_report/en/ [accessed 1 Nov 2017].
7. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, *et al.* Tuberculosis. *Nat Rev Dis Primer* 2016;2:16076.
8. Langlois-Klassen D, Senthilselvan A, Chui L, Kunimoto D, Saunders LD, Menzies D, *et al.* Transmission of Mycobacterium tuberculosis Beijing Strains, Alberta, Canada, 1991-2007. *Emerg Infect Dis* 2013;19(5):701–711.
9. Loudon RG, Spohn SK. Cough frequency and infectivity in patients with pulmonary tuberculosis. *Am Rev Respir Dis* 1969;99(1):109–111.
10. Iseman MD. *A Clinician's Guide to Tuberculosis*. Philadelphia (PA): 2000. Available: a-clinician-s-guide-to-tuberculosis-id-0781717493.aspx [accessed 1 Nov 2017].
11. Stead WW. The Clinical Spectrum of Primary Tuberculosis in Adults: Confusion with Reinfection in the Pathogenesis of Chronic Tuberculosis. *Ann Intern Med* 1968;68(4):731.
12. Smith I. Mycobacterium tuberculosis Pathogenesis and Molecular Determinants of Virulence. *Clin Microbiol Rev* 2003;16(3):463–496.

13. Achkar JM, Jenny-Avital ER. Incipient and Subclinical Tuberculosis: Defining Early Disease States in the Context of Host Immune Response. *J Infect Dis* 2011;204(Suppl 4):S1179–S1186.
14. Long R. Making a timely diagnosis of pulmonary tuberculosis. *Can Respir J* 2015;22(6):317–321.
15. Norbis L, Alagna R, Tortoli E, Codecasa LR, Migliori GB, Cirillo DM. Challenges and perspectives in the diagnosis of extrapulmonary tuberculosis. *Expert Rev Anti Infect Ther* 2014;12(5):633–647.
16. American Thoracic Society and the Centers for Disease Control and Prevention. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. *Am J Respir Crit Care Med* 2000;161:1376–1395.
17. WHO. *Guidelines for treatment of tuberculosis*. Geneva: World Health Organization; 2010. Available: http://www.who.int/tb/publications/2010/9789241547833/en/ [accessed 1 Nov 2017].
18. Johnston JC, Campbell JR, Menzies D. Effect of Intermittency on Treatment Outcomes in Pulmonary Tuberculosis: An Updated Systematic Review and Metaanalysis. *Clin Infect Dis* 2017;64(9):1211–1220.
19. Muñoz L, Stagg HR, Abubakar I. Diagnosis and Management of Latent Tuberculosis Infection. *Cold Spring Harb Perspect Med* 2015;5(11).
20. Campbell JR, Krot J, Elwood K, Cook V, Marra F. A systematic review on TST and IGRA tests used for diagnosis of LTBI in immigrants. *Mol Diagn Ther* 2015;19(1):9–24.
21. Campbell JR, Chen W, Johnston J, Cook V, Elwood K, Krot J, *et al.* Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis. *Mol Diagn Ther* 2015;19(2):107–117.
22. Talati NJ, Gonzalez-Diaz E, Mutemba C, Wendt J, Kilembe W, Mwananyanda L, *et al.* Diagnosis of latent tuberculosis infection among HIV discordant partners using interferon gamma release assays. *BMC Infect Dis* 2011;11:264.
23. Cohn DL. The Effect of BCG Vaccination on Tuberculin Skin Testing. *Am J Respir Crit Care Med* 2001;164(6):915–916.
24. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. *Ann Intern Med* 2007;146(5):340–354.

25. Rangaka MX, Wilkinson KA, Glynn JR, Ling D, Menzies D, Mwansa-Kambafwile J, *et al.* Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12(1):45–55.

26. Yang H, Kruh-Garcia NA, Dobos KM. Purified protein derivatives of tuberculin--past, present, and future. *FEMS Immunol Med Microbiol* 2012;66(3):273–280.

27. Jeanes CW, Davies JW, McKinnon NE. Sensitivity to "atypical" acid-fast mycobacteria in Canada. *Can Med Assoc J* 1969;100(19):888–895.

28. Menzies R, Vissandjee B. Effect of bacille Calmette-Guérin vaccination on tuberculin reactivity. *Am Rev Respir Dis* 1992;145(3):621–625.

29. Nayak S, Acharjya B. Mantoux test and its interpretation. *Indian Dermatol Online J* 2012;3(1):2–6.

30. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, *et al.* Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis* 2017;64(2):111–115.

31. Guld J. Quantitative aspects of the intradermal tuberculin test in humans. II. The relative importance of accurate injection technique. *Acta Tuberc Scand* 1954;30(1–2):16–36.

32. Kardjito T, Donosepoetro M, Grange JM. The Mantoux test in tuberculosis: correlations between the diameters of the dermal responses and the serum protein levels. *Tubercle* 1981;62(1):31–35.

33. Stead WW, To T. The significance of the tuberculin skin test in elderly persons. *Ann Intern Med* 1987;107(6):837–842.

34. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008;149(3):177–184.

35. Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, *et al.* Gamma Interferon Release Assays for Detection of Mycobacterium tuberculosis Infection. *Clin Microbiol Rev* 2014;27(1):3–20.

36. Mazurek GH, Villarino ME. Guidelines for Using the QuantiFERON-TB Test for Diagnosing Latent Mycobacterium tuberculosis Infection. *MMWR Recomm Rep* 2003;52(RR02):15–18.

37. Oxford Immunotec. How the T-SPOT.TB test works. 2017; Available: http://www.tspot.com/about-the-test/t-spot-tb-test-works/ [accessed 1 Nov 2017].

38. Mazurek G, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection --- United States, 2010. *MMWR Morb Mortal Wkly Rep* 2010;59(RR05):1–25.

39. Trajman A, Steffen RE, Menzies D. Interferon-Gamma Release Assays versus Tuberculin Skin Testing for the Diagnosis of Latent Tuberculosis Infection: An Overview of the Evidence. *Pulm Med* 2013;2013:601737.

40. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. *Int J Tuberc Lung Dis* 2008;12(11):1235–1254.

41. Tulsky JP, Pilote L, Hahn JA, Zolopa AJ, Burke M, Chesney M, *et al.* Adherence to isoniazid prophylaxis in the homeless: a randomized controlled trial. *Arch Intern Med* 2000;160(5):697–702.

42. Abubakar I, Stagg HR, Whitworth H, Lalvani A. How should I interpret an interferon gamma release assay result for tuberculosis infection? *Thorax* 2013;68(3):298–301.

43. van Zyl-Smit RN, Pai M, Peprah K, Meldau R, Kieck J, Juritz J, *et al.* Within-subject variability and boosting of T-cell interferon-gamma responses after tuberculin skin testing. *Am J Respir Crit Care Med* 2009;180(1):49–58.

44. van Zyl-Smit RN, Zwerling A, Dheda K, Pai M. Within-subject variability of interferon-g assay results for tuberculosis and boosting effect of tuberculin skin testing: a systematic review. *PLoS ONE* 2009;4(12):e8517.

45. Whitworth WC, Hamilton LR, Goodwin DJ, Barrera C, West KB, Racster L, *et al.* Within-subject interlaboratory variability of QuantiFERON-TB gold in-tube tests. *PLoS ONE* 2012;7(9):e43790.

46. Veerapathran A, Joshi R, Goswami K, Dogra S, Moodie EEM, Reddy MVR, *et al.* T-cell assays for tuberculosis infection: deriving cut-offs for conversions using reproducibility data. *PLoS ONE* 2008;3(3):e1850.

47. Metcalfe JZ, Cattamanchi A, McCulloch CE, Lew JD, Ha NP, Graviss EA. Test variability of the QuantiFERON-TB gold in-tube assay in clinical practice. *Am J Respir Crit Care Med* 2013;187(2):206–211.

48. Doberne D, Gaur RL, Banaei N. Preanalytical delay reduces sensitivity of QuantiFERON-TB gold in-tube assay for detection of latent tuberculosis infection. *J Clin Microbiol* 2011;49(8):3061–3064.

49. Sharma SK, Vashishtha R, Chauhan LS, Sreenivas V, Seth D. Comparison of TST and IGRA in Diagnosis of Latent Tuberculosis Infection in a High TB-Burden Setting. *PLoS ONE* 2017;12(1):e0169539.

50. Norton BL, Holland DP. Current management options for latent tuberculosis: a review. *Infect Drug Resist* 2012;5:163–173.

51. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. *Bull World Health Organ* 1982;60(4):555–564.

52. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis* 1999;3(10):847–850.

53. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2016;16(11):1269–1278.

54. Sandgren A, Vonk Noordegraaf-Schouten M, van Kessel F, Stuurman A, Oordt-Speets A, van der Werf MJ. Initiation and completion rates for latent tuberculosis infection treatment: a systematic review. *BMC Infect Dis* 2016;16.

55. Mallolas J, Sarasa M, Nomdedeu M, Soriano A, López-Púa Y, Blanco JL, *et al.* Pharmacokinetic interaction between rifampicin and ritonavir-boosted atazanavir in HIV-infected patients. *HIV Med* 2007;8(2):131–134.

56. López-Cortés LF, Ruiz-Valderas R, Viciana P, Alarcón-González A, Gómez-Mateos J, León-Jimenez E, *et al.* Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet* 2002;41(9):681–690.

57. Menzies D, Al Jahdali H, Al Otaibi B. Recent developments in treatment of latent tuberculosis infection. *Indian J Med Res* 2011;133(3):257–266.

58. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis* 1992;145(1):36–41.

59. Reichman LB, Lardizabal A, Hayden CH. Considering the Role of Four Months of Rifampin in the Treatment of Latent Tuberculosis Infection. *Am J Respir Crit Care Med* 2004;170(8):832–835.

60. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, *et al.* Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011;365(23):2155–2166.

61. WHO. *The top 10 causes of death*. Geneva: World Health Organization; 2017. Available: http://www.who.int/mediacentre/factsheets/fs310/en/ [accessed 1 Nov 2017].

62. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med* 2016;13(10):e1002152.

63. Bhargava A, Pinto L, Pai M. Mismanagement of tuberculosis in India: Causes, consequences, and the way forward. *Hypothesis* 2011;9(1):e7.

64. Hargreaves JR, Boccia D, Evans CA, Adato M, Petticrew M, Porter JDH. The Social Determinants of Tuberculosis: From Evidence to Action. *Am J Public Health* 2011;101(4):654–662.

65. Courtwright A, Turner AN. Tuberculosis and Stigmatization: Pathways and Interventions. *Public Health Rep* 2010;125(Suppl 4):34–42.

66. Frick M. Funding for tuberculosis research—an urgent crisis of political will, human rights, and global solidarity. *Int J Infect Dis* 2017;56:21–24.

67. Sulis G, Roggi A, Matteelli A, Raviglione MC. Tuberculosis: Epidemiology and Control. *Mediterr J Hematol Infect Dis* 2014;6(1):e2014070.

