The Preventing TB Overseas Pilot Study (PTOPS): Voluntary Latent Tuberculosis Infection Testing and Treatment for US-Bound Immigrants in Vietnam

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Preventing TB Overseas Pilot Study (PTOPS): Voluntary Latent Tuberculosis Infection Testing and Treatment for US-Bound Immigrants from Vietnam

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i. Declaration

I, Amera Khan, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Sign:

Full name: Amera Khan
Date: January 4, 2021

ii. Acronyms and Abbreviations

Acronym/Abbreviation	Definition
ACET	Advisory Council for the Elimination of Tuberculosis (US)
ALT (SGPT)	Alanine Aminotransferase
AST (SGOT)	Aspartate Aminotransferase
BCG	Bacille Calmette-Guerin
CDC	Centers for Disease Control and Prevention
CDC TB TIs	CDC Technical Instructions for Tuberculosis Screening and Treatment Using Cultures and Directly Observed Therapy
CRH VMD	Cho Ray Hospital Visa Medical Department
DGHT	Division of Global HIV and Tuberculosis (CDC)
DGMQ	Division of Global Migration and Quarantine (CDC)
DOT	Directly Observed Therapy
DrPH	Doctor of Public Health
DS	Department of State (US)
DTBE	Division of Tuberculosis Elimination (CDC)
EDN	Electronic Disease Notification
GTB	Global TB Branch (CDC)
HCMC	Ho Chi Minh City
HHS	US Health and Human Services
HIV	Human Immunodeficiency Virus
IGRA	Interferon Gamma Release Assay
INA	Immigration and Nationality Act
IOM	International Organization for Migration
IR	Implementation Research
IRB	Institutional Review Board
LFT	Liver Function Test
LSHTM	London School of Hygiene and Tropical Medicine
LTBI	Latent Tuberculosis Infection
NTP	National TB Program
NTSS	National TB Surveillance System (US)
OMB	Office of Management and Budget
PTOPS	The Preventing TB Overseas Pilot Study
QFT- GIT	QuantiFERON Gold In-Tube (IGRA)
RPT	Rifapentine
SAT	Self-Administered Therapy
TB	Tuberculosis
TPT	TB Preventive Treatment
TST	Tuberculin Skin Test
UCSF	University of California at San Francisco
US	United States
VNTP	Viet Nam National TB Programme
WHO	World Health Organization
3HP	3 months of 12 weekly doses of Isoniazid and Rifapentine
3HR	3 months daily Isoniazid and Rifampicin
4R	4 months of Rifampicin daily
6H or 9H	6 or 9 months of daily Isoniazid

iii. Abstract

In 1989, the United States declared a goal to eliminate tuberculosis (TB) by 2010, with elimination defined as <1 case per million. In 2019, the US reported 27 cases per million with 70% of cases occurring in the foreign-born. Over 80% of cases were reactivation of latent TB infection (LTBI) acquired prior to US arrival. Strategies to address LTBI have been suboptimal and innovations are critical to reach TB elimination.

Currently, the pre-arrival immigrant medical examination focuses on identifying TB disease. To address LTBI in immigrants, a potential strategy is to offer voluntary LTBI testing using an interferon-gamma release assay (IGRA) and 3 months of weekly isoniazid and rifapentine (3HP) treatment during the examination. A prospective cohort study was conducted among US-bound immigrant visa applicants undergoing the examination in Vietnam. This study assesses uptake, acceptability, and factors associated with three different points of the LTBI care cascade.

Of 5311 visa applicants recruited, 2438 (46%) consented; 2276 had an IGRA processed, and 484 (21%) tested positive. Among 452 participants eligible for 3HP, 304 (67%) initiated treatment and 268 (88%) completed treatment. Being female, aged 18-35, bacille Calmette-Guérin (BCG) vaccinated, currently in school or employed, knowing a family member with TB, or having a private mode of transportation were associated with test acceptance. Immigrating with family was associated with treatment and immigrating >2 months was associated with testing and treatment. No predictors emerged for treatment completion.

LTBI prevalence was high; however, test acceptance was low. The proportion initiating treatment overseas was similar to immigrant populations in the United States. Among those initiating treatment overseas, the proportion completing treatment was high at 88%. The study demonstrates that using the overseas medical examination to provide voluntary LTBI testing and treatment should be considered to address LTBI in US-bound immigrants to advance TB elimination efforts.

Word count:300

iv. DrPH Integrating Statement

It has been a long journey since the fall of 2014 when I enrolled in the London School of Hygiene and Tropical Medicine's (LSHTM) Doctor of Public Health (DrPH) program. I opted for the DrPH over the PhD because at that time I was already established as a public health professional with over 15 years of experience and on a senior level leadership track at the CDC. I wanted to expand my skills but remain in public health practice with a focus on designing, implementing, and evaluating interventions to improve health outcomes.

Leading, designing, and implementing successful public health programs requires a broad range of knowledge and skills from management, research design, data analysis, monitoring and evaluation, and socio-behavior change theories, communications, economics, and policy. While the PhD focuses more heavily on research and analytical skills, I was drawn to LSHTM's DrPH program because of its combined offering of leadership and management skills coupled with practical approaches for research and policy analysis. This program combined all of the skills I wanted for enhancing my public health career. The requirements of the DrPH are quite intensive and the following includes my experiences and learnings from my journey through the program.

Two Compulsory Courses with Three Graded Assignments

The DrPH consists of two, eleven-week, compulsory in-person courses: *Evidence-based Public Health Policy (EBPHP) and Understanding Leadership, Management and Organizations (ULMO).* Both courses have graded written assignments.

The *EBPHP* module provided me with an understanding of using research-based evidence to inform public health policy, but also how external factors play an often overlooked, yet influential, role on decision making. Our first assignment was to conduct a systematic review of the literature to provide us with the skills to systematically search, critically analyze, extract, and synthesize data from primary research. We were given a graded assignment to conduct a systematic review on the broad topic of the alcohol industry and marketing for which I chose a narrower research focus and question to conduct the review. While I did not conduct a systematic review for my thesis or OPA, the screening approach and analytical skills acquired from the assignment were still applicable to the narrative literature reviews I conducted for both of those projects. Moreover, I was able to directly put the acquired skills into use through serving as a

contributor to a published systematic review conducted to inform CDC recommendations on TB testing and treatment of US health care personnel.

Sosa, L. E., Njie, G. J., Lobato, M. N., Bamrah Morris, S., Buchta, W., Casey, M. L., Goswami, N. D., Gruden, M., Hurst, B. J., **Khan, A. R.,** Kuhar, D. T., Lewinsohn, D. M., Mathew, T. A., Mazurek, G. H., Reves, R., Paulos, L., Thanassi, W., Will, L., & Belknap, R. Tuberculosis Screening, Testing, and Treatment of US Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019. *Morbidity and mortality weekly report*, *68*(19), 439–443.

The second graded assignment for *EBPHP* was equally useful by providing an understanding of different processes used to influence policy. For this assignment I chose to propose a policy to implement TB screening for temporary US visa holders (students and businesspersons) as they contribute to the TB burden in the United States. For the assignment, I provided epidemiological evidence, and then using the policy process theories learned in class, I conducted a situational analysis of the political environment to develop an agenda-setting strategy. I centered my strategy around a stakeholder analysis while considering how framing and the use of different communication messages will influence different stakeholders in regard to the policy.

The second module, *ULMO,* provided us with a theoretical foundation for how leadership, management style, and organizational structure determine how organizations function. Several local and global health agency leaders served as guest lecturers to provide us with examples of how these theories were applied. We were also given an opportunity to reflect and critically assess our own leadership and management style through a residential workshop that we attended with our DrPH class cohort and through the crafting of a *Personal Development Plan.* The *ULMO* ended with a graded assignment to conduct a *Strategic Analysis of an Organisation* using the theories learned in class. For my analysis, I focused on analyzing the structure and strategic planning of the US National TB Program housed at the CDC. While this class allowed for reflection on leadership styles and management, at times it felt more academic than practical for those of us hoping to practically apply what we learned in this class in our professional lives.

Organizational and Policy Analysis (OPA)

Another required component of the DrPH, is the organizational and policy analysis (OPA). The OPA requires a 3-6-month attachment to an organization to allow DrPH students an opportunity to apply organizational and management theories while assessing a public

health organization through a case study method. The conclusion of the OPA consists of an extensive report with a comprehensive literature review, primary data collection, and analysis that is reviewed by two examiners.

My OPA was conducted at the CDC Division of Global HIV/AIDS (DGHA). The aim of my OPA was to critically analyze the management of the organizational change process as DGHA was restructuring to form a new Global TB Branch. My OPA specifically focused on understanding employees' beliefs and perceptions regarding the restructuring and strategies to help employees navigate and accept the changes.

Prior to starting the OPA, I conducted a comprehensive literature review on organizational change theories and measurements and developed a conceptual framework to guide the research. Data to understand the context of the organizational restructuring were derived through document reviews and key-informant interviews. Employee sentiments were assessed using a semi-structured questionnaire that I designed based on the theory, as well as previously validated organizational change scales from the literature. The questionnaire included both open-ended and structured questions and a mixed-methods approach was used for data analysis. The mixed-methods approach allowed for understanding of both what the staff were thinking about the change and why. The findings suggested that although employees were moving through the stages of organizational change, many employees were not clear on the rationale or benefits (personal and organizational) of the restructuring and felt left out of the decision-making process. Thus, it was recommended that leadership should focus on creating and delivering change messages designed to help employees understand the rationale and benefits of the merger. Additionally, leaders should ensure employees are engaged and empowered in the change process to facilitate their adoption and continued support for the organizational change.

While I learned about and applied organizational change theories and employ a mixed method approach for the assessment, I do think this assignment was more academic in nature than is useful for a DrPH student who already has managed and led public health programs. Additionally, the lengthy report and process was also less useful to the organization who hosted the practicum as they were more interested in a rapid assessment of their situation. Moreover, for a DrPH student, who presumably already has

leadership and management background in public health, a professional attachment to another agency or organization is not always practical and does not necessarily provide new skills or learning. In my opinion, what would be useful for public health professionals is to learn about practical and rapid assessment approaches that could be used to manage and improve programs in a timely fashion. My understanding is that the OPA requirement has since changed for incoming DrPH classes to reflect some of the concerns that I and other students voiced. Nevertheless, I did learn from the rigorous OPA process about conducting mixed-method research and the importance of introducing and managing organizational changes through employee engagement from a bottom-up approach rather than a top-down process.

Non-compulsory courses and transferable skills workshops

In addition to the compulsory courses, I audited masters level courses on social research, statistics, and evaluation of public health interventions. I also attended workshops on conducting a literature search, developing conceptual frameworks, and using *Stata.* All of these were useful in providing me with skills to conduct the research and analysis for my thesis.

Thesis

The final requirement for the DrPH is a research project which results in a thesis. This work is presented here in this document. While the document focuses on the outcomes of the study, what does not come across is the careful planning, designing, and implementation of the intervention using knowledge and skills acquired from the DrPH. I designed, led, and implemented this research project from the ground-up, based on lessons learned from my previous experiences and from the DrPH assignments. The compulsory and elective coursework helped me with the literature review, research design, and data analysis. The leadership and management skills proved useful for me in my role as the principal investigator overseeing the implementation of this project with multiple partners. Understanding the principals of behavior change, both on an organizational and individual level, were also useful for implementing the study. I worked with the study site to incorporate their ideas on how best to implement the intervention into their routine operations so that they felt more ownership of the intervention. I developed patient education materials based on behavior change communication

principals. Lastly, as I further disseminate the findings of the study, lessons learned about using evidence to inform policy will be applicable.

The DrPH journey has been long, but along the way I am grateful to say that I acquired new knowledge and skills that will further advance my public health career.

v. Role of DrPH Candidate in the Research

I, Amera Khan, served as the lead Principal Investigator (PI) for the *Preventing TB Overseas Pilot Study (PTOPS).* I conceptualized and developed this research study for the purposes of my DrPH requirements. This included developing the research question and objectives; study design; research protocol, study staff training materials, data collection tools, patient education materials, and the data management plan. I also conducted the data analysis and developed presentations, reports, and manuscripts to disseminate the results.

Additionally, I convened the PTOPS study team to include additional partners to effectively implement this project in Vietnam. Because this project was funded by the US Centers for Disease Control and Prevention (CDC), there were representatives from two different CDC Divisions (the Division of Global HIV and Tuberculosis (DGHT) and the Division of Global Migration and Quarantine) serving as co-PIs. These two PIs served as mentors and in an advisory role to me to ensure that the project followed CDC guidance and received the necessary approvals. They were also responsible for the administrative management of the project including disbursement of CDC project funds and had general oversight of the project.

An additional two Vietnamese-speaking US-based study coordinators were hired to follow-up with participants who moved to the United States during their treatment. These coordinators ensured that participants took their medicine and assessed if they experienced any side-effects.

The University of California as San Francisco (UCSF) study team was responsible for the importation of the study drugs (3HP) and the diagnostic tools into Vietnam. They also served as clinical experts with oversight of all issues related to patient management and side-effects.

The Cho Ray Hospital Visa Medical Department (CRH VMD) study team implemented the study in their clinic by recruiting and enrolling participants undergoing the required immigration visa medical examination. They collected data using the study forms I developed. They were also responsible for directly managing the medical care for the participants enrolled in the study.

This project could not have been done without this team approach.

vi. Acknowledgements

Acquiring this DrPH has been a self-funded labor of love over the past six to seven years. Despite the many challenges in getting this research project off the ground, including the naysayers who were skeptical about the project and about me pursuing a degree late in life, I am forever grateful that there were many more people who encouraged me, offered their support, and believed in this project's potential to contribute to the US TB elimination goal.

First, I am thankful for my LSHTM supervisors, Dr. Lucy Platt and Professor Richard Coker, for guiding me through the long DrPH journey with their support, reviews, and insightful comments on both this thesis as well as the OPA. I am also appreciative that Professor Nicki Thorogood and Anne-Marie Sue-Patt for their support and helping me navigate the administrative aspects of the DrPH process. Additionally, I would like to acknowledge Dr. Mishal Khan and Professor Alison Grant for serving as examiners for my DrPH review and providing suggestion on the research project. I would like to also thank Drs. Kathryn Oliver and Dalya Marks for their support.

I want to thank my former team members at the CDC Division of TB Elimination, Cheryl Tryon, Dr. Joan Mangan, Peri Hopkins, Allison Maiuri, and Sarah Segerlind for the unwavering support and for continuing the important work of our team in my absence as I completed my coursework. I am grateful to my current supervisor, Dr. Jacob Creswell, at the Stop TB Partnership in supporting me in finishing this work for my degree.

When I first pitched my DrPH research proposal at CDC, I was met with mixed result. While everyone thought that the idea was important for addressing TB in the United States, many did not think it was achievable given the complexities of implementing the intervention in the official context of the immigrant medical examination, the involvement of three different centers at the CDC, and the challenges for importation of 3HP into Vietnam. I am grateful that despite the complexities, Dr. Drew Posey of the CDC Division and Global Migration and Quarantine, encouraged me to pursue the proposal, even though he was concerned that finding funding to implement the project would be a long shot. Thankfully with her background in successfully revising the overseas medical examination's TB screening algorithm, Dr. Susan Maloney of the Global TB Branch, upon reviewing the proposal, enthusiastically supported the project and was able to find funding

to implement the research. Moreover, she was in full support of me serving as Principal Investigator despite me not being a member of her branch while at CDC and of me maintaining my role as Principal Investigator even after I left CDC.

Since this research project was designed and implemented from the ground-up and conducted in a real-world setting using federal funds, it required the convening of multiple partners with unique roles. Without the PTOPs team that I convened; this project would not have happened. I consider myself lucky to have worked with such an amazing group of people such as the team at Cho Ray Hospital Visa Medical Department (CRH VMD). Much of the success from this project rest upon the shoulders of Dr. Hoang Lan Phuong and her dedicated staff: Dr. Dang Thi Kieu Trinh, Nguyen Thi My Loc, Le Dieu Hien, Phan Thi Hong Le, Quach Thi Kim Lien, Sooc Ngoc Lan, Phan Thi Kim Thoa, and Le Tran Minh Thu. They tirelessly worked to implement this study in their already busy clinic. Their attention to detail, and care of and ability to connect with the study participants greatly contributed to the smooth implementation and successful outcomes of this project.

I am equally fortunate to have worked with the team from UCSF, Dr. Payam Nahid, Dr Phan Ha, and Cindy Merrifield, who are leading world experts in TB clinical research. Their ability to import 3HP into Vietnam was a feat for this project and the country. Their clinical expertise was instrumental in supporting the physicians at CRH VMD for managing patients on LTBI treatment for the first time. I am also very lucky to have had an amazing group of people from the CDC who provided support on this project. I want to acknowledge Dr. Cuc Tran and Tiffany Tran for reaching out to and connecting with the participants in Vietnamese. Drs. Nina Marano, Alyssa Finlay, and Carla Winston for their roles in protocol review and helping with IRB approvals and general support of the project.

Special thanks go to my former fellow CDC co-PI's, Dr. Christina Phares from the CDC Division of Global Migration and Quarantine and Dr. John Oeltmann, whom I now consider dear friends. I am eternally grateful to have worked with and learned from both of them. Christina's knowledge of the US immigration medical examination procedures and policies were instrumental for developing and implementing the intervention and her unique relaxed style made this project fun to work on as well. John Oeltmann is a legend at CDC, and I am so thankful for his mentorship, support, and friendship. When I first wrote my research proposal for this project, I recognized that I would need to have a more

senior PI and representation from the Global TB Branch (which I was not a part of) if I wanted to secure funding and support. I had not closely worked with John before, but he was the first person I thought of to serve in this role. Throughout my years at CDC, I had witnessed John successfully mentor many of the CDC Epidemiologic Intelligence Service Officers in the Division of TB Elimination. He is well known for allowing his mentees to own and lead their projects, while teaching them the principles of epidemiology and operational research. I feel very fortunate to have had John as an advisor and mentor.

I am grateful for the statistical review and consultations provided by Drs. Jodi Van Den Eng and Lauren Howe. Being able to talk through the analyses and calculations for the thesis was incredibly useful. I appreciate and recognize that many more people were involved in the IRB and clearance reviews from three different CDC centers, as well as UCSF, CRH VMD, LSHTM, and the Vietnam NTP.

Last but not least I want to thank all of my family and friends who supported me throughout this long process and encouraged me to continue even when the workload seemed to be overwhelming.

Thanks to Oliver, Catherine, and Sema for providing housing during my London stays. Omar for the company while studying and the support to get through the program. To my other DrPH colleagues and other friends who encouraged me (Sadhna, Reshma, Joy, Chris, Deb, Scott, Ali, Pauline, Enrica, Eric, Nita, Katina, Heather, Elisa, Nick, and so many more)

My family, Rahman, Zehra, Mujeeb, Asra, Saera, Fazal, Ali, Matt, Saif, Sohail, Raihan, and Samad for understanding when I had to work instead of participating in family events and for their proof-reading assistance when requested.

1. Chapter 1: Preventing TB Overseas Pilot Study (PTOPS) Thesis Overview

1.1 Preventing TB Overseas Pilot Study (PTOPS) Overview

In 1989, the United States' Advisory Council on the Elimination of Tuberculosis (ACET) declared a goal to eliminate TB in the United States by 2010.(1) While the United States has seen a continued decline in TB incidence for the past 20 years, with reported cases now numbering an all-time low of approximately 9,000 in 2019, the elimination goal is still far from a reality. Reaching the goal has been impeded by the fact that the percentage of TB cases occurring among non-US-born persons continues to steadily increase. In 2019, approximately 70 percent of TB cases in the United States occurred among the non-US-born.(2) Molecular studies suggest that TB disease among non-US-born persons is generally due to the reactivation of latent TB infection (LTBI) acquired prior to arrival in the United States.(3,4) Modeling studies show that for the United States to further progress towards TB elimination, efforts need to be strengthened for diagnosing and treating LTBI among non-US-born persons.(5,6)

Current US immigration medical screening policies focus on identifying and treating active TB disease pre-arrival at overseas panel physician sites in immigrants seeking permanent US residency. These screening activities have proven to be a high yield intervention for identifying TB disease in US-bound immigrants and are considered to be a factor associated with a temporal decline in TB cases among the non-US-born.(7)

With the availability of a shorter course 3-month LTBI treatment regimen of isoniazid (INH) and rifapentine (RPT) given once weekly (3HP), one potential strategy that has been repeatedly called for is to expand the overseas TB medical examination process for immigrants seeking permanent US residence to include testing of LTBI by an interferon-gamma release assay (IGRA) for those ≥14 years of age and the provision of voluntary LTBI treatment by 3HP.(8,9)

To determine if voluntary LTBI testing and 3HP treatment is an acceptable strategy that can contribute to US TB elimination goals, a prospective cohort study was conducted at the *Cho Ray Hospital Visa Medical Department* in Ho Chi Minh City, Vietnam. To guide the study and intervention, components from an implementation research (IR) framework were used in conjunction with the socio-ecological model (*SEM*). The framework and model were used to understand and assess contextual factors associated with the

adoption (uptake) and acceptability of LTBI testing, treatment initiation, and completion by the US-bound Vietnamese immigrants.

Results from the study will help inform if LTBI testing and voluntary treatment should be included as part of the pre-arrival overseas medical examination process for US-bound immigrants, and if so, what factors need to be considered for the successful scale-up and implementation of the strategy. The study additionally provides valuable information to the Vietnam National TB Programme on the first time use of the 3HP regimen in their country. This information can be used to support the country's LTBI strategy to meet the World Health Organization's End TB Strategy that was adopted by the World Health Assembly in 2014.(10)

1.2 Research Aim

Research Aim

The aim of this research is to assess if pre-arrival voluntary LTBI testing and 3HP treatment for US-bound immigrants should be considered as a strategy that can contribute towards TB elimination in the United States.

Further description of the research aim, study objectives, and the conceptual framework and methods used to assess the strategy are provided in the Chapter 2.

1.3 DrPH Thesis Structure

This DrPH thesis starts with a basic introduction of the research project, aim, objectives, and conceptual framework, followed by the main chapters which cover the background context of the study and narrative review of the literature, study justification, methods, results, discussion, and conclusions. The results of the study are presented in a research paper style format.

Paper 1: an assessment of the uptake of voluntary LTBI testing and treatment initiation and completion of 3HP among U.S-bound immigrant visa applicants in Vietnam.

Paper 2: an analysis of the factors associated with LTBI testing, treatment initiation, and treatment completion for Vietnamese US-bound immigrant visa applicant, guided by an adapted version of the socio-ecological model.

Since the papers presenting the findings of the study are meant to serve as stand-alone manuscripts, there inevitably is some repetition of information in the overall thesis. Both manuscripts have a methods section therefore the Methods chapter in the overall thesis may suggest reference to the manuscripts for more detailed information. Additionally, each manuscript has its own discussion and conclusion sections, so the Discussion and Conclusion chapter of this thesis draws upon the overall results, limitations, conclusions, and future considerations for the PTOPS approach.

Terms Used in the Thesis

Since I began research and development for my study proposal in 2014, terminologies used to describe TB epidemiology and treatment may have changed. In this thesis ‘foreign-born’ is synonymous with ‘non-US-born’. ‘LTBI treatment’ is increasingly being

referred to as ‘TB preventive treatment (TPT)’. These respective terminologies are sometimes used interchangeably. Additionally, for the purposes of this study the term ‘migrant’ is broadly used to refer to any person moving from their country of origin to another country. This can include documented or undocumented migrants: immigrants, refugees, asylums seekers, or those relocating to another country temporarily or permanently. For this study, particularly for the US context, the term ‘immigrant’ is used to refer to those who have or are seeking permanent relocation to the United States through an official visa application process.

Migrant TB screening programs are conducted either prior to the immigrant or refugee arriving to the host country (pre-arrival); when the immigrant or refugee arrives in country (upon-entry); or sometime after the immigrant moves to the host country (post-arrival). Different terms are often used to describes these screening settings. For the United States, the *pre-arrival screening* conducted at the panel physician sites is often referred to as the *overseas medical examination;* the terms *pre-entry* or *pre-departure* exam are also used. These terms may be used interchangeably in this document.

1.4 Study Funding

PTOPS was funded by the US CDC with a grant from the White House *Combating Anti-Microbial Resistant Bacteria* funds made possible by the Obama Administration. The rifapentine for the project was donated by Sanofi. My work on the project was mostly voluntary and my DrPH enrolment was self-funded.

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2. Chapter 2: Study Justification, Conceptual Framework, and Research Aim

2.1 Study Justification and Intended Use of Findings

Prevention of active TB through the diagnosis and treatment of LTBI is recognized as an important component of TB control. If the United States is to move towards TB elimination, it is essential to address the high burden of LTBI among non-US-born persons immigrating to the US. Current post-arrival strategies to find and treat LTBI in non-US-born persons residing in the United States have been resource-intensive and have suffered from low treatment initiation and completion rates.(1)

The recent availability of the 3HP treatment regimen allows for the potential to offer LTBI treatment to immigrant visa applicants during their pre-arrival overseas medical examination process. This shorter 3-month regimen could potentially be completed prior to the immigrant's departure to the United States.

The overseas medical examination is an ideal setting and opportunity to implement this strategy as it has already proven to be a high yield intervention for identifying and treating active TB disease in US-bound immigrants.(2) Moreover, the recent and successful implementation of the enhanced TB technical instructions to include cultures and directly observed therapy (DOT) for TB disease at overseas panel sites suggests that adding new TB-related screening and treatment initiatives, such as voluntary LTBI testing and treatment, is conceivable and scalable using this infrastructure.(2)

To determine if voluntary LTBI testing and treatment should be offered to immigrants prior to their US arrival as a component of the US TB elimination strategy, it is important to assess the appropriateness, adoption, and acceptability of this approach. Findings from the study will help inform if the US should expand the overseas medical examination process to include LTBI testing and voluntary treatment to US-bound immigrants as part of its TB elimination strategy.

2.2 Study Setting

Vietnam was selected as the site to implement this project. Vietnam has an estimated 128,000 new TB cases each year with a TB case rate of 137 cases/100,000 population and a reported TB mortality of 19,000 deaths per year.(2) Vietnam was chosen as a site

because it ranked as one of the top five countries of origin for foreign-born persons with TB in the United States. In 2019, 505 (7.9%) of the 6,364 cases of US TB in foreign-born persons were from Vietnam.(3) In 2019, 39,712 Vietnamese immigrants entered the United States.(4) Additionally, based on LTBI prevalence studies in the United States, immigrants from Vietnam had the highest LTBI reactivation rates and were in the top three non-US-born populations that had the highest prevalence of LTBI.(5,6)

Vietnam was also chosen as the site to help inform the future policies of the Vietnam National Tuberculosis Programme (NTP). The Vietnam NTP is committed to strengthen its efforts to control TB in Vietnam by scaling up TB preventive treatment (TPT) in order to meet the World Health Organization's End TB Strategy adopted by the World Health Assembly in 2014.(7) This study is the first time that the 3HP regimen is being used in Vietnam. Lessons from the study will inform the NTP on use of the 3HP regimen as part of its TB control efforts.

The study was implemented at the Cho Ray Hospital Visa Medical Department (CRH VMD) in Ho Chi Minh City (HCMC) which is the main panel physician site that is designated to medically screen US-bound Vietnamese immigrants. CRH VMD screens approximately 1500 US-bound visa applicants per month (CDC personal communication).