68. Abarca Tomás B, Pell C, Bueno Cavanillas A, Guillén Solvas J, Pool R, Roura M. Tuberculosis in Migrant Populations. A Systematic Review of the Qualitative Literature. *PLoS ONE* 2013;8(12):e82440.

69. Long R, Hoeppner V, Orr P, Ainslie M, King M, Abonyi S, *et al.* Marked disparity in the epidemiology of tuberculosis among Aboriginal peoples on the Canadian prairies: The challenges and opportunities. *Can Respir J* 2013;20(4):223–230.

70. WHO. *Framework towards tuberculosis elimination in low-incidence countries*. Geneva: World Health Organization; 2014. Available: http://www.who.int/tb/publications/elimination_framework/en/ [accessed 1 Nov 2017].

71. Alexander DC, Guthrie JL, Pyskir D, Maki A, Kurepina N, Kreiswirth BN, *et al.* Mycobacterium tuberculosis in Ontario, Canada: Insights from IS6110 restriction fragment length polymorphism and mycobacterial interspersed repetitive-unit-variable-number tandem-repeat genotyping. *J Clin Microbiol* 2009;47(8):2651–2654.

72. Chin DP, DeRiemer K, Small PM, de Leon AP, Steinhart R, Schecter GF, *et al.* Differences in contributing factors to tuberculosis incidence in U.S. -born and foreign-born persons. *Am J Respir Crit Care Med* 1998;158(6):1797–1803.

73. Shea KM, Kammerer JS, Winston CA, Navin TR, Horsburgh CR. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. *Am J Epidemiol* 2014;179(2):216–225.

74. WHO. *WHO End TB Strategy*. Geneva: World Health Organization; 2016. Available: http://www.who.int/tb/post2015_strategy/en/ [accessed 1 Nov 2017].

75. Vynnycky E, Fine PE. Interpreting the decline in tuberculosis: the role of secular trends in effective contact. *Int J Epidemiol* 1999;28(2):327–334.

76. Tapiéro BF, Lamarre V. Tuberculosis in Canada: Global view and new challenges. *Paediatr Child Health* 2003;8(3):139–140.

77. Government of Canada, Public Health Agency of Canada. Tuberculosis in Canada - Summary 2015. *Can Commun Dis Rep* 2017;43:77–82.

78. Kulmann K, Richmond C. Addressing the persistence of Tuberculosis Among the Canadian Inuit Population: The need for a social determinants of health framework. *Int Indig Policy J* 2011;2(1).

79. Greenwood ML, Leeuw SN de. Social determinants of health and the future well-being of Aboriginal children in Canada. *Paediatr Child Health* 2012;17(7):381.

80. Health Canada. *Epidemiology of Tuberculosis in First Nations Living On-Reserve in Canada, 2000–2008*. Ottawa (ON): Health Canada; 2012. Available: http://publications.gc.ca/collections/collection_2012/sc-hc/H34-244-2011-eng.pdf [accessed 1 Nov 2017].

81. Hoeppner VH, Marciniuk DD. Tuberculosis in aboriginal Canadians. *Can Respir J* 2000;7(2):141–146.

82. Cook V, Elwood K. The burden of tuberculosis in Aboriginal communities in BC. *BC Med J* 2008;50(4):219.

83. Møller H. Tales about tuberculosis and colonization: the socio-cultural experience of tuberculosis in Nunavut. *Alaska Med* 2007;49(2 Suppl):179–183.

84. Archibald L. *Evaluation of Models of Health Care Delivery in Inuit Regions*. Canada: Inuit Tapirisat of Canada; 2000.

85. Cook VJ, Hernández-Garduño E, Kunimoto D, Hershfield ES, Fanning EA, Hoeppner VH, *et al.* The lack of association between bacille Calmette-Guerin vaccination and clustering of Aboriginals with tuberculosis in western Canada. *Can Respir J* 2005;12(3):134–138.

86. Cook VJ, Kuramoto L, Noertjojo K, Elwood RK, Fitzgerald JM. BCG vaccination and the prevalence of latent tuberculosis infection in an aboriginal population. *Int J Tuberc Lung Dis* 2006;10(12):1347–1353.

87. Statistics Canada. 150 years of immigration in Canada. 2016; Available: http://www.statcan.gc.ca/pub/11-630-x/11-630-x2016006-eng.htm [accessed 1 Nov 2017].

88. Statistics Canada. *Health Reports*. Ottawa (ON): Government of Canada; 1996. Available: http://www5.statcan.gc.ca/olc-cel/olc.action?objId=82-003-X19960012824&objType=47&lang=en&limit=0 [accessed 1 Nov 2017].

89. Government of Canada. Permanent resident program. 2014; Available: http://www.cic.gc.ca/english/resources/tools/perm/index.asp [accessed 1 Nov 2017].

90. Figueroa-Munoz JI, Ramon-Pardo P. Tuberculosis control in vulnerable groups. *Bull World Health Organ* 2008;86(9):733–735.

91. SOS Canada. Medical Examination Instructions. 2000; Available: http://www.soscanada2000.com/migration/guide/medexaminst.html [accessed 1 Nov 2017].

92. Government of Canada. Reasons for inadmissibility. 2010; Available: http://www.cic.gc.ca/english/information/inadmissibility/who.asp [accessed 1 Nov 2017].

93. Statistics Canada. *Report on the Demographic Situation in Canada: Permanent and temporary immigration to Canada from 2012 to 2014*. Ottawa (ON): Government of Canada; 2016. Available: http://www.statcan.gc.ca/pub/91-209-x/2016001/article/14615-eng.htm [accessed 1 Nov 2017].

94. Khan K, Hirji MM, Miniota J, Hu W, Wang J, Gardam M, *et al.* Domestic impact of tuberculosis screening among new immigrants to Ontario, Canada. *Can Med Assoc J* 2015;187(16):E473–E481.

95. McBryde ES, Denholm JT. Risk of active tuberculosis in immigrants: effects of age, region of origin and time since arrival in a low-exposure setting. *Med J Aust* 2012;197(8):458–461.

96. Greenaway C, Sandoe A, Vissandjee B, Kitai I, Gruner D, Wobeser W, *et al.* Tuberculosis: evidence review for newly arriving immigrants and refugees. *Can Med Assoc J* 2011;183(12):E939–E951.

97. Campbell J, Marra F, Cook V, Johnston J. Screening immigrants for latent tuberculosis: Do we have the resources? *Can Med Assoc J* 2014;186(4):246–247.

98. Ayub A, Yale SH, Reed KD, Nasser RM, Gilbert SR. Testing for Latent Tuberculosis. *Clin Med Res* 2004;2(3):191–194.

99. Uppaluri A, Naus M, Heywood N, Brunton J, Kerbel D, Wobeser W. Effectiveness of the Immigration Medical Surveillance Program for tuberculosis in Ontario. *Can J Public Health* 2002;93(2):88–91.

100. Carvalho ACC, Saleri N, El-Hamad I, Tedoldi S, Capone S, Pezzoli MC, *et al.* Completion of screening for latent tuberculosis infection among immigrants. *Epidemiol Infect* 2005;133(1):179–185.

101. Levesque J-F, Dongier P, Brassard P, Allard R. Acceptance of screening and completion of treatment for latent tuberculosis infection among refugee claimants in Canada. *Int J Tuberc Lung Dis* 2004;8(6):711–717.

102. Marks SM, Taylor Z, Qualls NL, Shrestha-Kuwahara RJ, Wilce MA, Nguyen CH. Outcomes of contact investigations of infectious tuberculosis patients. *Am J Respir Crit Care Med* 2000;162(6):2033–2038.

103. American Thoracic Society and the Centers for Disease Control and Prevention. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. *Am J Respir Crit Care Med* 2000;161(4 Pt 2):S221–S247.

104. Sumartojo E. When tuberculosis treatment fails. A social behavioral account of patient adherence. *Am Rev Respir Dis* 1993;147(5):1311–1320.

105. Brassard P, Anderson KK, Schwartzman K, Macdonald ME, Menzies D. Challenges to tuberculin screening and follow-up in an urban Aboriginal sample in Montreal, Canada. *J Health Care Poor Underserved* 2008;19(2):369–379.

106. Olson NA, Davidow AL, Winston CA, Chen MP, Gazmararian JA, Katz DJ. A national study of socioeconomic status and tuberculosis rates by country of birth, United States, 1996-2005. *BMC Public Health* 2012;12:365.

107. Belo MTCT, Luiz RR, Teixeira EG, Hanson C, Trajman A. Tuberculosis treatment outcomes and socio-economic status: a prospective study in Duque de Caxias, Brazil. *Int J Tuberc Lung Dis* 2011;15(7):978–981.

108. United States Centers for Disease Control and Prevention. Diagnosis of Latent TB Infection. 2014; Available: https://www.cdc.gov/tb/publications/ltbi/diagnosis.htm [accessed 1 Nov 2017].

109. Trueba F, Haus-Cheymol R, Koeck J-L, Nombalier Y, Ceyriac A, Boiron S, *et al.* Contact tracing in a case of tuberculosis in a health care worker. *Rev Mal Respir* 2006;23(4 Pt 1):339–342.

110. Lobato MN, Leary LS, Simone PM. Treatment for latent TB in correctional facilities: a challenge for TB elimination. *Am J Prev Med* 2003;24(3):249–253.

111. Brassard P, Bruneau J, Schwartzman K, Sénécal M, Menzies D. Yield of tuberculin screening among injection drug users. *Int J Tuberc Lung Dis* 2004;8(8):988–993.

112. Langenskiold E, Herrmann FR, Luong BL, Rochat T, Janssens J-P. Contact tracing for tuberculosis and treatment for latent infection in a low incidence country. *Swiss Med Wkly* 2008;138(5–6):78–84.

113. Schluger NW, Huberman R, Holzman R, Rom WN, Cohen DI. Screening for infection and disease as a tuberculosis control measure among indigents in New York City, 1994-1997. *Int J Tuberc Lung Dis* 1999;3(4):281–286.

114. Lashley M. A targeted testing program for tuberculosis control and prevention among Baltimore city's homeless population. *Public Health Nurs* 2007;24(1):34–39.

115. Breuss E, Helbling P, Altpeter E, Zellweger J-P. Screening and treatment for latent tuberculosis infection among asylum seekers entering Switzerland. *Swiss Med Wkly* 2002;132(15–16):197–200.

116. Adhikari N, Menzies R. Community-based tuberculin screening in Montreal: a cost-outcome description. *Am J Public Health* 1995;85(6):786–790.

117. Cain KP, Garman KN, Laserson KF, Ferrousier-Davis OP, Miranda AG, Wells CD, *et al.* Moving toward tuberculosis elimination: implementation of statewide targeted tuberculin testing in Tennessee. *Am J Respir Crit Care Med* 2012;186(3):273–279.

118. Balkhy HH, Miller TL, Ali S, Nuzzo JB, Kentenyants K, El-Saed A, *et al.* Compliance with postexposure screening and treatment of latent tuberculosis infection among healthcare workers in a tertiary care hospital in Saudi Arabia. *Infect Control Hosp Epidemiol* 2014;35(2):176–181.

119. Holland DP, Sanders GD, Hamilton CD, Stout JE. Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection. *Am J Respir Crit Care Med* 2009;179(11):1055–1060.

120. Aspler A, Long R, Trajman A, Dion M-J, Khan K, Schwartzman K, *et al.* Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB. *Thorax* 2010;65(7):582–587.

121. Pina JM, Clotet L, Ferrer A, Sala MR, Garrido P, Salleras L, *et al.* Cost-effectiveness of rifampin for 4 months and isoniazid for 9 months in the treatment of tuberculosis infection. *Eur J Clin Microbiol Infect Dis* 2013;32(5):647–655.

122. Page KR, Sifakis F, Montes de Oca R, Cronin WA, Doherty MC, Federline L, *et al.* Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. *Arch Intern Med* 2006;166(17):1863–1870.

123. Menzies D, Dion M-J, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. *Am J Respir Crit Care Med* 2004;170(4):445–449.

124. Martínez Sanchís A, Calpe Calpe JL, Llavador Ros G, Ena Muñoz J, Calpe Armero A. Primary prevention and treatment of latent tuberculosis infection with isoniazid: efficacy of a control program, 1997-2002. *Arch Bronconeumol* 2005;41(1):27–33.

125. Sprinson JE, Flood J, Fan CS, Shaw TA, Pascopella L, Young JA, *et al.* Evaluation of tuberculosis contact investigations in California. *Int J Tuberc Lung Dis* 2003;7(12):S363–S368.

126. Bibi H, Weiler-Ravell D, Shoseyov D, Feigin I, Arbelli Y, Chemtob D. Compliance to treatment of latent tuberculosis infection in a region of Israel. *Isr Med Assoc J* 2002;4(1):13–16.

127. Minodier P, Lamarre V, Carle M-E, Blais D, Ovetchkine P, Tapiero B. Evaluation of a school-based program for diagnosis and treatment of latent tuberculosis infection in immigrant children. *J Infect Public Health* 2010;3(2):67–75.

128. Méda ZC, Sombié I, Sanon OWC, Maré D, Morisky DE, Chen Y-MA. Risk Factors of Tuberculosis Infection Among HIV/AIDS Patients in Burkina Faso. *AIDS Res Hum Retroviruses* 2013;29(7):1045–1055.

129. Selwyn P, Hartel D, Lewis V, Schoenbaum E, Vermund S, Klein R, *et al.* A Prospective Study of the Risk of Tuberculosis among Intravenous Drug Users with Human Immunodeficiency Virus Infection. *N Engl J Med* 1989;320(9):545–550.

130. Guelar A, Gatell JM, Verdejo J, Podzamczer D, Lozano L, Aznar E, *et al.* A prospective study of the risk of tuberculosis among HIV-infected patients. *AIDS* 1993;7(10):1345–1349.

131. Dodd PJ, Prendergast AJ, Beecroft C, Kampmann B, Seddon JA. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. *Thorax* 2017;72(6):559–575.

132. Van Rie A, Westreich D, Sanne I. Tuberculosis in patients receiving antiretroviral treatment: incidence, risk factors and prevention strategies. *J Acquir Immune Defic Syndr* 2011;56(4):349–355.

133. Linas BP, Wong AY, Freedberg KA, Horsburgh CR. Priorities for screening and treatment of latent tuberculosis infection in the United States. *Am J Respir Crit Care Med* 2011;184(5):590–601.

134. Andrew OT, Schoenfeld PY, Hopewell PC, Humphreys MH. Tuberculosis in patients with end-stage renal disease. *Am J Med* 1980;68(1):59–65.

135. Lundin AP, Adler AJ, Berlyne GM, Friedman EA. Tuberculosis in patients undergoing maintenance hemodialysis. *Am J Med* 1979;67(4):597–602.

136. Miller RA, Lanza LA, Kline JN, Geist LJ. Mycobacterium tuberculosis in lung transplant recipients. *Am J Respir Crit Care Med* 1995;152(1):374–376.

137. Torre-Cisneros J, Doblas A, Aguado JM, San Juan R, Blanes M, Montejo M, *et al.* Tuberculosis after Solid-Organ Transplant: Incidence, Risk Factors, and Clinical Characteristics in the RESITRA (Spanish Network of Infection in Transplantation) Cohort. *Clin Infect Dis* 2009;48(12):1657–1665.

138. Venkata RKC, Kumar S, Krishna RP, Kumar SB, Padmanabhan S, Kumar S. Tuberculosis in chronic kidney disease. *Clin Nephrol* 2007;67(4):217–220.

139. Romanowski K, Clark EG, Levin A, Cook VJ, Johnston JC. Tuberculosis and chronic kidney disease: an emerging global syndemic. *Kidney Int* 2016;90(1):34–40.

140. Cook VJ, Wong Q, Djurdjev O, Saunders S, Levin A, Morshed M, *et al.* Provincial tuberculosis screening for incident dialysis patients in BC. *BC Med J* 2015;57(8):349.

141. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, *et al.* Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008;3(5):1526–1533.

142. Muñoz L, Casas S, Juanola X, Bordas X, Martinez C, Santin M, *et al.* Prevention of anti-tumor necrosis factor-associated tuberculosis: a 10-year longitudinal cohort study. *Clin Infect Dis* 2015;60(3):349–356.

143. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. *Clin Infect Dis* 2006;43(6):717–722.

144. Gómez-Reino JJ, Carmona L, Ángel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Care Res* 2007;57(5):756–761.

145. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, *et al.* Tuberculosis Associated with Infliximab, a Tumor Necrosis Factor α–Neutralizing Agent. *N Engl J Med* 2001;345(15):1098–1104.

146. Bonfiglioli KR, Ribeiro ACM, Moraes JCB, Saad CGS, Souza FHC, Calich AL, *et al.* LTBI screening in rheumatoid arthritis patients prior to anti-TNF treatment in an endemic area. *Int J Tuberc Lung Dis* 2014;18(8):905–911.

147. Hazelwood G, Naimark D, Gardam M, Bykerk V, Bombardier C. Prophylaxis for Latent Tuberculosis Infection Prior to Anti–tumor Necrosis Factor Therapy in Low-Risk Elderly Patients With Rheumatoid Arthritis: A Decision Analysis. *Arthritis Care Res* 2013;65(11):1722–1731.

148. Swaminath A, Bhadelia N, Wang YC. Cost-effectiveness of QuantiFERON testing prior to initiation of biologic therapy in inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19(11):2444–2449.

149. Laskin BL, Goebel J, Starke JR, Schauer DP, Eckman MH. Cost-Effectiveness of Latent Tuberculosis Screening Before Steroid Therapy for Idiopathic Nephrotic Syndrome in Children. *Am J Kidney Dis* 2013;61(1).

150. Curtis JR, Singh JA. The Use of Biologics in Rheumatoid Arthritis: Current and Emerging Paradigms of Care. *Clin Ther* 2011;33(6):679–707.

151. Xie X, Li F, Chen J-W, Wang J. Risk of tuberculosis infection in anti-TNF-α biological therapy: From bench to bedside. *J Microbiol Immunol Infect* 2014;47(4):268–274.

152. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect Dis* 2009;9(12):737–746.

153. Dobler CC, Flack JR, Marks GB. Risk of tuberculosis among people with diabetes mellitus: an Australian nationwide cohort study. *BMJ Open* 2012;2(1):e000666.

154. Kim SJ, Hong YP, Lew WJ, Yang SC, Lee EG. Incidence of pulmonary tuberculosis among diabetics. *Tuber Lung Dis* 1995;76(6):529–533.

155. Silwer H, Oscarsson PN. Incidence and Coincidence of Diabetes Mellitus and Pulmonary Tuberculosis in a Swedish County. *Acta Med Scand* 1958;161(Suppl 335).

156. Pablos-Méndez A, Blustein J, Knirsch CA. The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. *Am J Public Health* 1997;87(4):574–579.

157. Restrepo BI, Fisher-Hoch SP, Pino PA, Salinas A, Rahbar MH, Mora F, *et al.* Tuberculosis in Poorly Controlled Type 2 Diabetes: Altered Cytokine Expression in Peripheral White Blood Cells. *Clin Infect Dis* 2008;47(5):634–641.

158. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol* 1999;26(3–4):259–265.

159. Thibault V, Bélanger M, LeBlanc E, Babin L, Halpine S, Greene B, *et al.* Factors that could explain the increasing prevalence of type 2 diabetes among adults in a Canadian province: a critical review and analysis. *Diabetol Metab Syndr* 2016;8:71.

160. Oxlade O, Huang C-C, Murray M. Estimating the Impact of Reducing Under-Nutrition on the Tuberculosis Epidemic in the Central Eastern States of India: A Dynamic Modeling Study. *PLoS ONE* 2015;10(6):e0128187.

161. Bhargava A, Benedetti A, Oxlade O, Pai M, Menzies D. Undernutrition and the incidence of tuberculosis in India: national and subnational estimates of the population-attributable fraction related to undernutrition. *Natl Med J India* 2014;27(3):128–133.

162. Pereira SM, de Araújo GS, Santos CA de ST, de Oliveira MG, Barreto ML. Association between diabetes and tuberculosis: case-control study. *Rev Saúde Pública* 2016;50.

163. WHO. *Diabetes*. Geneva: World Health Organization; 2017. Available: http://www.who.int/mediacentre/factsheets/fs312/en/ [accessed 1 Nov 2017].

164. WHO. *Guidelines on the management of latent tuberculosis infection*. Geneva: World Health Organization; 2015. Available: http://www.who.int/tb/publications/latent-tuberculosis-infection/en/ [accessed 1 Nov 2017].

165. Lin H-H, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med* 2007;4(1):e20.

166. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Arch Intern Med* 2007;167(4):335–342.

167. Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. *BMC Public Health* 2008;8:289.

168. Hassmiller KM. The association between smoking and tuberculosis. *Salud Publica Mex* 2006;48 Suppl 1:S201–S216.

169. Cois A, Ehrlich R. Problem drinking as a risk factor for tuberculosis: a propensity score matched analysis of a national survey. *BMC Public Health* 2013;13:871.

170. Robinson R. Economic evaluation and health care. What does it mean? *BMJ* 1993;307(6905):670–673.

171. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, *et al.* Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report. *Value Health* 2005;8(5):521–533.

172. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *Br Med Bull* 2010;96:5–21.

173. Sassi F. Calculating QALYs, comparing QALY and DALY calculations. *Health Policy Plan* 2006;21(5):402–408.

174. Gafni A. The standard gamble method: what is being measured and how it is interpreted. *Health Serv Res* 1994;29(2):207–224.