2.3 Conceptual Framework

This study's overall aim is to assess if implementing a new innovative strategy of offering LTBI testing and voluntary treatment at overseas panel sites should be considered by the United States to further progress to its TB elimination goal. To assess this strategy in a real-world setting, a prospective cohort study was conducted and was guided by an implementation research approach.

Conceptual frameworks are used to provide a map for contextualizing, operationalizing, or evaluating research. Theories provide insight into the relationship between variables and outcomes; helping to explain behaviors and decision-making (8,9). To help guide the study, I explored a variety of implementation research frameworks and affiliated theoretical models. Below is summary of the research frameworks and theoretical underpinnings (*Peter's Implementation Research Framework, the LTBI Cascade of Care, and the Social Ecological Model)* used to develop the *PTOPs Conceptual Framework,* the guide for this study.

Implementation Research Frameworks

Implementation research, also sometimes interchangeably referred to as implementation science, is still an emerging field with over 73 definitions.(10) Most definitions refer to addressing the gap between research evidence to practice, such as the one from the launch of the *Implementation Science Journal* in 2006: "*the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services and care*." (11)

In addition to the variability in definitions, there are over 60 implementation conceptual frameworks.(12) While many of these frameworks share common constructs, overall there is much heterogeneity in their aims and assumptions, resulting in challenges to forming solid conclusions regarding the relative quality and appropriateness of the competing frameworks and theories. This is further compounded by the inconsistent terminologies for what are the seemingly similar constructs in the different frameworks. The frameworks can also differ in their purposes, either being used to explore the process of implementation; the factors affecting implementation (determinants); or the evaluation of the outcomes of the implementation. The frameworks also vary from having theoretical underpinnings that focus on influences of individual behavior change to more complicated multi-level frameworks that incorporate influences of the social-political environment, but may or may not be based in theory.(12,13)(9) (14) (15)

To date, evidence suggesting that there is a particular framework or unifying theory that can predict implementation outcomes is lacking. However, what is known is that successful implementation of innovations is reliant on multi-factorial variables that can be related to the intervention itself, the socio-political environment, the organizational context, individual perceptions and behaviors (both patient and provider), and the availability of resources, among other factors.(15–18) (16)

Many of the newer implementation research frameworks have been built upon and influenced by earlier well-known theoretical models such as Rogers' classic *Diffusion of Innovations Theory*. While this model attempts to explain how an innovation or idea spreads over time and results in individuals adopting the new idea or behavior, the model is limited in that its main focus is on the individual and intermediaries/channels that influence the uptake of the innovations. The theory does not address other multi-factorial

reasons, such as the feasibility, cost, or resources, that can determine whether or not the intervention will be deemed successful or sustainable.(19)

In an attempt to harmonize the varying frameworks, constructs, and terminology, Damschroder et al., developed the *Consolidated Framework for Implementation Research (CFIR). CFIR* is composed of five major domains, each with additional affiliated constructs (39 in total). The domains include: intervention characteristics, outer setting, inner setting, characteristics of individuals involved, and the process of implementation (14). While *CFIR* is comprehensive and comes with a website with tools (www.cfirguide.org), the large number of constructs make it cumbersome to use. Moreover, its main utility is for developing the intervention and understanding the determinants affecting implementation. The framework is limited in its use for evaluating implementation outcomes and for making conclusions on whether an intervention is successful and if it should be scaled-up and how.(12)(14)(20)

RE-AIM, another implementation research framework, is widely used to evaluate implementation outcomes of evidence-based interventions. The framework consists of five dimensions: reach, efficacy/effectiveness, adoption, implementation consistency (fidelity), and maintenance. A systematic review of the use of *RE-AIM* concluded that while the framework has been widely used to help evaluate interventions and considers issues related to internal and external validity; the criteria for reporting on the dimensions has been inconsistent due to confusion in definitions and as well as confusion in using valid denominators to assess the dimensions of reach and adoption.(21) While *RE-AIM* does focus on evaluating implementation outcomes, it is most useful for understanding the effectiveness of implementing interventions that are already proven to work and are already being disseminated. It is limited in its use for understanding interventions that are currently being tested to determine if they should be further implemented or scaled-up.

Since the purpose of the PTOPS study is to understand the factors that hinder or facilitate the uptake of testing, treatment initiation, and completion, the *RE-AIM* dimensions do not offer the guidance needed. Thus, for my study, I chose and adapted an *implementation research outcome (IR) framework* based on both the work of Proctor et al. (22) and Peters et al. (23)(24). This *IR framework* serves as part of the basis of the World Health Organization's 2013 Implementation Research Toolkit. (25,26) The framework includes multiple components to consider when implementing and evaluating interventions. It

emphasizes the importance of including and understanding stakeholders' roles in the success or failure of an intervention. It is simultaneously simplistic and broad enough to be adapted for use at any stage of implementation research (development, implementation, and evaluation) in complex settings and can be used for mixed methods study approaches.

The *IR Framework* provides a taxonomy for distinct constructs that have had inconsistent definitions throughout the literature. For example, in much of the literature, terms such as appropriateness, acceptability, and feasibility are used interchangeably. To provide distinction for these terms and others, the *IR framework* provides definitions for 8 constructs that are based in theory (appropriateness, acceptability, adoption, feasibility, fidelity, cost, coverage, and sustainability.) These factors combined help assess the effectiveness of the implementation of an intervention. Definitions for the components assessed in PTOPS are listed in the Table below. Assessing these components allows for understanding how to refine and improve implementation efforts as well as evaluating the intervention. Additionally, the *IR framework*, like other implementation frameworks, allows for adaptations and inclusion of the use of other socio-behavioral theories to further understand how and which determinants influence the outcomes of the different *IR* components.(12,13,25)

For the purposes of the DrPH thesis, I will be focusing on the components of *appropriateness, adoption,* and *acceptability.* To further operationalize and assess the components of adoption and acceptability, two additional frameworks, the LTBI cascade of care (26) (Figure 2.1) and the Social Ecological Model (27,28) (Figure 2.2) will be adapted and utilized for this study. Components from these different frameworks are combined together to assess whether this study strategy should be considered for future implementation and scale-up.

Table 2.1 Implementation Research Framework Components Assessed in PTOPS

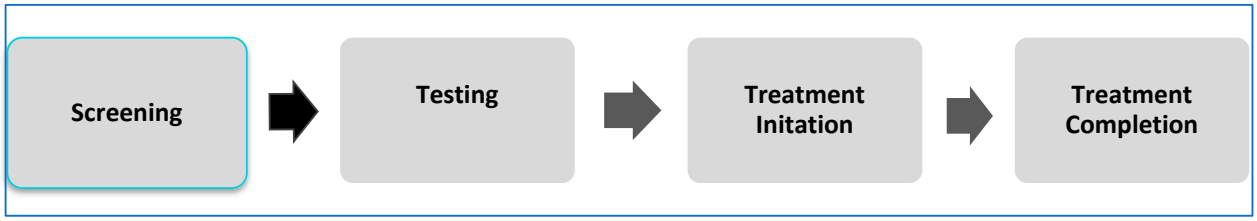
IR Components for Study (22,23)	**Working Definition**
Appropriateness*	Perceived fit or relevance of the intervention in a particular setting
Adoption*	Intention or action to try and employ new intervention (uptake)
Acceptability*	Perceptions among stakeholders that the intervention is agreeable and the factors that are associated with acceptability

Appropriateness is the perceived fit or relevance of the innovation for a given setting to address a particular issue or problem. While *appropriateness* can conceptually be similar to both acceptability and feasibility, the IR framework provides a distinction, because an intervention may be perceived as *appropriate* by some stakeholders or policymakers but may not be *acceptable* by the intervention's intended target group, or operationally it may not work in a certain setting (*feasibility)*. For PTOPS, evidence from the literature is used to determine the *appropriateness* of piloting and implementing LTBI testing and treatment at the overseas medical examination panel site in Vietnam.(9,22,29)

Acceptability is the perception that the intervention or innovation is agreeable to the intended target audience. Understanding why or why not an intervention is acceptable can potentially help implementers refine the intervention if warranted. (9,22,24,29)

Adoption is defined as the "uptake" of the intervention by the intended target audience.(22,29) To further understand which components of the intervention (LTBI testing, treatment initiation, and treatment completion) are being "adopted", the *LTBI Cascade of Care* framework is also used. This is a recently established framework to help understand and identify loss of patients at various points in the LTBI screening to treatment completion continuum. This *LTBI Cascade of Care* framework is modelled after the *HIV Cascade of Care* first established in 2009. Alsdurf et. al, outlines the steps of the *LTBI Cascade of Care* as shown in the Figure 2.1 below (26,30).

Figure 2. 1 LTBI Cascade of Care Steps



Understanding when attrition is occurring can help to identify challenges and potential solutions to improve interventions and increase treatment completion rates. For my study, the *LTBI Cascade of Care* is adapted and represented in the PTOPS Conceptual Framework (*Figure 2.3)* below and additionally in *Figure 4.1: Study Schematic,* depicted in the Methods Chapter, to help guide the study and data collection.

Social Ecological Model

In addition, to understanding where acceptance and losses are occurring during the LTBI Care Cascade, it is also important to understand why acceptance and losses are occurring at each of those steps. To characterize and understand the factors associated with uptake (adoption) LTBI testing, treatment initiation, and treatment completion, *the Social Ecological Model (SEM)* is used to further guide this research and to identify how to target efforts to improve treatment uptake and completion as needed. This model considers the complex interaction between personal and interpersonal factors and structural and environmental forces that can influence behavior and decision-making. Traditionally, the *SEM* identifies five hierarchical levels of influence: individual, interpersonal, community, organizational, and policy/enabling environment (31–33). For this study context, the *SEM* is modified to accommodate 3-levels of influence: *Individual, Intrapersonal, and Structural or Environmental*. This adapted model was developed and based on the narrative review presented in Chapter 3 of the existing literature on factors associated with LTBI testing and treatment; an unpublished 2010 Evaluation of the Tuberculosis Screening and Treatment Program for US-Bound Immigrants and Refugees in Vietnam (for which I was a co-author); and solicited input from experts overseeing the TB immigrant screening program. Additionally, the model was similarly adapted by Munro et al., who conducted a systematic review of qualitative studies to determine and categorize factors associated with TB treatment initiation and completion (34).

The narrative literature review conducted for this study allowed for further operationalization of the model with *a priori* identification of factors at each level that could influence the uptake of testing and treatment for immigrants participating in this study. These factors are presented below in Table 2.2. At the individual level, factors include sex, age, employment or school enrollment, and prior bacille Calmette-Guérin (BCG)vaccination as potential factors. The interpersonal level factors include knowing a family member with TB, being a household contact of someone who had TB, and immigrating with family members. The structural and environmental level factors include departure date for immigration to the United States, travel time to the clinic, and travel mode. These factors were incorporated in a structured data collection tool and were used for analysis.

Figure 2. 2: Adapted Social Ecological Model levels of influence on three outcomes of the LTBI care cascade for PTOPS.