175. Attema AE, Edelaar-Peeters Y, Versteegh MM, Stolk EA. Time trade-off: one methodology, different methods. *Eur J Health Econ* 2013;14(Suppl 1):53–64.

176. Gandhi PK, Ried LD, Bibbey A, Huang I-C. SF-6D utility index as measure of minimally important difference in health status change. *J Am Pharm Assoc* 2012;52(1):34–42.

177. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI®): concepts, measurement properties and applications. *Health Qual Life Outcomes* 2003;1:54.

178. Coretti S, Ruggeri M, McNamee P. The minimum clinically important difference for EQ-5D index: a critical review. *Expert Rev Pharmacoecon Outcomes Res* 2014;14(2):221–233.

179. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care* 1989;27(3 Suppl):S217–S232.

180. Ware JE, Gandek B, Guyer R, Deng N. Standardizing disease-specific quality of life measures across multiple chronic conditions: development and initial evaluation of the QOL Disease Impact Scale (QDIS®). *Health Qual Life Outcomes* 2016;14:84.

181. Parker M, Haycox A, Graves J. Estimating the relationship between preference-based generic utility instruments and disease-specific quality-of-life measures in severe chronic constipation: challenges in practice. *PharmacoEconomics* 2011;29(8):719–730.

182. Sauerland S, Weiner S, Dolezalova K, Angrisani L, Noguera CM, García-Caballero M, *et al.* Mapping utility scores from a disease-specific quality-of-life measure in bariatric surgery patients. *Value Health* 2009;12(2):364–370.

183. Longworth L, Rowen D. Mapping to Obtain EQ-5D Utility Values for Use in NICE Health Technology Assessments. *Value Health* 2013;16(1):202–210.

184. Byford S, Raftery J. Perspectives in economic evaluation. *BMJ* 1998;316(7143):1529–1530.

185. Drummond M, Weatherly H, Ferguson B. Economic evaluation of health interventions. *BMJ* 2008;337:a1204.

186. Torgerson DJ, Raftery J. Discounting. *BMJ* 1999;319(7214):914–915.

187. Smith DH, Gravelle H. The practice of discounting in economic evaluations of healthcare interventions. *Int J Technol Assess Health Care* 2001;17(2):236–243.

188. Severens JL, Milne RJ. Discounting Health Outcomes in Economic Evaluation: The Ongoing Debate. *Value Health* 2004;7(4):397–401.

189. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, *et al.* Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 2016;316(10):1093–1103.

190. CADTH. *Guidelines for the Economic Evaluation of Health Technologies: Canada - 4th Edition*. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017.

191. Verdier JE, de Vlas SJ, Baltussen R, Richardus JH. A systematic review of economic evaluation studies of tuberculosis control in high-income countries. *Int J Tuberc Lung Dis* 2011;15(12):1587–1598.

192. Campbell JR, Sasitharan T, Marra F. A Systematic Review of Studies Evaluating the Cost Utility of Screening High-Risk Populations for Latent Tuberculosis Infection. *Appl Health Econ Health Policy* 2015;13(4):325–340.

193. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J. Modeling using Discrete Event Simulation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-4. *Value Health* 2012;15(6):821–827.

194. Briggs A. Handling uncertainty in economic evaluation. *BMJ* 1999;319(7202):120.

195. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ* 1994;3(2):95–104.

196. Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model Parameter Estimation and Uncertainty: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. *Value Health* 2012;15(6):835–842.

197. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* 2013;16(2):231–250.

198. Cohen DJ, Reynolds MR. Interpreting the Results of Cost-Effectiveness Studies. *J Am Coll Cardiol* 2008;52(25):2119–2126.

199. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. *Br J Psychiatry* 2005;187(2):106–108.

200. Caro JJ, Nord E, Siebert U, McGuire A, McGregor M, Henry D, *et al.* The efficiency frontier approach to economic evaluation of health-care interventions. *Health Econ* 2010;19(10):1117–1127.

201. Auguste P, Tsertsvadze A, Court R, Pink J. A systematic review of economic models used to assess the cost-effectiveness of strategies for identifying latent tuberculosis in high-risk groups. *Tuberculosis* 2016;99:81–91.

202. Zammarchi L, Casadei G, Strohmeyer M, Bartalesi F, Liendo C, Matteelli A, *et al.* A scoping review of cost-effectiveness of screening and treatment for latent tuberculosis infection in migrants from high-incidence countries. *BMC Health Serv Res* 2015;15:412.

203. Khan K, Muennig P, Behta M, Zivin JG. Global Drug-Resistance Patterns and the Management of Latent Tuberculosis Infection in Immigrants to the United States. *N Engl J Med* 2002;347(23):1850–1859.

204. Oxlade O, Schwartzman K, Menzies D. Interferon-gamma release assays and TB screening in high-income countries: a cost-effectiveness analysis. *Int J Tuberc Lung Dis* 2007;11(1):16–26.

205. National Collaborating Centre for Chronic Conditions (UK), Centre for Clinical Practice at NICE (UK). *Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for Its Prevention and Control*. London (UK): National Institute for Health and Care Excellence (UK); 2011. Available: http://www.ncbi.nlm.nih.gov/books/NBK97852/ [accessed 1 Nov 2017].

206. Pareek M, Bond M, Shorey J, Seneviratne S, Guy M, White P, *et al.* Community-based evaluation of immigrant tuberculosis screening using interferon γ release assays and tuberculin skin testing: observational study and economic analysis. *Thorax* 2013;68(3):230–239.

207. Pareek M, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, *et al.* Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. *Lancet Infect Dis* 2011;11(6):435–444.

208. Porco TC, Lewis B, Marseille E, Grinsdale J, Flood JM, Royce SE. Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. *BMC Public Health* 2006;6:157.

209. Schwartzman K, Menzies D. Tuberculosis screening of immigrants to low-prevalence countries. A cost-effectiveness analysis. *Am J Respir Crit Care Med* 2000;161(3 Pt 1):780–789.

210. Schwartzman K, Oxlade O, Barr RG, Grimard F, Acosta I, Baez J, *et al.* Domestic returns from investment in the control of tuberculosis in other countries. *N Engl J Med* 2005;353(10):1008–1020.

211. Shrestha RK, Mugisha B, Bunnell R, Mermin J, Odeke R, Madra P, *et al.* Cost-utility of tuberculosis prevention among HIV-infected adults in Kampala, Uganda. *Int J Tuberc Lung Dis* 2007;11(7):747–754.

212. Burgos JL, Kahn JG, Strathdee SA, Valencia-Mendoza A, Bautista-Arredondo S, Laniado-Laborin R, *et al.* Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost-effective in Mexico. *Int J Tuberc Lung Dis* 2009;13(8):962–968.

213. Azadi M, Bishai DM, Dowdy DW, Moulton LH, Cavalcante S, Saraceni V, *et al.* Cost-Effectiveness of Tuberculosis Screening and Isoniazid Treatment in the TB/HIV in Rio de Janeiro (THRio) Study. *Int J Tuberc Lung Dis* 2014;18(12):1443–1448.

214. Capocci S, Smith C, Morris S, Bhagani S, Cropley I, Abubakar I, *et al.* Decreasing cost effectiveness of testing for latent TB in HIV in a low TB incidence area. *Eur Respir J* 2015;46(1):165–174.

215. Kowada A. Cost effectiveness of interferon-γ release assay for TB screening of HIV positive pregnant women in low TB incidence countries. *J Infect* 2014;68(1):32–42.

216. Kowada A. Cost effectiveness of interferon-gamma release assay for tuberculosis screening of rheumatoid arthritis patients prior to initiation of tumor necrosis factor-α antagonist therapy. *Mol Diagn Ther* 2010;14(6):367–373.

217. van der Have M, Oldenburg B, Fidder HH, Belderbos TDG, Siersema PD, van Oijen MGH. Optimizing screening for tuberculosis and hepatitis B prior to starting tumor necrosis factor-α inhibitors in Crohn's disease. *Dig Dis Sci* 2014;59(3):554–563.

218. Kowada A. Cost effectiveness of the interferon-γ release assay for tuberculosis screening of hemodialysis patients. *Nephrol Dial Transplant* 2013;28(3):682–688.

219. Horsburgh CR. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med* 2004;350(20):2060–2067.

220. Public Health Agency of Canada. *Tuberculosis in Canada 2014: Pre-release*. Ottawa (ON): Government of Canada; 2016. Available: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/tuberculosis-canada-2014-pre-release.html [accessed 1 Nov 2017].

221. Menzies D, Lewis M, Oxlade O. Costs for tuberculosis care in Canada. *Can J Public Health* 2008;99(5):391–396.

222. Dasgupta K, Schwartzman K, Marchand R, Tennenbaum TN, Brassard P, Menzies D. Comparison of Cost-Effectiveness of Tuberculosis Screening of Close Contacts and Foreign-Born Populations. *Am J Respir Crit Care Med* 2000;162(6):2079–2086.

223. Cobelens FG, Egwaga SM, van Ginkel T, Muwinge H, Matee MI, Borgdorff MW. Tuberculin skin testing in patients with HIV infection: limited benefit of reduced cutoff values. *Clin Infect Dis* 2006;43(5):634–639.

224. Badar S, Araújo T, Zwerling A, Pai M. BCG World Atlas. 2017; Available: http://www.bcgatlas.org/index.php [accessed 1 Nov 2017].

225. Smith R, Cattamanchi A, Steingart KR, Denkinger C, Dheda K, Winthrop KL, *et al.* Interferon-γ release assays for diagnosis of latent tuberculosis infection: evidence in immune-mediated inflammatory disorders. *Curr Opin Rheumatol* 2011;23(4):377–384.

226. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, *et al.* The impact of diabetes on tuberculosis treatment outcomes: A systematic review. *BMC Med* 2011;9:81.

227. Suchindran S, Brouwer ES, Rie AV. Is HIV Infection a Risk Factor for Multi-Drug Resistant Tuberculosis? A Systematic Review. *PLoS ONE* 2009;4(5):e5561.

228. Johnston J, Elwood K. Screening renal failure patients for tuberculosis. *BC Med J* 2010;52(9):413.

229. CATIE. The epidemiology of HIV in Canada. 2017; Available: http://www.catie.ca/en/fact-sheets/epidemiology/epidemiology-hiv-canada [accessed 1 Nov 2017].

230. Boasso A, Shearer GM, Chougnet C. Immune dysregulation in human immunodeficiency virus infection: know it, fix it, prevent it? *J Intern Med* 2009;265(1):78–96.

231. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: the epidemiology and the response. *Clin Infect Dis* 2010;50(Suppl 3):S201–S207.

232. Canadian Institute for Health Information. CORR Annual Statistics 2017. 2017; Available: https://www.cihi.ca/en/corr-annual-statistics-2017 [accessed 1 Nov 2017].

233. Aguado JM, Torre-Cisneros J, Fortún J, Benito N, Meije Y, Doblas A, *et al.* Tuberculosis in Solid-Organ Transplant Recipients: Consensus Statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. *Clin Infect Dis* 2009;48(9):1276–1284.

234. Al-Efraij K, Mota L, Lunny C, Schachter M, Cook V, Johnston J. Risk of active tuberculosis in chronic kidney disease: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2015;19(12):1493–1499.

235. Dobler CC, McDonald SP, Marks GB. Risk of Tuberculosis in Dialysis Patients: A Nationwide Cohort Study. *PLoS ONE* 2011;6(12):e29563.

236. Canadian Diabetes Association. Diabetes Statistics in Canada. *Can Diabetes Assoc* 2017; Available: http://www.diabetes.ca/how-you-can-help/advocate/why-federal-leadership-is-essential/diabetes-statistics-in-canada [accessed 1 Nov 2017].

237. Sudre P, ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. *Bull World Health Organ* 1992;70(2):149–159.

238. Nathanson E, Nunn P, Uplekar M, Floyd K, Jaramillo E, Lönnroth K, *et al.* MDR Tuberculosis — Critical Steps for Prevention and Control. *N Engl J Med* 2010;363(11):1050–1058.

239. Raviglione MC, Smith IM. XDR Tuberculosis — Implications for Global Public Health. *N Engl J Med* 2007;356(7):656–659.

240. Raviglione MC, Snider DE, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. *JAMA* 1995;273(3):220–226.

241. Pareek M, Baussano I, Abubakar I, Dye C, Lalvani A. Evaluation of immigrant tuberculosis screening in industrialized countries. *Emerg Infect Dis* 2012;18(9):1422–1429.

242. Alvarez GG, Gushulak B, Abu Rumman K, Altpeter E, Chemtob D, Douglas P, *et al.* A comparative examination of tuberculosis immigration medical screening programs from selected countries with high immigration and low tuberculosis incidence rates. *BMC Infect Dis* 2011;11:3.

243. Klinkenberg E, Manissero D, Semenza JC, Verver S. Migrant tuberculosis screening in the EU/EEA: yield, coverage and limitations. *Eur Respir J* 2009;34(5):1180–1189.

244. Walter ND, Painter J, Parker M, Lowenthal P, Flood J, Fu Y, *et al.* Persistent latent tuberculosis reactivation risk in United States immigrants. *Am J Respir Crit Care Med* 2014;189(1):88–95.

245. Cohen T, Murray M. Incident Tuberculosis among Recent US Immigrants and Exogenous Reinfection. *Emerg Infect Dis* 2005;11(5):725–728.

246. Jerant AF, Bannon M, Rittenhouse S. Identification and Management of Tuberculosis. *Am Fam Physician* 2000;61(9):2667–2678.

247. Mazurek GH, Villarino ME, CDC. Guidelines for using the QuantiFERON-TB test for diagnosing latent Mycobacterium tuberculosis infection. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2003;52(RR-2):15–18.

248. Chee CBE, KhinMar KW, Gan SH, Barkham TMS, Pushparani M, Wang YT. Latent tuberculosis infection treatment and T-cell responses to Mycobacterium tuberculosis-specific antigens. *Am J Respir Crit Care Med* 2007;175(3):282–287.

249. Arshad S, Bavan L, Gajari K, Paget SNJ, Baussano I. Active screening at entry for tuberculosis among new immigrants: a systematic review and meta-analysis. *Eur Respir J* 2010;35(6):1336–1345.

250. Muñoz L, Santin M. Interferon-γ release assays versus tuberculin skin test for targeting people for tuberculosis preventive treatment: an evidence-based review. *J Infect* 2013;66(4):381–387.

251. Joos TJ, Miller WC, Murdoch DM. Tuberculin reactivity in bacille Calmette-Guérin vaccinated populations: a compilation of international data. *Int J Tuberc Lung Dis* 2006;10(8):883–891.

252. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151(4):264–269.

253. Scottish Intercollegiate Guidelines Network. Methodology Checklist 5: Diagnostic Studies. 2017; Available: http://www.sign.ac.uk/checklists-and-notes.html [accessed 1 Nov 2017].

254. Trauer JM, Krause VL. Assessment and management of latent tuberculosis infection in a refugee population in the Northern Territory. *Med J Aust* 2011;194(11):579–582.

255. Lifson AR, Thai D, O'Fallon A, Mills WA, Hang K. Prevalence of tuberculosis, hepatitis B virus, and intestinal parasitic infections among refugees to Minnesota. *Public Health Rep* 2002;117(1):69–77.

256. Tafuri S, Martinelli D, Melpignano L, de Palma M, Quarto M, Prato R, *et al.* Tuberculosis screening in migrant reception centers: results of a 2009 Italian survey. *Am J Infect Control* 2011;39(6):495–499.

257. Fernández Sanfrancisco MT, Díaz Portillo J, Sánchez Romero JM, Pérez Fernández A, Vadillo Andrade J. Prevalence of tuberculosis among the immigrant population in Ceuta, Spain. *Rev Esp Salud Publica* 2001;75(6):551–558.

258. Perez-Stable EJ, Slutkin G, Paz EA, Hopewell PC. Tuberculin reactivity in United States and foreign-born Latinos: results of a community-based screening program. *Am J Public Health* 1986;76(6):643–646.

259. Menzies D, Vissandjee B, Amyot D. Factors Associated With Tuberculin Reactivity Among the Foreign-Born in Montreal. *Am Rev Respir Dis* 1992;146(3):752–756.

260. El-Hamad I, Casalini C, Matteelli A, Casari S, Bugiani M, Caputo M, *et al.* Screening for tuberculosis and latent tuberculosis infection among undocumented immigrants at an unspecialised health service unit. *Int J Tuberc Lung Dis* 2001;5(8):712–716.

261. Asgary R, Naderi R, Swedish KA, Smith CL, Sckell B, Doorley S. Communicable and non-communicable diseases among recent immigrants with implications for primary care; a comprehensive immigrant health approach. *J Immigr Minor Health* 2011;13(6):990–995.

262. Robertson JM, Burtt DS, Edmonds KL, Molina PL, Kiefe CI, Ellner JJ. Delayed tuberculin reactivity in persons of Indochinese origin: implications for preventive therapy. *Ann Intern Med* 1996;124(9):779–784.

263. Padovese V, Egidi AM, Melillo TF, Farrugia B, Carabot P, Didero D, *et al.* Prevalence of latent tuberculosis, syphilis, hepatitis B and C among asylum seekers in Malta. *J Public Health* 2014;36(1):22–27.

264. Alperstein G, Morgan KR, Fett MJ, Nossar V, Stewart GJ. Prevalence of tuberculosis infection among primary school-entry children in Sydney. *Aust N Z J Public Health* 1996;20(2):123–128.

265. Geltman PL, Radin M, Zhang Z, Cochran J, Meyers AF. Growth status and related medical conditions among refugee children in Massachusetts, 1995-1998. *Am J Public Health* 2001;91(11):1800–1805.

266. Sheikh M, Pal A, Wang S, MacIntyre CR, Wood NJ, Isaacs D, *et al.* The epidemiology of health conditions of newly arrived refugee children: a review of patients attending a specialist health clinic in Sydney. *J Paediatr Child Health* 2009;45(9):509–513.

267. Gray K, Wood N, Gunasekera H, Sheikh M, Hazelton B, Barzi F, *et al.* Vitamin d and tuberculosis status in refugee children. *Pediatr Infect Dis J* 2012;31(5):521–523.

268. Losi M, Bergamini BM, Venturelli C, Del Giovane C, Sighinolfi G, Rumpaneisi F, *et al.* Tuberculosis infection in foreign-born children: a screening survey based on skin and blood testing. *Int J Tuberc Lung Dis* 2011;15(9):1182–1184.

269. Hladun O, Grau A, Esteban E, Jansà JM. Results from screening immigrants of low-income countries: data from a public primary health care. *J Travel Med* 2014;21(2):92–98.

270. Baussano I, Mercadante S, Pareek M, Lalvani A, Bugiani M. High Rates of Mycobacterium tuberculosis among Socially Marginalized Immigrants in Low-Incidence Area, 1991–2010, Italy. *Emerg Infect Dis* 2013;19(9):1437–1445.

271. Kowatsch-Beyer K, Norris-Turner A, Love R, Denkowski P, Wang S-H. Utilization of a latent tuberculosis infection referral system by newly resettled refugees in central Ohio. *Int J Tuberc Lung Dis* 2013;17(3):320–325.

272. Martin JA, Mak DB. Changing faces: A review of infectious disease screening of refugees by the Migrant Health Unit, Western Australia in 2003 and 2004. *Med J Aust* 2006;185(11–12):607–610.

273. Varkey P, Jerath AU, Bagniewski SM, Lesnick TG. The epidemiology of tuberculosis among primary refugee arrivals in Minnesota between 1997 and 2001. *J Travel Med* 2007;14(1):1–8.

274. MacIntyre CR, Plant AJ. Longitudinal incidence of tuberculosis in South-East Asian refugees after re-settlement. *Int J Tuberc Lung Dis* 1999;3(4):287–293.

275. Chai SJ, Davies-Cole J, Cookson ST. Infectious disease burden and vaccination needs among asylees versus refugees, district of columbia. *Clin Infect Dis* 2013;56(5):652–658.

276. Hobbs M, Moor C, Wansbrough T, Calder L. The health status of asylum seekers screened by Auckland Public Health in 1999 and 2000. *N Z Med J* 2002;115(1160):U152.

277. Bran C, Gómez i Prat J, Caylá JA, García de Olalla P. Factors associated with latent tuberculous infection in immigrants less than 35 years old. *Enferm Infecc Microbiol Clin* 2006;24(5):322–325.

278. Li J, Munsiff SS, Agerton TB. Prevalence of tuberculin skin test positivity in clinical population in New York City. *J Immigr Minor Health* 2010;12(6):816–822.

279. Desale M, Bringardner P, Fitzgerald S, Page K, Shah M. Intensified case-finding for latent tuberculosis infection among the Baltimore City Hispanic population. *J Immigr Minor Health* 2013;15(4):680–685.

280. Truong DH, Hedemark LL, Mickman JK, Mosher LB, Dietrich SE, Lowry PW. Tuberculosis among Tibetan immigrants from India and Nepal in Minnesota, 1992-1995. *JAMA* 1997;277(9):735–738.

281. Mulder C, Mulleners B, Borgdorff MW, van Leth F. Predictive value of the tuberculin skin test among newly arriving immigrants. *PLoS ONE* 2013;8(3):e60130.

282. Hayes EB, Talbot SB, Matheson ES, Pressler HM, Hanna AB, McCarthy CA. Health status of pediatric refugees in Portland, ME. *Arch Pediatr Adolesc Med* 1998;152(6):564–568.

283. Fortin K, Carceller A, Robert M, Chevalier I, Lamarre V, Lebel MH. Prevalence of positive tuberculin skin tests in foreign-born children. *J Paediatr Child Health* 2007;43(11):768–772.