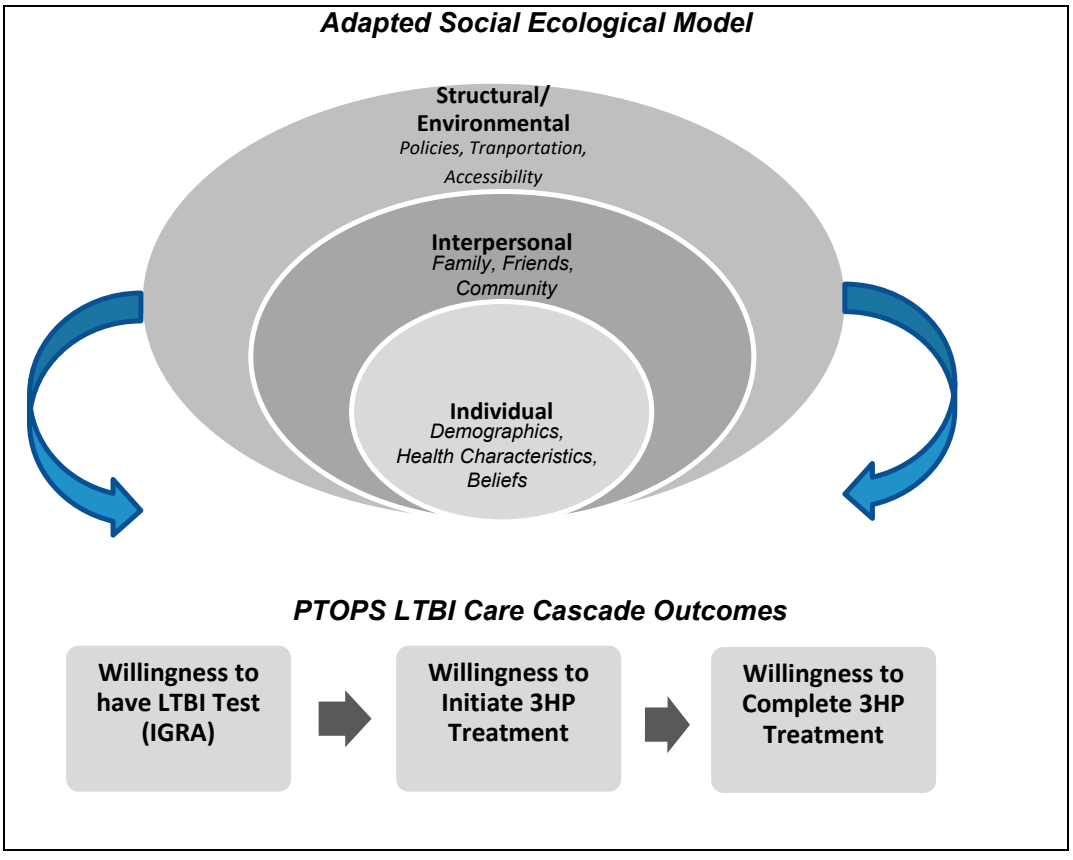
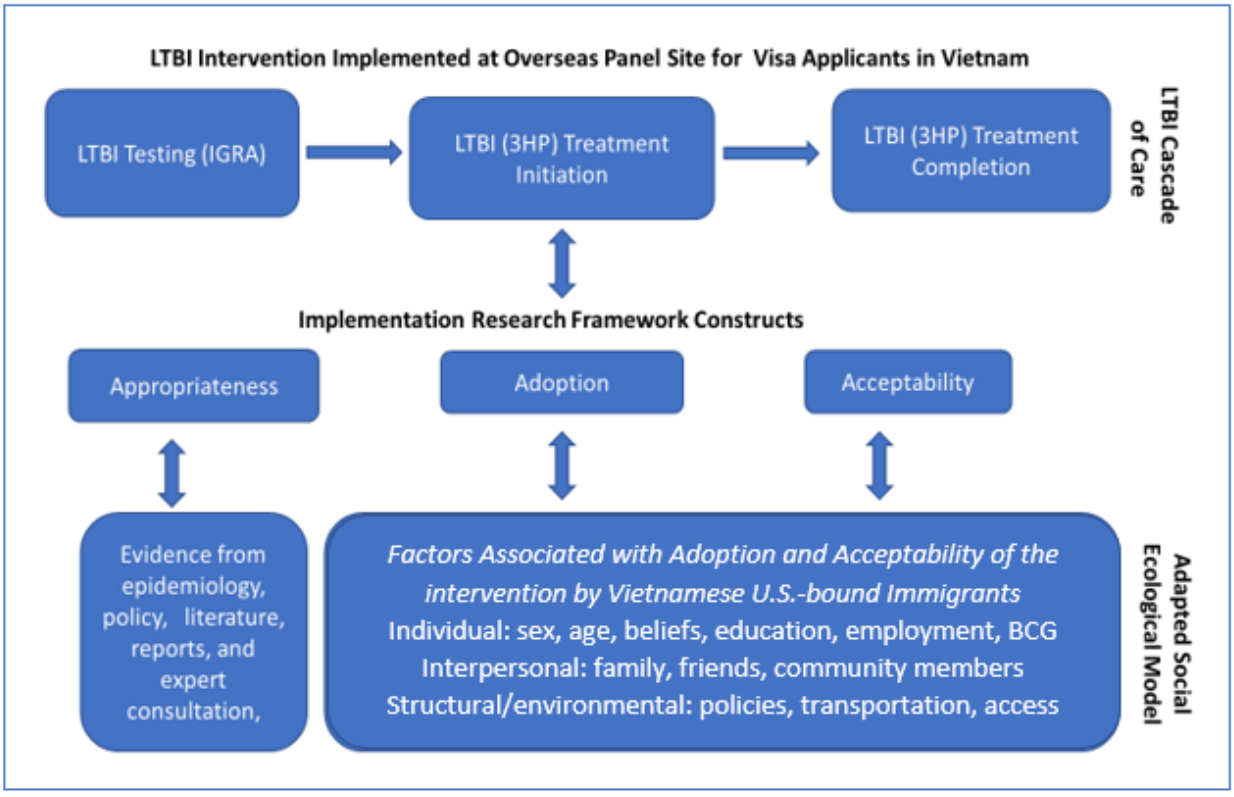


Table 2.2: SEM Levels and Factors Associated with LTBI Testing and Treatment

SEM Level	***Common/known SEM factors that may influence decision making at each level***	***Factors Investigated in this Study for association with LTBI testing and treatment acceptance***
Individual	Knowledge, attitudes, beliefs, psychological, physical, or health characteristics, economic and/or education status.	-Sex -Age -Employment or in school -BCG vaccination
Interpersonal	Formal and informal social relationships such as family, close friends, or community	-Family member with TB -TB contact -Immigrating with family
Structural and Environmental	Government of organizational policies, accessibility to services including transportation, clinic hours, work and school requirements or conflicts.	-Planned immigration date to the US -Travel time to the clinic -Mode of transportation (personal or public)

Figure 2. 3: PTOPS Conceptual Framework
The figure below depicts combination of multiple frameworks to develop the conceptual framework used to guide the study. The intervention implemented at the panel site follows the LTBI Cascade of Care through the offer of a LTBI test and treatment to immigrant visa applicants. Appropriateness of the intervention was established through the literature review, Adoption and acceptance, constructs from the IR framework, are assessed for the different steps of the LTBI care cascade. The Social Ecological Model is used to categorize factors associated with adoption and acceptance of the testing and treatment.



2.4 Research Aim

The aim of this research is to assess if pre-arrival voluntary LTBI testing and 3HP treatment for US-bound immigrants should be considered as a strategy that can contribute towards TB elimination in the United States.

Three components of the IR framework (*Appropriateness, Adoption, and Acceptability*) are assessed to help determine if the pre-arrival voluntary LTBI testing and treatment should be considered as a strategy to contribute towards TB elimination.

Objectives and sub-objectives

1. Describe current US TB epidemiology and strategies to address TB and LTBI among immigrants to identify practice and research gaps. *(Appropriateness- Literature Review)*

a. Explore research on US TB and LTBI epidemiology.
b. Explore research on current migrant TB screening programs and US's pre-arrival and post-arrival screening programs.
c. Explore research on factors associated with LTBI testing and treatment acceptance.

2. Determine the adoption (uptake) and acceptability of LTBI testing and 3HP treatment among Vietnamese US-bound immigrants, if offered during the required pre-arrival overseas medical examination. *(Paper 1)*

a. Estimate the prevalence of LTBI among US-bound Vietnamese immigrants participating in the study.
b. Estimate the proportion of US-bound immigrants at CRH VMD (following the LTBI Care Cascade): who are willing to be tested for LTBI; who initiate 3HP treatment if indicated; and who complete treatment.
c. Compare the proportion of US-bound immigrants initiating and completing LTBI treatment from PTOPS pre-arrival strategy to current US post-arrival follow-up evaluation.
d. Describe the reasons for declining LTBI testing, treatment initiation, or treatment completion among Vietnamese US-bound immigrants

3. Determine individual, interpersonal, and structural and environmental factors significantly associated with US-bound Vietnamese immigrants' acceptance of (1) the LTBI test, (2) LTBI treatment initiation, and (3) LTBI treatment completion. *(Paper 2)*

a. Describe the demographic characteristics of US-bound Vietnamese immigrants accepting an IGRA test and initiating and completing 3HP treatment.
b. Determine individual, interpersonal, and structural and environmental factors significantly associated with US-bound Vietnamese immigrants' willingness to (1) be tested for LTBI, (2) initiate LTBI treatment, and (3) complete LTBI treatment.
c. Demonstrate the utility of an adapted version of the *Socio-Ecological Model* to identify and categorize predictors of LTBI testing and treatment acceptance.

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3. Chapter 3: Background and Literature Review

3.1 Overview of the Background and Narrative Review of the Literature

For this thesis, I conducted a narrative style literature review. This type of review focuses on critically appraising and synthesizing what has been published previously on the topic to allow for the identification of research gaps and to build the rationale for the study. Unlike a systematic review, a narrative review allows for a wider literature search scope and the ability to address more than one question to gain an understanding of the background, context, and further research needs for the topic area.(1,2)

The aim of this thesis is to determine if the pre-arrival, overseas medical examination process for US-bound visa applicants seeking permanent relocation can be used to offer voluntary LTBI testing and treatment to help the United States further progress towards its TB elimination goal. As this strategy has never been implemented before, the narrative review allowed for an identification of factors to consider in the design and evaluation of the intervention. Additionally, because of the global interest in addressing LTBI, many systematic reviews and meta-analyses on migrant TB screening programs as well as LTBI testing and treatment recently have been conducted. To avoid duplication of efforts, the narrative approach allows for the incorporation of findings from these reviews.

In the review, I start out by summarizing the epidemiology of TB and LTBI to establish the background and context for the project; I then synthesize the literature on practices and effectiveness of migrant screening programs to address TB and LTBI in low TB incidence countries, with a particular focus on the United States pre-and post-arrival screening programs; and finally describes the challenges and factors associated with the uptake and completion of LTBI testing and treatment. The review addresses the following questions to help guide the study:

- What is the epidemiology of TB globally and in the United States?
- What are the screening practices and gaps to address TB and LTBI in immigrants in low TB incidence countries, particularly the United States?
- What factors are associated with LTBI testing, treatment initiation, and treatment completion in immigrants?

To search for the literature, I used the CDC Online Stephen B. Thacker Library, the LSHTM Online Discover System, and Google Scholar. The following databases were searched: MEDLINE, PubMED, EMBASE, and CINAHL.

Search terms and criteria for the three different questions comprising the narrative review are listed in each section below.

3.2 Background: Global and US TB and LTBI Epidemiology

To broadly understand global TB epidemiology and, more specifically, US TB epidemiology, the most recent annual World Health Organization (WHO) Global TB Report, the annual Centers for Disease Control and Prevention's (CDC) surveillance publication on the number of US reported and verified cases of tuberculosis (TB) derived from the National TB Surveillance System (NTSS), along with US-based prevalence surveys and cross-sectional epidemiologic studies describing characteristics of the current US TB and LTBI burden were reviewed. Additionally, modeling studies looking at the potential trajectory of the US TB epidemic based on various strategies to progress towards TB elimination were reviewed.

Search terms for this background and narrative review included (tuberculosis OR TB OR latent tuberculosis infection OR LTBI) AND (United States) AND (prevalence OR epidemiology OR burden OR elimination) AND (immigrants OR migrants OR new arrivals OR foreign-born OR non-US-born). I additionally identified articles through a manual review of references in publications and in CDC guidelines and reports, and through expert consultations. Global and US surveillance reports and CDC guidelines describing TB epidemiology were limited to the most currently available, those published in 2020. US specific prevalence studies describing the TB and LTBI burden and modeling studies describing TB elimination strategies were limited to the past decade, 2010-2020, to reflect the current situation most accurately. Studies focusing on the epidemiology of specific states and localities in the United States were not included due to the substantial heterogeneity in local TB epidemiology across the country.

Global TB Epidemiology

Tuberculosis (TB) is an airborne disease that is spread from person to person. Worldwide, TB is in the top ten of all leading causes of death and is the actual leading cause of death by a single infectious disease agent, surpassing deaths by HIV/AIDS. In 2019, a staggering estimated 10 million people became ill with TB and 1.3 million died from the disease. Eighty-seven percent of all new TB cases were reported from the 30 highest TB burden countries.(3)

Approximately 1.7 billon people (close to one-quarter of the world's population) are latently infected with *Mycobacterium tuberculosis (M. tuberculosis),* the bacterium that causes the disease.(4)These people with latent tuberculosis infection (LTBI) serve as a reservoir for future cases of TB. To tackle the global problem of TB, the World Health Organisation (WHO) adopted the World Health Assembly's 2014 End TB Strategy with the ambitious aim to reduce global TB incidence by 90% and TB deaths by 95% by 2035. To achieve these targets, the strategy promotes scaling up of efforts to find and treat people with TB and, for the first time, includes the promotion of systematic screening and treatment of groups with LTBI who are at high risk of developing TB disease.(5)

The TB Infection Spectrum

TB infection is caused by exposure to and inhalation of *M. tuberculosis.* Once infected, persons have traditionally been classified as having either of two conditions: LTBI or active TB disease. People with active TB generally exhibit signs and symptoms of the disease and can transmit the bacterium to others. Active TB disease can be diagnosed clinically or with bacteriological confirmation. In this binary framework, people classified as having LTBI are diagnosed using a tuberculin skin test (TST) or an interferon-γ release assay (IGRA). People with LTBI are asymptomatic and cannot transmit the disease but are at risk for progressing to active TB disease. An estimated 5-10% of these persons with LTBI and no other risk factors will go on to develop TB disease and potentially transmit the disease if not appropriately treated.(6) The risk of developing disease increases for those with immune-compromising conditions. For example, persons living with HIV are 15-22 times more likely to develop active TB disease compared to those without HIV.(7) The risk for developing disease is 2-3.6 times higher for those with diabetes compared to those with no known risk factors.(8) However, the chances for individuals with LTBI to progress to TB disease can be significantly decreased by taking and completing LTBI treatment.(8,9)

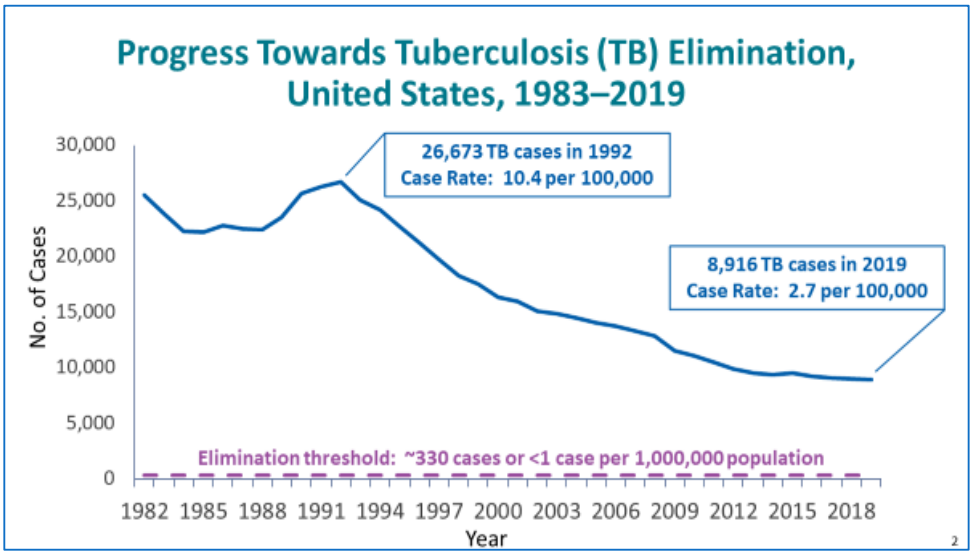
Current thinking is evolving from classifying *M. tuberculosis* infection as a binary state to viewing it as a spectrum of dynamic disease states where the bacilli can be eliminated, persist, or reactivate and lead to active TB disease. Various nomenclature and frameworks have been proposed for understanding the differing states of the infection spectrum, however all suggest that those who were traditionally classified as having LTBI can also include those who have completely cleared the infection to those who have actively replicating bacteria without clinical symptoms (subclinical TB).(10–12) Understanding the

different states in the infection spectrum can help determine who is most at risk for progressing to active TB disease and will benefit most from preventive treatment. However, challenges still remain; currently available diagnostic tools for detecting infection are not yet sophisticated enough to allow for assessment of where someone with infection is on the spectrum. Both the TST and the IGRAs function indirectly by detecting an immune response. Neither can confirm the presence of viable bacilli. A person who has cleared their infection, either innately or through treatment, can still have a positive result on either test. Compared to the TST, the IGRAs' predictive power are generally better, and they are less prone to false positives as they do not cross-react with the BCG vaccination or other mycobacteria. However, neither test can accurately identify persons at risk for progression to disease. Solely relying on test positivity can be problematic as the majority of people with a positive TST or IGRA may not progress to active TB disease and thus may not need preventive treatment.(13) For this reason it is still important to employ targeted testing strategies, which use epidemiology to identify those who are at high risk for infection or progression to TB disease, to focus LTBI testing and treatment efforts. As continued global efforts to address LTBI are being scaled-up, more research is needed to better understand biomarkers and the different states in the spectrum and improved diagnostic tools are needed to allow for identification of individuals for whom preventive treatment will be most beneficial.