284. Brassard P, Steensma C, Cadieux L, Lands LC. Evaluation of a school-based tuberculosis-screening program and associate investigation targeting recently immigrated children in a low-burden country. *Pediatrics* 2006;117(2):e148–e156.

285. Bodenmann P, Vaucher P, Wolff H, Favrat B, de Tribolet F, Masserey E, *et al.* Screening for latent tuberculosis infection among undocumented immigrants in Swiss healthcare centres; a descriptive exploratory study. *BMC Infect Dis* 2009;9:34.

286. Mulder C, Deutekom H van, Huisman EM, Toumanian S, Koster BFPJ, Meijer-Veldman W, *et al.* Role of the QuantiFERON®-TB Gold In-Tube assay in screening new immigrants for tuberculosis infection. *Eur Respir J* 2012;40(6):1443–1449.

287. Garfein RS, Burgos JL, Rodriquez-Lainz A, Brodine S, Pietrucha A, Rondinelli A, *et al.* Latent Tuberculosis Infection in a Migrant Agricultural Community in Baja California, Mexico. *J Immigr Minor Health* 2011;13(5):940–947.

288. Harstad I, Winje BA, Heldal E, Oftung F, Jacobsen GW. Predictive values of QuantiFERON-TB Gold testing in screening for tuberculosis disease in asylum seekers. *Int J Tuberc Lung Dis* 2010;14(9):1209–1211.

289. Bennett RJ, Brodine S, Waalen J, Moser K, Rodwell TC. Prevalence and treatment of latent tuberculosis infection among newly arrived refugees in San Diego County, January 2010-October 2012. *Am J Public Health* 2014;104(4):e95–e102.

290. Banfield S, Pascoe E, Thambiran A, Siafarikas A, Burgner D. Factors Associated with the Performance of a Blood-Based Interferon-γ Release Assay in Diagnosing Tuberculosis. *PLoS ONE* 2012;7(6):e38556.

291. Simpson T, Tomaro J, Jobb C. Implementation of an Interferon-Gamma Release Assay to Screen for Tuberculosis in Refugees and Immigrants. *J Immigr Minor Health* 2013;15(4):686–692.

292. Paxton GA, Sangster KJ, Maxwell EL, McBride CRJ, Drewe RH. Post-Arrival Health Screening in Karen Refugees in Australia. *PLoS ONE* 2012;7(5):e38194.

293. Orlando G, Merli S, Cordier L, Mazza F, Casazza G, Villa AM, *et al.* Interferon-gamma releasing assay versus tuberculin skin testing for latent tuberculosis infection in targeted screening programs for high risk immigrants. *Infection* 2010;38(3):195–204.

294. Saracino A, Scotto G, Fornabaio C, Martinelli D, Faleo G, Cibelli D, *et al.* QuantiFERON-TB Gold In-Tube test (QFT-GIT) for the screening of latent tuberculosis in recent immigrants to Italy. *New Microbiol* 2009;32(4):369–376.

295. Baker CA, Thomas W, Stauffer WM, Peterson PK, Tsukayama DT. Serial testing of refugees for latent tuberculosis using the QuantiFERON-gold in-tube: effects of an antecedent tuberculin skin test. *Am J Trop Med Hyg* 2009;80(4):628–633.

296. Weinfurter P, Blumberg HM, Goldbaum G, Royce R, Pang J, Tapia J, *et al.* Predictors of discordant tuberculin skin test and QuantiFERON®-TB Gold In-Tube results in various high-risk groups. *Int J Tuberc Lung Dis* 2011;15(8):1056–1061.

297. Pottumarthy S, Morris AJ, Harrison AC, Wells VC. Evaluation of the Tuberculin Gamma Interferon Assay: Potential To Replace the Mantoux Skin Test. *J Clin Microbiol* 1999;37(10):3229–3232.

298. Carvalho ACC, Pezzoli MC, El-Hamad I, Arce P, Bigoni S, Scarcella C, *et al.* QuantiFERON-TB Gold test in the identification of latent tuberculosis infection in immigrants. *J Infect* 2007;55(2):164–168.

299. Winje BA, Oftung F, Korsvold GE, Mannsåker T, Jeppesen AS, Harstad I, *et al.* Screening for tuberculosis infection among newly arrived asylum seekers: Comparison of QuantiFERON®TB Gold with tuberculin skin test. *BMC Infect Dis* 2008;8:65.

300. Painter JA, Graviss EA, Hai HH, Nhung DTC, Nga TTT, Ha NP, *et al.* Tuberculosis Screening by Tuberculosis Skin Test or QuantiFERON®-TB Gold In-Tube Assay among an Immigrant Population with a High Prevalence of Tuberculosis and BCG Vaccination. *PLoS One* 2013;8(12):e82727.

301. Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, *et al.* Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. *BMJ* 2014;349:g4643.

302. Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon-γ release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. *Chest* 2012;142(1):63–75.

303. Bettache N, Schwartzman K, Cnossen S, Sandoe A, Assayag D, Menzies D, *et al.* Effectiveness Of Post-Arrival Latent Tuberculosis Screening Programs In The Foreign Born: A Systematic Review And Meta-Analysis. *Am J Respir Crit Care Med* 2012;185:A3325.

304. Gilbert RL, Antoine D, French CE, Abubakar I, Watson JM, Jones JA. The impact of immigration on tuberculosis rates in the United Kingdom compared with other European countries. *Int J Tuberc Lung Dis* 2009;13(5):645–651.

305. Huebner RE, Schein MF, Bass JB. The tuberculin skin test. *Clin Infect Dis* 1993;17(6):968–975.

306. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557–560.

307. Ballew KA, Becker DM. Tuberculosis screening in adults who have received bacille Calmette-Guérin vaccine. *South Med J* 1995;88(10):1025–1030.

308. Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM. A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. *Thorax* 2002;57(9):804–809.

309. Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, Kampmann B, *et al.* Interferon-γ release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. *Eur Respir J* 2011;37(1):88–99.

310. Machado A, Emodi K, Takenami I, Finkmoore BC, Barbosa T, Carvalho J, *et al.* Analysis of discordance between the tuberculin skin test and the interferon-gamma release assay. *Int J Tuberc Lung Dis* 2009;13(4):446–453.

311. Connell TG, Curtis N, Ranganathan SC, Buttery JP. Performance of a whole blood interferon gamma assay for detecting latent infection with Mycobacterium tuberculosis in children. *Thorax* 2006;61(7):616–620.

312. Chiappini E, Bonsignori F, Mazzantini R, Sollai S, Venturini E, Mangone G, *et al.* Interferon-gamma release assay sensitivity in children younger than 5 years is insufficient to replace the use of tuberculin skin test in western countries. *Pediatr Infect Dis J* 2014;33(12):1291–1293.

313. Wlodarczyk M, Rudnicka W, Janiszewska-Drobinska B, Kielnierowski G, Kowalewicz-Kulbat M, Fol M, *et al.* Interferon-gamma assay in combination with tuberculin skin test are insufficient for the diagnosis of culture-negative pulmonary tuberculosis. *PLoS ONE* 2014;9(9):e107208.

314. Roth D, Johnston J, Cook VJ. TB in foreign-born patients. *BC Med J* 2012;54(8):387–388.

315. Long R, Sutherland K, Kunimoto D, Cowie R, Manfreda J. The epidemiology of tuberculosis among foreign-born persons in Alberta, Canada, 1989-1998: identification of high risk groups. *Int J Tuberc Lung Dis* 2002;6(7):615–621.

316. WHO, UNICEF. *WHO-UNICEF estimates of BCG coverage*. Geneva: World Health Organization; 2017. Available: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragebcg.html [accessed 1 Nov 2017].

317. Aldridge RW, Zenner D, White PJ, Williamson EJ, Muzyamba MC, Dhavan P, *et al.* Tuberculosis in migrants moving from high-incidence to low-incidence countries: a population-based cohort study of 519 955 migrants screened before entry to England, Wales, and Northern Ireland. *Lancet* 2016;388(10059):2510–2518.

318. Ferebee SH, Mount FW, Murray FJ, Livesay VT. A Controlled Trial of Isoniazid Prophylaxis in Mental Institutions. *Am Rev Respir Dis* 1963;88:161–175.

319. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc* 1970;26:28–106.

320. Edwards LB, Livesay VT, Acquaviva FA, Palmer CE. Height, weight, tuberculous infection, and tuberculous disease. *Arch Environ Health* 1971;22(1):106–112.

321. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974;99(2):131–138.

322. Chan IHY, Kaushik N, Dobler CC. Post-migration follow-up of migrants identified to be at increased risk of developing tuberculosis at pre-migration screening: a systematic review and meta-analysis. *Lancet Infect Dis* 2017;17(7):770–779.

323. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992;146(4):473–481.

324. Marseille E, Larson B, Kazi D, Kahn J, Rosen S. Thresholds for the cost–effectiveness of interventions: alternative approaches. *Bull World Health Organ* 2015;93:118–124.

325. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014;371(9):796–797.

326. Statistics Canada. Life Tables, Canada, Provinces and Territories. 2016; Available: http://www5.statcan.gc.ca/olc-cel/olc.action?objId=84-537-X&objType=2&lang=en&limit=0 [accessed 1 Nov 2017].

327. Comstock GW, Palmer CE. Long-term results of BCG vaccination in the southern United States. *Am Rev Respir Dis* 1966;93(2):171–183.

328. Horsburgh CR, O'Donnell M, Chamblee S, Moreland JL, Johnson J, Marsh BJ, *et al.* Revisiting Rates of Reactivation Tuberculosis. *Am J Respir Crit Care Med* 2010;182(3):420–425.

329. Palmer CE, Jablon S, Edwards PQ. Tuberculosis morbidity of young men in relation to tuberculin sensitivity and body build. *Am Rev Tuberc* 1957;76(4):517–539.

330. Marra F, Marra CA, Sadatsafavi M, Morán-Mendoza O, Cook V, Elwood RK, *et al.* Cost-effectiveness of a new interferon-based blood assay, QuantiFERON-TB Gold, in screening tuberculosis contacts. *Int J Tuberc Lung Dis* 2008;12(12):1414–1424.

331. Bauer M, Ahmed S, Benedetti A, Greenaway C, Lalli M, Leavens A, *et al.* The impact of tuberculosis on health utility: a longitudinal cohort study. *Qual Life Res* 2015;24(6):1337–1349.

332. Guo N, Marra CA, Marra F, Moadebi S, Elwood RK, Fitzgerald JM. Health state utilities in latent and active tuberculosis. *Value Health* 2008;11(7):1154–1161.

333. Marra CA, Marra F, Colley L, Moadebi S, Elwood RK, Fitzgerald JM. Health-related quality of life trajectories among adults with tuberculosis: differences between latent and active infection. *Chest* 2008;133(2):396–403.

334. Roth DZ, Ronald LA, Ling D, Chiang LY, Cook VJ, Morshed MG, *et al.* Impact of interferon-γ release assay on the latent tuberculosis cascade of care: a population-based study. *Eur Respir J* 2017;49(3):1601546.