United States TB Epidemiology

Compared to the global burden, the TB disease situation for the United States is markedly different but still comes with its challenges. The United States is considered a low TB incidence country, with low incidence being defined as <10 cases per 100,000 in the general population.(14,15) In 1989, the US Advisory Council for the Elimination of TB (ACET) set a goal of TB elimination for the United States by 2010, with elimination being defined as less than 1 case per million (approximately a total report of 330 cases).(16) Although the country has continued to see an annual decline in TB incidence for the past 25 years, with an all-time reported low of approximately 9,000 cases in 2019, the goal of elimination is still far from reality. The current case rate remains at 27 cases per 1 million (2.7 cases per 100,000) and the rate of annual decline in incidence has been slowing, making it difficult to achieve the TB elimination goal (*Figure 3.1*).(15)

Figure 3. 4: United States Progess Towards TB Elimination Goal, 1993–2019
In 2019, 8.916 cases of TB were reported in the US for a case rate of 2.7 per 100,000. While the incidence of TB is declining, the rate of decline is slowing, making it difficult to achieve TB elimination (<1 case per 100,000).

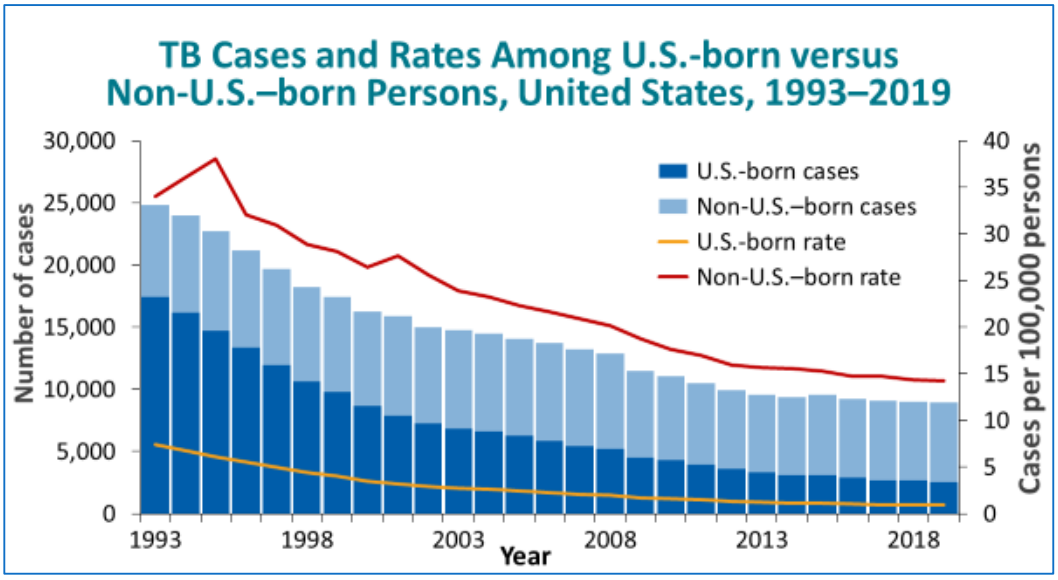


Source: CDC, Reported Cases of TB, 2019 www.cdc.gov/tb/statistics/surv/surv2019/default.htm#

Traditionally, US TB control strategies have focused on the early detection of active TB disease, prompt treatment initiation, and treatment completion.(16,17) While these strategies have helped the United States achieve the observed decline in incidence, the main challenge for meeting the elimination goal is that the percentage of TB cases occurring among non-US-born persons in the United States continues to remain high (18). In 2019, 71.4 percent of TB cases in the United States occurred among non-US-born persons. The rate of TB among non-US-born persons (14.2 per 100,000) was 16 times higher than that of US-born persons (.9 per 100,000) (Figure 3.2).(15)

In the United States, in addition to being foreign-born, the following comorbidities and risk factors are associated with developing TB among people with LTBI: diabetes mellitus (20.7%), HIV (4.7%, among those with known status), and other immunocompromising conditions (8.2%); close-contact of some with TB (8.2%), homelessness (4.6%), residence in correctional facility (14.0%); excessive alcohol use (8.1%); non-injection drug use (7.5%); or injection drug use (1.2%).(15)

Figure 3. 5: **TB Cases Among US-Born versus Non-US-Born Persons, United States, 1993–2018**
In 2019, 8,916 cases of TB were reported in the US; 70.2% occurred among non-US-born persons.

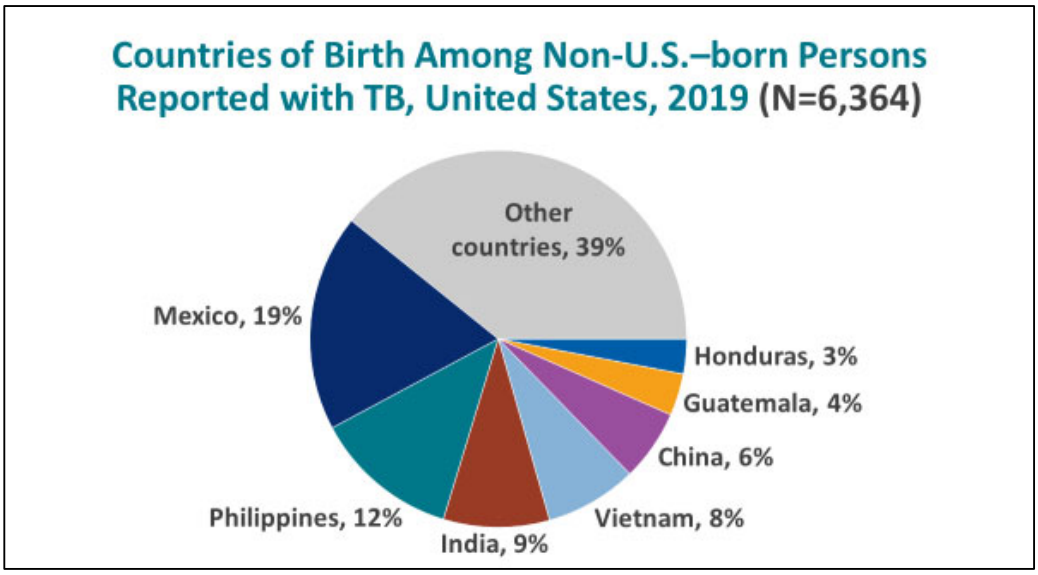


Source: CDC, Reported Cases of TB, 2019 www.cdc.gov/tb/statistics/surv/surv2019/default.htm#

Over 50% of non-US-born persons with TB come from five countries: Mexico (19%), Philippines (12%), India (9%), Vietnam (8%), and China (6%) (Figure 3.3). These numbers reflect US immigration patterns as well as the immigrants' risk of TB exposure in their country of origin.(19) Four of five of these countries (Philippines, India, Vietnam, and China) are considered high-burden TB countries by the WHO.(14) Although immigrants from these countries are at higher risk for TB compared to US-born persons, as suggested by two recent studies it is also important to note that the WHO TB incidence rates for a country are not necessarily representative of the individual risk of TB for non-US-born persons hailing from those countries. Tsang et al. examined TB rates among non-US- born persons compared to their country of origin from 2012-2016 and showed that WHO rates were 5.4 times higher for the country of origin than the US rates for immigrants from those countries. (20) Similarly, a study by Menzies et al., looking at the 30 countries affiliated with the highest number of cases in the United States, found that TB incidence was 6.8 times higher in countries of birth compared to the US TB incidence of persons who immigrated from those countries.(21) These discrepancies demonstrated by both studies, suggest that persons who immigrate to the United States may not reflect the population from their country of birth who do not immigrate to the United States and thus may not be representative of the overall birth country population in terms of TB risk.

Nevertheless, immigrants hailing from high burden countries are at an elevated risk for TB compared to the US-born population.

Figure 3.6: Countries of Birth Among Non-US-born Persons Reported with TB, 2019
In 2019, the top five countries of birth among non-US-born persons reported with TB included Mexico, Philippines, India, Vietnam, and China



Source: CDC, Reported Cases of TB, 2019 www.cdc.gov/tb/statistics/surv/surv2019/default.htm#

Molecular epidemiology studies using genotyping suggests that TB disease among non-US-born persons is generally due to the reactivation of LTBI that was acquired prior to arrival in the United States (22–24). A more recent study further supports these findings by suggesting that over 80% of TB disease cases in the United States resulted from reactivated LTBI, not recent transmission.(25) Both of these findings are consistent with other studies that suggests that 70% of TB cases in non-US born persons occur at least 2 years after entry to the United States and that non-U.S-born persons have an elevated risk for developing TB even 10 years after entry to the United States due to infection acquired prior to arrival. (24,26,27).

Prevalence of LTBI in the United States

While the United States does track country of origin for TB cases, detailed estimates for LTBI prevalence among non-US-born populations are still lacking. TB disease is required to be nationally notified, however LTBI currently is not.(15,18) The primary source for estimating US LTBI prevalence is from the National Health and Nutrition Survey (NHANES), a series of cross-sectional population-based surveys which were most

recently completed in 2011-2012. Based on NHANES, Miramontes et al. estimated that in the United States 4.7% (95%CI 3.4-6.3%) of the population, amounting to 13.2 million people (95%CI 9.6-17.8 million), have LTBI. Non-US-born persons, compared to U.S-born persons in the study, had a higher positivity rate for LTBI based on both the tuberculin skin test (20.5% vs 1.5%) and an IGRA, the QuantiFERON Gold-in-Tube, (15.9% vs 2.8%).(28)

Another analysis conducted by Mancuso et al. using the NHANES data found similar but slightly lower estimates of LTBI prevalence in the United States of 4.4% (95%CI 3.1-6.1%) based on TST and 4.8% (95%CI [4.0-5.8%]) using the IGRA. The slight differences in the study results were most likely related to the differing analysis methods and TST cut-off points used to determine positive results. Mancuso et al.'s analysis found LTBI prevalence to be highest among Asians based on ethnicity.(29)

While these studies help describe the burden of LTBI in the United States, there are limitations for using the NHANES survey data. First, neither TST nor IGRA serve as a gold standard reference for LTBI diagnosis.(30) The estimates may be elevated as they do not take into account that some participants in the survey may have previously taken TB or LTBI treatment, and thus still had a positive TST or IGRA result.(31) The numbers based on the TST may also be elevated for non-US-born persons who likely had the bacille Calmette-Guérin (BCG) vaccination which can result in false-positive TST results. Moreover, there may actually be an underestimation for the US-born population as NHANES does not include representation from groups at higher risk for infection including those living in congregate settings such as correctional facilities or long-term care, nor does it include persons experiencing homelessness.

Second, the NHANES survey does not disclose information on LTBI prevalence estimates by country of birth. To address this gap, two analyses were recently published. Woodruff et al., using IGRA results from NHANES and publicly available data by race/ethnicity, calculated that LTBI prevalence was highest for persons from India at (31.7% 95% CI 21.2-44.5%) and the reactivation rate, defined as the number of TB cases not associated with recent transmission per 100 person years of life, was highest for persons born in Vietnam (0.2, 95%CI 0.1-0.3).(32) Collins et al.'s prospective study, using Bayesian latent class analysis, estimated LTBI prevalence among non-US-born populations and found that overall LTBI prevalence was 31% for the non-US-born populations, but it varied based on country of origin. The top three countries of birth with the highest

prevalence of LTBI in non-US-born persons included Haiti (54.8%, 95%CI 47.7-61.8); Vietnam (53.0%, 95%CI 46.7-59.4%), and Somalia (51.0%, 95%CI 46.4-55.1).(33) However, the estimates from the study may be artificially high as the investigators specifically sought to enroll persons likely to have LTBI as part of a larger TB infection study. Nevertheless, the study does provide a picture of which non-US-born populations should be prioritized for additional LTBI screening and treatment.

United States TB Elimination Modeling Studies

To progress towards TB elimination in the United States, two national modeling studies resulted in similar conclusions that efforts need to be strengthened for diagnosing and treating LTBI among non-US-born persons. Hill et al.'s 2012 mathematical transmission modeling study, based on 2000-2008 US TB data, suggested that TB elimination would not be achieved before the end of this century without any additional advances in TB control. The model further suggests that it can possibly be achieved for the US-born population by 2063 with the current level of TB control efforts; however, for the foreign-born population, the TB case rate would plateau at about 50 per 1 million because of the continued importation of LTBI among immigrants. Their study suggests that domestic efforts to address LTBI cannot solely be relied on and efforts need to be increased on a global-level to help reduce the importation of LTBI.(34)

A more recent deterministic modeling study by Menzies et al. was more pessimistic than Hill et al. It predicted, with the current level of TB control efforts, elimination of LTBI for the US-born population would not be achieved until 2100. The study compared five scenarios to determine the impact of the different TB interventions on US TB incidence between 2017-2100. The scenarios included 1) maintain current level of TB control activities, 2) provide LTBI testing and treatment for new documented immigrants, 3) increase uptake of LTBI screening and treatment among high-risk populations, 4) improve TB case detection, and 5) improve TB treatment quality. The results suggest immigration serves as the major driver for LTBI prevalence and that intensifying TB prevention and treatment among non-US-born persons before, during, and after immigration could reduce incidence and help further the goal towards TB elimination. (35) However, because it is difficult to anticipate future epidemiological trends, the study was not able to confidently conclude the time to elimination. In all of the scenarios, the US did not reach TB elimination before the end of this century.

While both of these models provide useful information on the need to scale-up efforts to progress towards TB elimination, the models are limited by the quality of the data that is used to build them. Empirical data for the number of people with LTBI is not directly available. These models are also limited in that they cannot anticipate the effects of changes in immigration policy or innovations in LTBI diagnosis or treatment on U.S TB epidemiology. For example, since Hill et al. published their model, the IGRAs diagnostic capabilities have improved and have been recommended over the use of TST in non-US-born populations. Additionally, shorter LTBI treatment regimens, such as 3HP and 4R (four months of rifampicin) have been included in CDC LTBI treatment guidelines, potentially resulting in higher uptake and completion of LTBI treatment which could help accelerate the progression towards elimination. The Trump administration had also taken a harsh stance on immigrants and refugees which has impacted immigration numbers and patterns, potentially influencing the TB burden for the United States in the coming years. These models also assume sustained political and funding commitment to combat TB, which may change as public health priorities may shift. Nevertheless, both modeling studies suggest that the key to reducing TB incidence in the United State is enhanced and innovative approaches to address LTBI in non-US-born persons and increased efforts to prevent TB globally to help further reduce importation of TB into the United States. The studies specifically conclude with the suggestion of strengthening post-arrival screening and follow-up of immigrants as well as exploring the offering of pre-arrival LTBI testing and treatment for immigrants.(34,36) Additional modeling studies that were conducted for specific state TB control efforts have had similar conclusions.(37–39)

3.3 TB and LTBI Migrant Screening Approaches

As demonstrated by the surveillance data and the modeling studies, addressing TB, and particularly LTBI, in non-US-born persons has the greatest potential to move the United States further towards TB elimination. One strategy that has historically been used as a TB control measure by the United States and many other countries is migrant screening. These programs have existed for over a century as a means for a host country to protect their population from the importation of communicable diseases.(40) Several high-income, low TB incidence countries have migrant medical screening programs that focus on identifying active TB disease and a few have an additional component of LTBI testing.(41–44) These strategies were, and are still, often implemented with the aim to reduce transmission of TB to the general public of the host country; although risk of TB transmission to host populations from migrants has been determined to generally be moderate to low.(21,45) Migrant screening programs offer a unique opportunity for the detection and treatment TB for those in need who might otherwise be missed and are considered a high-risk group for TB in low incidence countries. These screenings are in line with the 2013 WHO conditional recommendation for TB screening of people migrating from high to low incidence countries.(46)

To first broadly understand the differences and utility of the varied migrant screening programs for addressing TB and LTBI, the literature assessing the practices of different low-incidence countries was reviewed. This was done with the intent of understanding how different country models and practices may inform how to enhance the current US system to address LTBI in non-US-born persons. Systematic and comparative reviews and meta-analyses were reviewed to get the broad understanding of different formal systematic migrant screening programs. The reviews and meta-analyses were limited to those that described the various practices and the outcomes of the screening programs focused on documented migrants (mainly immigrant visa applicants, refugees, and asylum seekers). Systematic reviews focused on cost-effectiveness or country-specific studies (other than the United States) or programmatic community-based approaches to address TB in migrants were not included for this assessment. The literature search was limited to articles published between the years 2000- 2020 and in the English language.

Second, a more in-depth review of US-specific immigrant pre-arrival and post-arrival TB and LTBI screening practices was conducted to understand effectiveness and gaps and

how the system could be optimized to improve LTBI testing and treatment uptake by immigrants. A more inclusive approach to the literature was taken for this in-depth look. US policy reports, guidelines, prospective and retrospective cross-sectional or cohort observational studies and evaluations were reviewed for inclusion. Literature on community based LTBI screening programs (not part of the formal immigrant visa application process), cost-effectiveness studies, and other studies looking at the use and accuracy of diagnostic tools (i.e., TST v IGRA) and LTBI treatment regimens were excluded from this review. For this section of the review, articles on the US overseas medical examination and post-arrival evaluation activities were limited to those published between the years 2007-2020. This timeframe more accurately reflects the current US practices since the addition of mycobacterial culture-based TB diagnosis for the overseas medical examination (47) and the establishment of the electronic disease notification (EDN) system to track immigrants in need of a post-arrival follow-up evaluation.(48)

Search terms for this narrative review included (tuberculosis OR TB OR latent tuberculosis infection OR LTBI) AND (migrants OR immigrants OR refugees OR new arrivals OR foreign-born) AND (screening OR overseas medical examination OR panel physicians) AND (United States OR low TB incidence countries). Additional articles were identified through a manual review of references in publications and expert consultation.

Review of Migrant Screening Policies and Practices of Low-Incidence Countries

Migrant screening programs for TB are conducted either pre-arrival (mostly in country of origin [also referred to as the *overseas medical examination in the United States*]), upon-entry (airports or other ports of arrival), or post-arrival (in host country; often used as follow-up to findings during pre-arrival screenings).(49) Programs generally use a chest x-ray as part of the screening for TB, and countries such as the United States, Canada, Australia, New Zealand, and the United Kingdom additionally perform sputum and culture for chest x-rays that are abnormal.(42,50) Over the years various reviews and assessments have been conducted to understand the differences and utility of migrant screening programs. These studies have all pointed to the heterogeneity of the programs of the different countries in terms of policies, practices, screening algorithms, tests, settings, target populations, and whether or not they test or provide treatment for LTBI. (41,44,49,51,52)

In 2004, Coker et al. reported on a survey of 26 of 51 eligible European countries' national policies for migrant screening. Thirteen of the 26 countries reported TB screening activities mainly for refugees and asylum seekers and the other 13 reported having no screening activities. At this time none on of the countries surveyed reported conducting pre-arrival screening. Eight countries reported offering some groups LTBI treatment if indicated, but it was unclear which specific migrant group (e.g., immigrant, refugee, or asylum seeker) if any, were targeted for testing and treatment for LTBI. Screening approaches for all countries varied and most were not based in national regulations or guidelines, potentially suggesting that evidence and tools used to support the screening were lacking. This study was limited to the review of national policies of the countries that chose to participate, and did not assess the implementation or the effectiveness of the screening practices.(51) As a follow-up to this study, in 2006 Coker et al. reviewed service delivery of select migrant screening units of a few European countries (Norway, Switzerland, UK and the Netherlands) and again found wide variations in screening practices and limited collection of output data which made it difficult to draw comparisons across countries. While the findings were not generalizable and subject to bias with the pre-selection of sites, the diversity in screening practices indicated a lack of coherence in service delivery and the lack of common data elements made it challenging to determine effectiveness of approaches.(53)

Since the publication of both reviews, guidance and screening practices have evolved for most countries; however, variability in approaches across countries still exist. In 2008 Alvarez et al., noted high variability in screening criteria across countries. In their comparative examination of 16 of 18 eligible low TB incidence countries with high immigration rates, 13 of the 16 countries reported having TB screening programs with the primary objective to detect active TB. However, each country used differing criteria to measure migrant category, TB incidence of country of origin, and length of stay to determine which migrant populations to screen. Moreover, there was also variability of when screening was conducted. Eight countries reported using pre-arrival screening; three countries used on-entry screening; two countries reported exclusively using post-arrival screening while six additional countries used post-arrival screening as a follow-up on findings detected during a previous screening. The countries that screened pre-arrival required the immigrant applying for a visa to pay for the medical examination, but also reported challenges with quality assurance for the medical examination (e.g., radiographic

reading expertise and laboratory capacity). In terms of LTBI testing, Alvarez and colleagues did report that Israel and Sweden provided routine testing for LTBI by TST, while the United States, Australia, and Norway reported using an infection test (IGRA or TST) only for migrant children and as part of the TB disease screening algorithm. Countries not conducting LTBI testing reported not using the TST because of false positives affiliated with BCG vaccination, low risk of reactivation to TB, and poor treatment completion rates to LTBI treatment. While the study did report on the offering of LTBI testing, information on LTBI treatment initiation or completion for those found to be LTBI positive was lacking.(49)

Building upon these previous reviews, Pareek et al. in 2010 surveyed 29 industrialized countries on their migrant screening programs. Twenty-five (86.2%) of the 29 countries screened migrants for TB disease. The authors noted, as with the other reviews, heterogeneity still existed in terms of populations targeted for TB screening, where and when exams took place, and the methods used for screenings. There was wide variation in the use of a TB incidence threshold from the country of origin (>20/100,000 to >500/100,000) to determine which migrant populations to target for screening. Among the countries conducting screening, only about half (55.2%) of the countries reported testing for LTBI, and efforts were mostly focused on refugee and asylum seekers. As with the other descriptive studies reviewing the policies of multiple countries, limitations include the responder bias to the surveys as well difficulties in making comparisons of approaches given the lack of evidence generated.(41)

The two most recent reviews of country screening policies suggest that heterogeneity in screening approaches and policies still exist. Garner-Purkis et al. survey in 2018 reviewed policy documents of high-income, high net-migration countries with an estimated TB incidence of <30 per 100,000. Fifteen countries and additional Gulf Cooperation Council (GCC) countries were included in the study. Compared to previous studies, there was an increase in countries requiring pre-arrival screening (14 of the 15); however, screening criteria, algorithms, and tests still varied across countries. (54) The authors made no mention if LTBI testing or treatment was part of the country policies they reviewed. Kunst et al.'s review of TB and LTBI screening policies in Europe Union (EU) and European Free Trade Association (EFTA) countries reported that 7 of 11 countries surveyed screened migrants for LTBI, although the screening varied by migrant category, age for screening, and TB incidence threshold used to determine target population. Their review

found that limited information about LTBI yield and screening coverage was available in published studies. Additionally, despite previous recommendations to harmonize approaches and systematically collect data across European countries, policies, methods for screening, and data collection for TB and LTBI still differed, making it challenging to compare study outcomes.(52)

Effectiveness of screening approaches is generally measured by coverage (number of persons who completed screening out of the number of persons eligible for screening) and yield (the number of TB or LTBI cases identified out of the number of migrants screened for TB or LTBI). Several reviews and meta-analyses have been conducted to determine the yield of screening approaches for TB and LTBI among migrants, however, most of these have concluded that meaningful comparisons across programs and studies is challenging due to the diversity in screening approaches, varied definitions used for yield, and differing collection of data.

Arshad and colleagues conducted a systematic review and meta-analysis of upon-entry migrant screening based on 22 studies. They found the yield for TB screening was 4 times higher among refugees compared to immigrants and 3 times higher among African and 5 times higher among Asian migrants compared to European migrants. The authors were not able to draw conclusions about LTBI screening as there was insufficient data in the articles they reviewed.(55)

Klinkenberg and colleagues' study examined the coverage and yield for screening of active TB conducted at different time and whether it was voluntary or mandatory. They found that the median coverage for mandatory screening (90.6%) was higher than compared to voluntary screening (48.5%) for EU countries but reached 100% for non-EU countries conducting mandatory pre-arrival screenings. They additionally found that there was no significant difference in indicators of effectiveness for screening at entry (holding center) or post-arrival screening (community-based). However, for countries conducting pre-arrival screening during the timeframe of their study (Australia and the United States) the yield (1.21%) was higher compared to countries only using post-arrival screening (.31%).(56) However, this comparison should be viewed with caution as pre-arrival results were abstracted from US studies only and those that were specifically looking at Asian immigrant populations who tend to have higher rates of TB compared to immigrants from many other non-Asian countries.(3)

In another meta-analysis of pre-arrival screening of 15 observational studies, Aldridge et al. found pre-arrival screening contributed to high yield of TB detection (339 per 100 000 persons, 95%CI 283–393), among migrants from countries with higher incidence of TB. Their results suggest that targeting immigrants from high-prevalence countries could be the most effective approach towards improving disease detection (57). However, the quality of the underlying studies contributing to the review were low and the screening methods and migrant groups (immigrant, asylum seeker, undocumented migrant, refugee) targeted varied greatly in the studies thus bringing into question some of the conclusions drawn in the review.