335. Patel AR, Campbell JR, Sadatsafavi M, Marra F, Johnston JC, Smillie K, *et al.* Burden of non-adherence to latent tuberculosis infection drug therapy and the potential cost-effectiveness of adherence interventions in Canada: a simulation study. *BMJ Open* 2017;7(9):e015108.

336. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13(5):509–518.

337. Tan MC, Marra CA, Sadatsafavi M, Marra F, Morán-Mendoza O, Moadebi S, *et al.* Cost-effectiveness of LTBI treatment for TB contacts in British Columbia. *Value Health* 2008;11(5):842–852.

338. Fassbender K, Fainsinger RL, Carson M, Finegan BA. Cost trajectories at the end of life: the Canadian experience. *J Pain Symptom Manage* 2009;38(1):75–80.

339. Lardizabal A, Passannante M, Kojakali F, Hayden C, Reichman LB. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. *Chest* 2006;130(6):1712–1717.

340. Salpeter SR. Fatal isoniazid-induced hepatitis. Its risk during chemoprophylaxis. *West J Med* 1993;159(5):560–564.

341. Jasmer RM, Bozeman L, Schwartzman K, Cave MD, Saukkonen JJ, Metchock B, *et al.* Recurrent tuberculosis in the United States and Canada: relapse or reinfection? *Am J Respir Crit Care Med* 2004;170(12):1360–1366.

342. Schmit KM, Wansaula Z, Pratt R, Price S, Langer A. Tuberculosis - United States, 2016. *MMWR Morb Mortal Wkly Rep* 2017;66:289–294.

343. Lillebaek T, Andersen ÅB, Dirksen A, Smith E, Skovgaard LT, Kok-Jensen A. Persistent High Incidence of Tuberculosis in Immigrants in a Low-Incidence Country. *Emerg Infect Dis* 2002;8(7):679.

344. Taylor Z, Nolan CM, Blumberg HM, American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Controlling Tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR Recomm Rep* 2005;54:1–81.

345. AGDH. *Tuberculosis (TB): CDNA National Guidelines for Public Health Unites - Management of TB*. Australia: Australian Government Department of Health; 2015. Available: http://www.health.gov.au/internet/main/publishing.nsf/content/cdna-song-tuberculosis [accessed 1 Nov 2017].

346. National Institute for Health and Care Excellence. *Tuberculosis: Guidance and guidelines*. London (UK): National Institute for Health and Care Excellence; 2016. Available: https://www.nice.org.uk/guidance/ng33/chapter/Recommendations#latent-tb [accessed 1 Nov 2017].

347. Institute of Medicine (US) Committee on the Elimination of Tuberculosis in the United States. *Ending Neglect: The Elimination of Tuberculosis in the United States*. In: Geiter L, editor. Washington (DC): National Academies Press (US); 2000. Available: http://www.ncbi.nlm.nih.gov/books/NBK225606/ [accessed 1 Nov 2017].

348. Coker R, Weezenbeek KL van. Mandatory screening and treatment of immigrants for latent tuberculosis in the USA: just restraint? *Lancet Infect Dis* 2001;1(4):270–276.

349. Erkens CGM, Slump E, Verhagen M, Schimmel H, Cobelens F, van den Hof S. Risk of developing tuberculosis disease among persons diagnosed with latent tuberculosis infection in the Netherlands. *Eur Respir J* 2016;48(5):1420–1428.

350. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What Is the Price of Life and Why Doesn't It Increase at the Rate of Inflation? *Arch Intern Med* 2003;163(14):1637–1641.

351. Orr PH, Manfreda J, Hershfield ES. Tuberculosis surveillance in immigrants to Manitoba. *Can Med Assoc J* 1990;142(5):453–458.

352. Wang J-S, Allen EA, Enarson DA, Grzybowski S. Tuberculosis in recent Asian immigrants to British Columbia, Canada: 1982–1985. *Tubercle* 1991;72(4):277–283.

353. DeRiemer K, Chin DP, Schecter GF, Reingold AL. Tuberculosis Among Immigrants and Refugees. *Arch Intern Med* 1998;158(7):753–760.

354. Pang SC, Harrison RH, Brearley J, Jegathesan V, Clayton AS. Tuberculosis surveillance in immigrants through health undertakings in Western Australia. *Int J Tuberc Lung Dis* 2000;4(3):232–236.

355. LoBue PA, Moser KS. Screening of immigrants and refugees for pulmonary tuberculosis in San Diego County, California. *Chest* 2004;126(6):1777–1782.

356. Harstad I, Heldal E, Steinshamn SL, Garåsen H, Jacobsen GW. Tuberculosis screening and follow-up of asylum seekers in Norway: a cohort study. *BMC Public Health* 2009;9:141.

357. Liu Y, Weinberg MS, Ortega LS, Painter JA, Maloney SA. Overseas screening for tuberculosis in U.S.-bound immigrants and refugees. *N Engl J Med* 2009;360(23):2406–2415.

358. Mor Z, Leventhal A, Weiler-Ravell D, Peled N, Lerman Y. Chest radiography validity in screening pulmonary tuberculosis in immigrants from a high-burden country. *Respir Care* 2012;57(7):1137–1144.

359. Gacek P, Sosa L, Lobato MN. Assessment of postarrival tuberculosis examinations among immigrants and refugees screened overseas. *Conn Med* 2013;77(6):325–330.

360. Liu Y, Posey DL, Cetron MS, Painter JA. Effect of a culture-based screening algorithm on tuberculosis incidence in immigrants and refugees bound for the United States: a population-based cross-sectional study. *Ann Intern Med* 2015;162(6):420–428.

361. Nuzzo JB, Golub JE, Chaulk P, Shah M. Postarrival Tuberculosis Screening of High-Risk Immigrants at a Local Health Department. *Am J Public Health* 2015;105(7):1432–1438.

362. NIH. *Randomized Clinical Trial Comparing 4RIF vs. 9INH for LTBI Treatment-effectiveness*. Maryland: United States National Institutes of Health; 2009. Available: https://clinicaltrials.gov/ct2/show/NCT00931736 [accessed 1 Nov 2017].

363. Tagmouti S, Slater M, Benedetti A, Kik SV, Banaei N, Cattamanchi A, *et al.* Reproducibility of Interferon Gamma (IFN-γ) Release Assays. A Systematic Review. *Ann Am Thorac Soc* 2014;11(8):1267–1276.

364. Pouchot J, Grasland A, Collet C, Coste J, Esdaile JM, Vinceneux P. Reliability of tuberculin skin test measurement. *Ann Intern Med* 1997;126(3):210–214.

365. Douglas P, Posey DL, Zenner D, Robson J, Abubakar I, Giovinazzo G. Capacity strengthening through pre-migration tuberculosis screening programmes: IRHWG experiences. *Int J Tuberc Lung Dis* 2017;21(7):737–745.

366. Patel S, Parsyan AE, Gunn J, Barry MA, Reed C, Sharnprapai S, *et al.* Risk of progression to active tuberculosis among foreign-born persons with latent tuberculosis. *Chest* 2007;131(6):1811–1816.

367. Comstock GW. Frost revisited: the modern epidemiology of tuberculosis. *Am J Epidemiol* 1975;101(5):363–382.

368. CDC. *Latent Tuberculosis Infection: A Guide for Primary Health Care Providers*. Atlanta (GA): United States Centers for Disease Control and Prevention; 2013. Available: https://www.cdc.gov/tb/publications/ltbi/default.htm [accessed 1 Nov 2017].

369. Moore DAJ, Lightstone L, Javid B, Friedland JS. High Rates of Tuberculosis in End-Stage Renal Failure: the Impact of International Migration. *Emerg Infect Dis* 2002;8(1):77–78.

370. Chia S, Karim M, Elwood RK, FitzGerald JM. Risk of tuberculosis in dialysis patients: a population-based study. *Int J Tuberc Lung Dis* 1998;2(12):989–991.

371. García-Leoni ME, Martín-Scapa C, Rodeño P, Valderrábano F, Moreno S, Bouza E. High incidence of tuberculosis in renal patients. *Eur J Clin Microbiol Infect Dis* 1990;9(4):283–285.

372. Hussein MM, Mooij JM, Roujouleh H. Tuberculosis and chronic renal disease. *Semin Dial* 2003;16(1):38–44.

373. Salgame P, Geadas C, Collins L, Jones-López E, Ellner JJ. Latent tuberculosis infection--Revisiting and revising concepts. *Tuberculosis* 2015;95(4):373–384.

374. Poduval RD, Hammes MD. Tuberculosis screening in dialysis patients--is the tuberculin test effective? *Clin Nephrol* 2003;59(6):436–440.

375. Abdelrahman M, Sinha AK, Karkar A. Tuberculosis in end-stage renal disease patients on hemodialysis. *Hemodial Int* 2006;10(4):360–364.

376. Shankar MSR, Aravindan AN, Sohal PM, Kohli HS, Sud K, Gupta KL, *et al.* The prevalence of tuberculin sensitivity and anergy in chronic renal failure in an endemic area: tuberculin test and the risk of post-transplant tuberculosis. *Nephrol Dial Transplant* 2005;20(12):2720–2724.

377. Lee JY, Choi HJ, Park I-N, Hong S-B, Oh Y-M, Lim C-M, *et al.* Comparison of two commercial interferon-gamma assays for diagnosing Mycobacterium tuberculosis infection. *Eur Respir J* 2006;28(1):24–30.

378. Mandalakas AM, Hesseling AC, Chegou NN, Kirchner HL, Zhu X, Marais BJ, *et al.* High level of discordant IGRA results in HIV-infected adults and children. *Int J Tuberc Lung Dis* 2008;12(4):417–423.

379. Ferrara G, Losi M, D'Amico R, Roversi P, Piro R, Meacci M, *et al.* Use in routine clinical practice of two commercial blood tests for diagnosis of infection with Mycobacterium tuberculosis: a prospective study. *Lancet* 2006;367(9519):1328–1334.

380. Arend SM, Thijsen SFT, Leyten EMS, Bouwman JJM, Franken WPJ, Koster BFPJ, *et al.* Comparison of two interferon-gamma assays and tuberculin skin test for tracing tuberculosis contacts. *Am J Respir Crit Care Med* 2007;175(6):618–627.

381. Carrero JJ, Stenvinkel P. Inflammation in end-stage renal disease--what have we learned in 10 years? *Semin Dial* 2010;23(5):498–509.

382. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. *Lancet* 2005;365(9456):331–340.

383. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, *et al.* Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015;385(9981):1975–1982.

384. Campbell JR, Krot J, Marra F. Latent tuberculosis diagnostic tests to predict longitudinal tuberculosis during dialysis: a meta-analysis. *Int J Tuberc Lung Dis* 2016;20(6):764–770.

385. Ronald LA, Campbell JR, Balshaw RF, Roth DZ, Romanowski K, Marra F, *et al.* Predicting tuberculosis risk in the foreign-born population of British Columbia, Canada: study protocol for a retrospective population-based cohort study. *BMJ Open* 2016;6(11).

386. Population Data BC. Population Data BC. 2017; Available: https://www.popdata.bc.ca/ [accessed 1 Nov 2017].

387. Immigration, Refugees, and Citizenship Canada [creator] (2015): Population Data BC [publisher]. Data Extract. IRCC (2014). http://www.popdata.bc.ca/data.

388. Canadian Institute for Health Information [creator] (2015): Discharge Abstract Database (Hospital Separations). Population Data BC [publisher]. Data Extract. MOH (2014). http://www.popdata.bc.ca/data.

389. British Columbia Ministry of Health [creator] (2015): Medical Service Plan (MSP) Payment Information File. Population Data BC [publisher]. Data Extract. MOH (2014). http://www.popdata.bc.ca/data.

390. BC Ministry of Health [creator] (2015): PharmaNet. BC Ministry of Health [publisher]. Data Extract. Data Stewardship Committee (2014). http://www.popdata.bc.ca/data.

391. British Columbia Ministry of Health [creator] (2015): Consolidation File (MSP Registration & Premium Billing). Population Data BC [publisher]. Data Extract. MOH (2014). http://www.popdata.bc.ca/data.

392. BC Vital Statistics Agency [creator] (2015): BC Vital Statistics. Population Data BC [publisher]. Data Extract. BC Vital Statistics Agency (2014). http://www.popdata.bc.ca/data.

393. BC Centre for Disease Control [creator] (2015): BC Provincial TB Registry (BCCDC-iPHIS). Population Data BC [publisher]. Data Extract. BCCDC (2014). http://www.popdata.bc.ca/data.

394. BC Centre for Disease Control [creator] (2015): BC Provincial HIV/ AIDS Surveillance Database (BCCDC-HAISIS). Population Data BC [publisher]. Data Extract. BCCDC (2014). http://www.popdata.bc.ca/data.

395. BC Renal Agency [creator] (2015): BC Provincial Renal Agency Database (PROMIS). Population Data BC [publisher]. Data Extract. PROMIS (2014). http://www.popdata.bc.ca/data.

396. Levey AS, de Jong PE, Coresh J, Nahas ME l., Astor BC, Matsushita K, *et al.* The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011;80(1):17–28.

397. Ronksley PE, Tonelli M, Quan H, Manns BJ, James MT, Clement FM, *et al.* Validating a case definition for chronic kidney disease using administrative data. *Nephrol Dial Transplant* 2012;27(5):1826–1831.

398. Leong A, Dasgupta K, Bernatsky S, Lacaille D, Avina-Zubieta A, Rahme E. Systematic Review and Meta-Analysis of Validation Studies on a Diabetes Case Definition from Health Administrative Records. *PLoS ONE* 2013;8(10):e75256.

399. Antoniou T, Zagorski B, Loutfy MR, Strike C, Glazier RH. Validation of case-finding algorithms derived from administrative data for identifying adults living with human immunodeficiency virus infection. *PLoS ONE* 2011;6(6):e21748.

400. Rajagopalan S. Tuberculosis and aging: a global health problem. *Clin Infect Dis* 2001;33(7):1034–1039.

401. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* 1999;94(446):496–509.

402. Cole SR, Chu H, Greenland S. Maximum likelihood, profile likelihood, and penalized likelihood: a primer. *Am J Epidemiol* 2014;179(2):252–260.

403. Baciewicz AM, Self TH. Rifampin drug interactions. *Arch Intern Med* 1984;144(8):1667–1671.

404. Chen J, Raymond K. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. *Ann Clin Microbiol Antimicrob* 2006;5:3.

405. Fraser SDS, Roderick PJ, May CR, McIntyre N, McIntyre C, Fluck RJ, *et al.* The burden of comorbidity in people with chronic kidney disease stage 3: a cohort study. *BMC Nephrol* 2015;16.

406. Tonelli M, Wiebe N, Guthrie B, James MT, Quan H, Fortin M, *et al.* Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. *Kidney Int* 2015;88(4):859–866.

407. Canadian Institute for Health Information. Patient Cost Estimator. 2017; Available: https://www.cihi.ca/en/patient-cost-estimator [accessed 1 Nov 2017].

408. Davison SN, Jhangri GS, Feeny DH. Comparing the Health Utilities Index Mark 3 (HUI3) with the Short Form-36 preference-based SF-6D in chronic kidney disease. *Value Health* 2009;12(2):340–345.

409. Yang F, Lau T, Lee E, Vathsala A, Chia KS, Luo N. Comparison of the preference-based EQ-5D-5L and SF-6D in patients with end-stage renal disease (ESRD). *Eur J Health Econ* 2015;16(9):1019–1026.

410. Awan MS, Waqas M, Aslam MA, Sarwar M. Measurement of SF-6D Utility among Patients with Active Tuberculosis. *Glob J Health Sci* 2011;3(1):203.

411. Ates G, Yildiz T, Danis R, Akyildiz L, Erturk B, Beyazit H, *et al.* Incidence of tuberculosis disease and latent tuberculosis infection in patients with end stage renal disease in an endemic region. *Ren Fail* 2010;32(1):91–95.

412. Chung WK, Zheng ZL, Sung JY, Kim S, Lee HH, Choi SJ, *et al.* Validity of interferon-γ-release assays for the diagnosis of latent tuberculosis in haemodialysis patients. *Clin Microbiol Infect* 2010;16(7):960–965.

413. Cisse MM, Kabouss RE, Kane Y, Seck SM, Lemrabott AT, Faye M, *et al.* Tuberculosis among Chronic Hemodialysis Patients: A Senegalese Single Center Experience. *Open J Nephrol* 2015;05(04):117.

414. Inoue T, Nakamura T, Katsuma A, Masumoto S, Minami E, Katagiri D, *et al.* The value of QuantiFERON TB-Gold in the diagnosis of tuberculosis among dialysis patients. *Nephrol Dial Transplant* 2009;24(7):2252–2257.

415. Lai C-C, Tan C-K, Liao C-H, Chou C-H, Huang Y-T, Hsueh P-R. Diagnosis of pulmonary tuberculosis among dialysis patients by enzyme-linked immunospot assay for interferon-γ. *Nephrol Dial Transplant* 2009;24(8):2605–2606.

416. Unsal A, Ahbap E, Basturk T, Koc Y, Sakaci T, Sinangil Arar A, *et al.* Tuberculosis in dialysis patients: a nine-year retrospective analysis. *J Infect Dev Ctries* 2013;7(3):208–213.

417. Harris M, Johnston J, Ronald L. Latent Tuberculosis Treatment Cascade in Chronic Kidney Disease Patients: The Vancouver Experience. *Open Forum Infect Dis* 2016;3(Suppl 1):S599.

418. International Diabetes Federation. *Diabetes Atlas - 7th Edition*. Belgium: International Diabetes Federation; 2015. Available: http://www.diabetesatlas.org/ [accessed 1 Nov 2017].

419. USRDS. *United States Renal Data System Annual Report 2014*. Michigan: United States Renal Data System; 2014. Available: https://www.usrds.org/2014/view/ [accessed 1 Nov 2017].

420. FitzGerald JM, Elwood RK, Chia S. Dialysis patients with tuberculosis. *Can Med Assoc J* 1999;161(5):489–489.

421. Pisu M, Gerald J, Shamiyeh JE, Bailey WC, Gerald LB. Targeted Tuberculosis Contact Investigation Saves Money Without Sacrificing Health. *J Public Health Manag Pract* 2009;15(4):319–327.

422. Hoffmann M, Tsinalis D, Vernazza P, Fierz W, Binet I. Assessment of an Interferon-gamma release assay for the diagnosis of latent tuberculosis infection in haemodialysis patient. *Swiss Med Wkly* 2010;140(19–20):286–292.

423. Diel R, Loddenkemper R, Nienhaus A. Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a metaanalysis. *Chest* 2010;137(4):952–968.

424. Shu C-C, Hsu C-L, Lee C-Y, Wang J-Y, Wu V-C, Yang F-J, *et al.* Comparison of the Prevalence of Latent Tuberculosis Infection among Non-Dialysis Patients with Severe Chronic Kidney Disease, Patients Receiving Dialysis, and the Dialysis-Unit Staff: A Cross-Sectional Study. *PLoS ONE* 2015;10(4):e0124104.

425. Chagas ACF, Hans Filho G, de Oliveira SM do VL, Ivo ML, Corrêa Filho RAC, Donatti MI. Prevalence of latent tuberculosis and treatment adherence among patients with chronic kidney disease in Campo Grande, State of Mato Grosso do Sul. *Rev Soc Bras Med Trop* 2014;47(2):204–211.

426. Smith BM, Schwartzman K, Bartlett G, Menzies D. Adverse events associated with treatment of latent tuberculosis in the general population. *Can Med Assoc J* 2011;183(3):E173–E179.

427. Ronald LA, FitzGerald JM, Benedetti A, Boivin J-F, Schwartzman K, Bartlett-Esquilant G, *et al.* Predictors of hospitalization of tuberculosis patients in Montreal, Canada: a retrospective cohort study. *BMC Infect Dis* 2016;16(1):679.

428. Guthrie JL, Kong C, Roth D, Jorgensen D, Rodrigues M, Hoang L, *et al.* Molecular Epidemiology of Tuberculosis in British Columbia, Canada – A 10-Year Retrospective Study. *Clin Infect Dis* 2017;https://doi.org/10.1093/cid/cix906.

429. Hoff ST, Peter JG, Theron G, Pascoe M, Tingskov PN, Aggerbeck H, *et al.* Sensitivity of C-Tb: a novel RD-1-specific skin test for the diagnosis of tuberculosis infection. *Eur Respir J* 2016;47(3):919–928.

430. Ruhwald M, Aggerbeck H, Gallardo RV, Hoff ST, Villate JI, Borregaard B, *et al.* Safety and efficacy of the C-Tb skin test to diagnose Mycobacterium tuberculosis infection, compared with an interferon γ release assay and the tuberculin skin test: a phase 3, double-blind, randomised, controlled trial. *Lancet Respir Med* 2017;5(4):259–268.

431. Aggerbeck H, Giemza R, Joshi P, Tingskov PN, Hoff ST, Boyle J, *et al.* Randomised clinical trial investigating the specificity of a novel skin test (C-Tb) for diagnosis of M. tuberculosis infection. *PLoS ONE* 2013;8(5):e64215.

432. Goletti D, Petruccioli E, Joosten SA, Ottenhoff THM. Tuberculosis Biomarkers: From Diagnosis to Protection. *Infect Dis Rep* 2016;8(2):6568.

433. Ruhwald M, Ravn P. Biomarkers of latent TB infection. *Expert Rev Respir Med* 2009;3(4):387–401.

434. Oxlade O, Murray M. Tuberculosis and Poverty: Why Are the Poor at Greater Risk in India? *PLoS ONE* 2012;7(11):e47533.