Chan et al.'s systematic review and evaluation of post-arrival follow-up of migrants identified to be at high-risk for TB during the pre-arrival screening found that the pooled cumulative incidence of TB from 22 cohorts was 2794 per 100,000 persons (95%CI 2179-3409), suggesting that post-arrival follow-up screening can be effective. However, from the studies included in the meta-analyses it is unclear how the pre-arrival screenings where conducted and what tests were used to detect TB. Potentially, if the pre-arrivals screenings were strengthened, the yield from the post-arrival follow-up would decrease.(58)

Zenner et al conducted a narrative review of the literature on the effectiveness and cost-effectiveness of screening migrants for active tuberculosis and latent tuberculosis to help identify research gaps They found that effectiveness and cost-effectiveness of TB screening depends on the setting, migrant group, and screening algorithm. As previously indicated, several countries are conducting pre-arrival screening, and there is some evidence to indicate that these can have an impact on the epidemiology of the host-country. Additionally, empirical evidence on the effectiveness of LTBI screening in migrants is limited, but models suggest that screening targeted to migrants from high-burden countries can potentially be effective at identifying more cases of TB. As experienced by the other reviews the underlying studies contributing to the review were of varying quality and were heterogeneous in terms of migrant group, screening methodologies, and settings making it challenging to draw meaningful conclusions.(44)

The reviews over the years on migrant screening programs of low TB incidence countries have had similar conclusions that, in general, the criteria for screening vary across countries and may not necessarily be evidence-based. Screening policies do evolve but are often based on observational study data as randomized controlled trials are generally not feasible. The practices often reflect the context and migration patterns of the country conducting the screening. Mandatory pre-arrival screenings are more likely to have higher coverage but yield and effectiveness can depend on many factors (diagnostic tools, screening algorithms, and population targeted for screening).(57,59) Drawing meaningful conclusion on which screening approaches for TB and LTBI are most effective remains challenging due to the lack of systematic and standardized data collection. Moreover, the heterogeneity and quality of studies included in all of the reviews suggest that caution should be taken with conclusions that were drawn. Additionally, the reviews were all high-level and did not assess how and if the policies were practiced as intended, which invariably would have implications for the effectiveness of the approaches.

As indicated by both Pareek et al. and Zenner et al., migrant screening programs have mainly focused on active TB disease screening, although the epidemiological data suggests that reactivation of LTBI is the main contributor to TB cases in low incidence countries.(44,50) All of the above reviews had very limited information on LTBI testing and treatment during the screening process, pointing to the fact that neither are currently widely offered through these platforms for most countries. Among the countries reporting LTBI testing, most targeted efforts to refugees, asylum seekers, individuals from high TB burden countries, or children as part of the TB disease screening. Among the few countries that offered LTBI testing, not much was reported about LTBI treatment initiation and completion.

For LTBI screening to be effective it is essential to have high rates of both screening uptake and treatment completion. However, both uptake of screening and treatment are dependent upon multiple factors such as the type of test used, treatment offered, and additional behavioral, structural, and supportive measures to help with treatment adherence. Many programs struggle with the poor predictive value of both the TST and IGRA for TB disease as well as low rates of LTBI treatment initiation and completion. Moreover, empirical evidence on the impact of LTBI screening and treatment on TB incidence has been lacking. To date, there have been limited studies following migrants

through the entire LTBI care cascade as part of a formal migrant screening program.(44,45,50,60)

United States Pre-Arrival Overseas TB Medical Examination for Immigrants and Refugees

While the yield of migrant screening programs across many low incidence countries has had mixed results, there has been some success with reducing the importation of TB to the United States through its migrant screening program. Similar to Australia, Canada, New Zealand, and the United Kingdom, the United States conducts *pre-arrival* medical examinations for visa applicants seeking permanent residency (immigrants and refugees) at what are called overseas panel physician sites.(43) The medical examination is not required for those applying for tourist, student, worker, or temporary visas.(61)

Annually about 500,000 immigrant and refugee visa applicants are required to undergo the pre-arrival medical examination in their country of origin, prior to traveling to the United States.(19) The overseas medical examinations are conducted by panel physicians who are appointed by the US Department of State. There are 351 US Panel Sites in 160 countries and about 600-700 trained panel physicians worldwide (CDC communication).

The CDC TB Technical Instructions (61) provide guidance on conducting the overseas TB medical examination for US-bound immigrants and refugees. For those ≥15 years of age the examination includes a chest x-ray, and if abnormal or any other signs and symptoms of TB, sputum smear microscopy with culture confirmation is required. For those 2-14 years of age from a country with a TB incidence of ≥20 cases/100,000 per year, an IGRA (previously a TST or IGRA) is required and if positive is followed by a chest x-ray and the other tests as indicated. Completion of TB treatment by direct observation is required for those diagnosed with pulmonary TB. Once the TB treatment is completed, the visa applicant can immigrate and is given what is called a Class B condition that requires a post-arrival follow-up in the United States. Since LTBI is non-infectious, LTBI testing is currently limited to children aged 2-14 and sometimes offered to known contacts to TB cases. LTBI treatment is not required as part of the immigration medical examination as LTBI is not transmissible. Those with chest x-ray abnormalities, history of TB, IGRA positive, or a known contact of TB case are given a Class B condition which allows them

to immigrate but comes with a recommendation to complete a post-arrival follow-up evaluation within 30 days after relocation to the United States.(61)

The CDC TB Technical Instructions were last updated in 2018 to recommend the use of the IGRA over the TST to test for infection for children, 2-14 years of age. Prior to this latest update, the CDC Technical Instructions were revised in 2007 based on a study conducted by Maloney et al. that showed that in Vietnamese immigrant visa applicants, smear microscopy missed 65.6% of culture-confirmed cases during the overseas medical examination. This important study resulted in the addition of sputum mycobacteriological cultures as part of the diagnostic algorithm for the overseas medical examination.(62) To implement these revised guidelines at nearly all panel sites, CDC employed a variety of infrastructure building, training, and monitoring tactics to implement the revised CDC TB Technical Instructions from 2007-2013.(63)

Several studies have documented the impact of the inclusion of the culture-based algorithm as part of the pre-arrival screening. In 2011, Lowenthal and colleagues' retrospective analysis showed that there was a reduction in the number of TB cases in California attributed to immigrants and refugees coming from countries where the culture-based algorithm was implemented.(64) A preliminary analysis by CDC showed that of approximately 1100 TB cases diagnosed overseas with cultures, 60% were smear-negative/culture-positive.(63) Another retrospective cohort study among Filipino immigrants moving to California, compared the rate of TB detected post-arrival in Filipino immigrants who moved to the United States before the implementation of 2007 culture-based examination to Filipino immigrants who moved after the enhanced screening using cultures. The findings showed that after the implementation of 2007 CDC Technical Instructions, there was a 75% reduction in the post-arrival detection of TB, suggesting that the culture-based screening algorithm was detecting more smear-negative TB during the pre-arrival screening for Filipino immigrants. Although a limitation of the study is that it was not confirmed whether these immigrants took LTBI treatment at any point.(24) In 2015, Liu et al. conducted a more comprehensive nationwide evaluation of the effect of the culture-based algorithm. Their population-based cross-sectional study found, between 2007-2012, among 4032 TB cases diagnosed pre-arrival by culture, 2195 (54.4%) were sputum smear negative but culture positive. Without the addition of cultures these persons would likely not have been diagnosed during the medical examination, but

potentially after arrival in the United States and subsequently reported as a new case of TB in the United States.(65) Thus, the addition of the cultures during the pre-arrival screening has been associated with a reduction in post-arrival TB case detection; although it is important to note that temporal factors may have also contributed to this decline.

These studies not only demonstrated the impact of the addition of the culture-based algorithm on US TB incidence, but they also point to utility of the pre-arrival screening platform in reducing the importation of TB to the United States. The successful roll-out and scale-up of the culture-based algorithm at each overseas panel site suggests TB screening innovations can be systematically introduced to this platform.

United States Immigrant and Refugee Post- Arrival Follow-Up Evaluation

The recommended post-arrival follow-up evaluation is generally performed at a local health department. The local health department is alerted of the arrival of an immigrant with a Class A or B condition in their jurisdiction through the CDC Electronic Diseases Notification (EDN) system. The health department receives the contact information that the immigrant provides and is responsible for following-up with the immigrant or refugee to complete their evaluation. The post-arrival evaluation allows for an opportunity to rescreen the immigrant and to ensure that appropriate TB treatment is provided or LTBI treatment is offered if indicated.(48)

Assessments of the post-arrival follow-up evaluation have suggested mixed results and have called for the strengthening of the platform to optimize its yield and impact. After the full implementation of the EDN system in 2009, CDC conducted a preliminary analysis of the post-arrival follow-up evaluation. They found that in 2009, 23,321 people immigrated to the United States with a Class B condition and with the recommendation to complete the post-arrival follow-up evaluation. Of these people, 75.4% completed their follow-up evaluation, suggesting that up to a quarter of immigrants and refugees did not complete their evaluation.(48)

Similarly, Nuzzo et al.'s retrospective chart review of 205 Class B immigrants and refugees notified to the Baltimore Health Department from 2010-2012, found that 153 (74.6%) attended their post-arrival follow-up evaluation and 144 (94.1%) of those

received a complete medical evaluation. Of those who attended, 6 (4.2%) were diagnosed with active TB and 76 (52.8%) were diagnosed with LTBI. All persons diagnosed with active TB completed treatment and 60 (78.9%) of those with LTBI completed treatment. The high prevalence of active TB and LTBI as well as the high proportion of treatment completion in this study suggest that the post-arrival evaluation serves as an important case-finding component of migrant screening. However, it is important to note that this study's results may not be generalizable to other cities and settings as most of the study participants were refugees.(66) Refugees may be more likely to complete their post-arrival follow-up evaluation compared to immigrants as they often have resettlement programs that provide assistance with access to health care.(67)

Another retrospective cohort analysis by Gacek et al. looked at the post-arrival follow-up for immigrants in the state of Connecticut. Of 184 immigrants recommended for post-arrival follow-up, 109 (59%) completed their TB evaluation. Of these, 4 (4%) persons were diagnosed with TB and 105 persons were diagnosed with LTBI. Of those with LTBI, only 49 (47%) initiated treatment and 15 (30%) completed treatment, suggesting that improvements in the proportions of those completing the evaluation as well as for LTBI treatment completion are needed.(68)

More recently CDC conducted a nationwide comprehensive analysis of post-arrival follow-up evaluations from 2013-2016. Among 2.1 million US-bound immigrants and refugees completing the overseas pre-arrival screening, a total of 90,737 were identified as being at risk for TB and were recommend a post-arrival follow-up. Of these 58,560 (64.5%) completed their post-arrival evaluation resulting in 667 additional cases of TB diagnosed, which is a 15.8% increase in case detected from the 4,225 who were diagnosed during the pre-arrival screening. Among the 30,574 persons who were diagnosed with LTBI overseas, only 18,466 (60%) completed their post-arrival evaluation. 21,714 persons (including those identified with LTBI pre-arrival and those identified with LTBI post-arrival) were recommended LTBI treatment during the post-arrival evaluation; of these 14,977 (69%) initiated treatment and only 8,695 (40%) completed treatment. These findings suggest that while the post-arrival evaluation can be highly effective at identifying additional cases of TB missed during the pre-arrival screening, there are losses in the diagnostic and treatment cascade particularly for those with LTBI that need to be improved.(67)

The low numbers of immigrants and refugees that are successfully engaged post-US arrival in all steps of the LTBI care cascade (testing, diagnosis, treatment initiation, and treatment completion), may be attributed to the fact that finding and treating LTBI is considered resource intensive, burdensome, and a lower priority by health departments that need to prioritize finding and treating active TB disease due to shrinking public health funds. (66,69,70) Furthermore, post-arrival immigrants themselves may have barriers and challenges to seeking medical care for LTBI treatment in a new environment. Barriers can include, but are not limited to language, transportation, distrust, and employment conflicts.(71)

While efforts to strengthen the post-arrival follow-up evaluation have been recommended to improve the uptake of LTBI testing and treatment, expanding the pre-arrival screening to include voluntary LTBI testing (for those ≥ age 15) and treatment is another option that should also be explored. To date empirical evidence on whether this approach is feasible, acceptable, and effective is lacking. While there are many questions and concerns on how to implement pre-arrival LTBI testing and treatment, one of the main concerns is the historic low uptake of LTBI testing and low treatment initiation and completion rates. For this approach to be effective, high rates of LTBI testing uptake and treatment completion are required. However, many factors can influence LTBI testing and treatment uptake, some of these are further explored in the next section.

3.4 Factors Associated with Latent TB Infection Testing and Treatment

Targeted LTBI testing and treatment is a major component of the US TB elimination strategy.(72) However, the effectiveness of this strategy is dependent upon acceptance and completion of LTBI testing and treatment. Several systematic reviews and meta-analyses have been conducted on LTBI testing and treatment and all have pointed to the wide ranging, and mostly suboptimal treatment initiation and completion rates.(73–77) Understanding reasons for these low rates and where losses are occurring in the *LTBI Care Cascade* can help inform programmatic interventions. Risk factor studies can provide insight into characteristics of persons who are more likely to accept/not accept or complete/not complete treatment. This insight can facilitate the tailoring of the interventions to improve the uptake of LTBI testing, treatment initiation, and treatment

completion across the LTBI care cascade. For this section, the literature was reviewed to inform the study intervention through a better understanding of the factors associated with the uptake of LTBI testing, treatment initiation, and treatment completion in immigrant populations.

For this narrative review, an exploration and synthesis of existing systematic reviews and meta-analyses on LTBI was first conducted to understand factors associated with LTBI testing and treatment rates. Then a review looking at the specific studies describing factors associated with migrants and LTBI testing and treatment was conducted. To get an understanding of challenges and motivators of foreign-born, migrant populations in accepting LTBI testing and treatment, both quantitative and qualitative studies were reviewed. Studies were limited to those published from 2000-2019 and in the English language. Studies were also limited to those containing analyses or sub-analyses on acceptance of LTBI testing, treatment initiation, or treatment completion for immigrant populations. Studies that exclusively focused on the accuracy of LTBI tests, on the comparison of different treatment regimens, or pediatric LTBI were not included. Studies that only included immigrant or foreign-born as a risk factor without differentiating risk factors within this group were excluded. In line with the focus of my study on implementing a LTBI intervention during a migrant screening process as part of a visa application, the review focused on exploring and identifying factors described in the literature that might be relevant in this context of a quick, generally 1–2-time clinical encounter, in an official setting. Studies which focused on conditions such as substance or excessive alcohol use, homelessness, or previous incarceration were not included as these conditions could impact the immigrant's visa application status. Although my study is specifically on LTBI testing and treatment for a US-bound Vietnamese immigrant population, there is a scarcity of research particularly focused on this population and topic. An unpublished dissertation found during the literature search, on LTBI and Vietnamese immigrants living in the United States, was included in the review because of the similarity in my study population and topic. However, there was a need to broaden the search to other migrant populations and settings to understand factors related to LTBI testing and treatment uptake. This allowed me to explore and identify potential facilitators or barriers for implementing a LTBI intervention beyond my study population to enable recommendations for rollout of the PTOPS approach to other panel sites. One additional

systematic review on LTBI interventions and the cascade of care published in 2020 and identified after the literature search was included because of its relevance to the topic.

Search terms for this topic included (latent tuberculosis infection OR LTBI) AND (testing OR treatment initiation OR adherence OR compliance OR treatment completion) AND (factors OR uptake OR acceptance OR barriers) AND (migrants OR immigrants OR refugees OR foreign-born OR Vietnamese). I additionally identified articles through a manual review of references in publications, systematic reviews, and expert consultations.

Systematic Reviews on Latent TB Infection Testing and Treatment Initiation and Completion

Several systematic reviews and meta-analyses have been conducted on LTBI testing and treatment and all have pointed to the wide ranging, and mostly suboptimal treatment initiation and completion rates.

Alsdurf et al.'s systematic review was the first to conceptualize steps from LTBI screening through LTBI treatment completion in what they have referred to as the *LTBI Cascade of Care Framework*. Through their systematic review of LTBI studies, they showed that there are reported losses of patients at each step of the cascade and that the losses at the beginning of the cascade (screening or testing) accounted for a greater net reduction of public health benefit than when just focusing on the losses associated with treatment incompletion after treatment initiation. Their meta-analyses of 58 studies with a total of 748,572 people showed that steps in the cascade that accounted for substantial losses included completion of testing at 71.9% (95% CI 71.8-72.0) for those identified for screening; completion of medical evaluation for those recommended at 43.7% (95% CI 42.5-44.9%); and completion of treatment is started at 18.8% (95% CI 16.3-19.7%). The attrition was particularly high for migrant populations for the cascade steps of screening and treatment completion. From 13 studies, a pooled estimate of 43.4% (95% CI 20-67%) of eligible migrants were screened for LTBI; 54.6% (95% CI 36-73%) of those eligible initiated treatment; and only 14.3% (95% CI 5-24%) completed treatment. While they did not provide reasons for high attrition for migrant populations, Alsdurf et al. concluded that factors associated with fewer losses across the cascade included having an immunocompromised condition and being identified as a contact during an investigation, perhaps as these groups may have more focused medical attention than others with

LTBI. The use of shorter, rifamycin-based regimens was also associated with fewer losses.(75)

A more recent review and meta-analysis by Barss et al., 2020, similarly used the *LTBI Cascade of Care Framework* to identify interventions that promoted retention through the different steps. They identified 32 different interventions, but in their pooled analysis concluded that insufficient evidence existed to support a single intervention that promoted retention. However, various interventions such as patient incentives, provider education, and supportive measures using digital tools, reminders, and home visits aided in improving treatment completion in different the different studies. Similar to Alsdurf et al., their review found that very few studies reported on all steps of the care cascade, making it challenging to map and assess the interventions to the different steps of the cascade. Additionally, the majority of the studies included in the review were observational and only two of the included randomized control trials met their quality criteria. They concluded that since losses vary by step and population, that different interventions may be required to increase uptake and retention along the entire cascade.

Hirsch-Moverman et al.'s systematic review looking at 78 studies conducted in North America found that LTBI adherence and completion rates were mostly suboptimal. When particularly looking at studies among recent immigrants they found a wide range of completion rates from 22% to 90%. Moreover, across all studies reviewed there was much heterogeneity in predictors of adherence. Most studies examining demographic characteristics such as age, sex, and race did not report significant associations with adherence. The few studies that did report significant associations had inconsistent results. Other patient related factors such as recent TB exposure and higher education were positively associated with LTBI adherence; but BCG vaccination, injection drug use, or excessive alcohol use were associated with treatment incompletion. Their review also found that interventions for LTBI treatment adherence such as directly observed therapy (DOT), incentives, and counseling and support did not produce consistent results across settings, suggesting that a 'one-size-fits-all' approach would not be a solution for improving LTBI treatment completion rates.(73)

Another recent review conducted by Liu et al. in 2018 on barriers to LTBI treatment adherence found that in 54 studies the proportion of people initiating LTBI treatment ranged from 24% to 98% and the proportion of people completing treatment ranged from

19% to 90%. Reported barriers to adherence for patients included concerns about adverse events, to treatment; length of treatment; financial constraints; and lack of transportation to the clinic.

Stuurman et al. looked at 62 articles that reported on determinants of LTBI treatment initiation and completion and 23 articles on interventions. Similar to other reviews, they found that regimen length, directly observed therapy (DOT), adverse events, alcohol use, and socio-demographic factors served as determinants for treatment completion. Interventions using shorter regimens and social support interventions tended to have more favorable outcomes while DOT and incentives for treatment completion had mixed results.(76)

Sandgren et al.'s systematic review looking at LTBI treatment initiation and completion for the general population also reported that initiation and completion rates greatly varied between and within population groups and were mostly suboptimal. Initiation rates from 45 studies varied between 26-99% across different populations groups. The studies focusing on immigrants (4 prospective and 5 retrospective studies) found that initiation rates varied from 23 to 97%. Completion rates from 83 studies ranged from 39-96% across different population groups and for immigrants (nine prospective and 18 retrospective studies) ranged between 7-86% for immigrants.(74)

Most of the studies included in these reviews were observational and of varying quality. In each review, there was also much heterogeneity in the included studies in terms of settings, target populations and differences in diagnostic tools and treatment regimens used. Moreover, included studies used different measures of associations and reference groups thereby making the identification of salient factors and comparison of conclusions from studies challenging. Nevertheless, all reviews point to the low and inconsistent results of LTBI testing and treatment programs and the need to identify interventions to improve uptake and completion.

LTBI Treatment Regimens

Several of the systematic reviews pointed to the possibility that the historic low LTBI treatment initiation and completion rates for the past couple of decades was because, for a long time, the preferred treatment regimen of LTBI was isoniazid daily for 9 months (9H). The long duration of that treatment regimen, along with the risk of hepatoxicity, the asymptomatic nature of LTBI, and the potential of never developing TB disease most likely contributed to low treatment initiation and completion rates. (75,76)

Currently new and shorter TB regimens have become available. One relatively new treatment regimen that has been helping to improve LTBI treatment initiation and completion rates, is 3HP [3 months of 12 once-weekly doses of rifapentine (RPT) and isoniazid (INH)]. In December 2011, CDC published the *MMWR: Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection.* An update to the guideline was published in 2018 to include the option of self-administered therapy (SAT).(78) Based on three randomized controlled trials, the recommendations suggest that the 3HP LTBI regimen is as efficacious as 9H and had greater completion rates in a study setting (82% versus 69%).(79) Subsequent studies have also shown higher completion rates with the 3HP regimen in programmatic settings and that the regimen has less hepatotoxicity compared to the 9H regimen, making it a potentially better option to increase treatment completion rates.(80,81) Other recently approved short regimens include 3HR (3 months of daily isoniazid and rifampin) and 4R (4 months of daily rifampin).(82)

While shorter regimens are showing promising results in improving LTBI treatment initiation and completion rates, there are still many other social, demographic, environmental, and clinical factors that can influence an individual's decision or ability to start and adhere to LTBI treatment. The below section explores the literature on factors associated with testing and treatment in immigrant populations.

Factors Associated with LTBI Testing, Treatment Initiation, and Treatment Completion

Understanding characteristics of persons and factors that may influence the uptake of LTBI testing and treatment initiation and completion can provide useful information for designing and improving LTBI interventions. The risk factors associated with LTBI testing and treatment for foreign-born/migrant populations identified through the literature are

presented according to an adapted version of a social ecological model (SEM) which is also used to guide the study.(83) As previously mentioned, the review explored factors identified in the literature that might be relevant in a quick clinical encounter in the context of an official migrant screening exam affiliated with a visa application. The adapted SEM categorizes the identified risk factors into 3 levels (*Individual, Interpersonal, and Structural/Environmenta*l) as described in the *Conceptual Framework* section of this study.

Individual Factors –Demographic, Personal Characteristics, and Beliefs

Sex

Globally, the prevalence of TB is higher in men than in women. The WHO Global TB Report estimated that in 2019 men account for 56% of all TB cases, compared to 32% of cases in adult women and 12% in children.(14) Studies suggest that the higher TB burden and mortality in men may be a result of increased risk of progression to disease once infected.(84) Some studies suggest that notions of masculinity can play a negative role in the health seeking behaviors of men, which can in result lower rates of TB treatment initiation and completion.(85–87) Less is known about the influence of gender on LTBI infection and treatment. Studies reporting on gender and LTBI testing and treatment among migrants have had inconsistent results. Some studies have found no significant difference between males and females in regards to LTBI treatment initiation or completion.(66,88,89) For example, Nuzzo et al.'s retrospective cohort analysis looking at LTBI screening and treatment of refugees and immigrants in the Baltimore TB Program found no evidence of differences in treatment initiation (AOR=0.93; 95%CI 0.67-1.3) or treatment completion between males and females. (66) However, a few studies noted gender differences. Codecasa et al.'s prospective study conducted in Italy looking at treatment completion rates of 6H (6 months of isoniazid) in a foreign-born population found males were at a higher risk for not completing treatment compared to females (OR 1.42; 95%CI 1.29-1.56).(90) In Milinkovich et al.'s study of mostly immigrants to Canada, females were more likely to complete treatment than males (OR=1.8, p<.05). Similarly, in Lobue and Moser's retrospective cohort study looking at factors related to 6H LTBI treatment completion in San Diego County, of 3,788 persons (79% foreign-born), the females in the study were more likely to complete treatment than males (OR 1.2; 95% CI 1.0–1.4).(91) None of the authors provided further insight as to why these differences existed. Conversely, another study by Sweeney et al. looking at 3HP treatment

completion in refugees relocated in Vermont from Bhutan and Nepal, males had higher completion rates than females (80% v 56%, p=0.02, n=82).(92) Reasons for these differences are unclear but could either be attributed to some unexplored socio-cultural factor or potentially due to less tolerability of the treatment regimen by women because of lower body mass index.

Age

Studies have also reported inconsistent findings with the association of age and LTBI testing and treatment. Most studies reported treatment completion being significantly associated with younger age. In Truax's cohort study looking at factors affecting LTBI treatment adherence among Vietnamese immigrants in California, older age groups, including those aged 45-65 (OR=2.2; 95%CI 1.2-3.9) and age ≥ 65 (OR=6.3; 95%CI 1.5-26.4) were significant predictors for refusing LTBI treatment compared to those aged 18-44 years; and age ≥ 65 (OR=6.1; 95%CI 1.3-27.7) was a significant predicator for non-completion. Truax suggests that older Vietnamese populations may be less likely to accept treatment because they may be more likely to believe in traditional eastern medicine and less likely to complete treatment due to increased side-effects. Additionally, she posits that among recent immigrants, older adults may be less likely to speak English making it challenging for them to seek health care.(93,94) Contrarily, Colson et al. found those who had lower acculturation and presumably lower English-speaking skills were more likely to accept treatment, potentially because they felt obligated to say yes to treatment due to lack of language comprehension.(95) In Milinkovich et al.'s study of immigrants to Canada, relative to young adults (18-30 years), middle-aged adults (31-49 years) were less likely to complete treatment.(96) Trauer and Krause's prospective study of recently arrived refugees in Australia, suggested that increasing age was associated with failure to complete treatment, potentially due to higher incidences of medication-related adverse events. The mean age of those discontinuing treatment due was significantly greater than for those completing treatment (27.2 years v 19.8 years; t test, p=0.009).(88) Lobue and Moser's study also found a higher completion rate with the 6H regimen was associated with younger age groups (15 to 34) (OR= 2.1, 95%CI 1.1-3.9).(97) One potential reason for treatment incompletion among older age groups is the higher rates of side effects associated with isoniazid among those ≥35 years of age. Additionally, clinicians may be less likely to offer LTBI treatment for older age groups

because of risk of potential side-effects, particularly with isoniazid. (8) However, other studies found no association with age and treatment initiation or completion. In Goswami et al.'s study looking at predictors of LTBI initiation and completion in North Carolina in a predominately foreign-born population, factors significantly associated with treatment initiation ($p<0.10$) included older age in the univariate analysis, but not the multivariable analysis. Additionally, no association with age was detected with treatment completion.(98) Similarly Shieh et al. and Ailinger et al., found no association between age and completion rates.(99,100) Comparisons regarding age across studies is challenging considering the differing age cutoffs and methods for categorizing age groups. Most studies used 6H or 9H which is known to be less tolerable for those older in age, therefore more understanding on how age is associated with treatment initiation and completion using more tolerable regimens such as 3HP, 4R, and 3HR is needed.

BCG Vaccination

Another individual level factor associated with LTBI testing and treatment initiation in the literature is history of BCG vaccination. While BCG is known to offer some protection for children from developing TB, it is thought that its protection against TB wanes over time. The TST, one of the most common tools to diagnose TB infection, is prone to false-positive results due to cross-reactivity with the BCG vaccination.(101) Hence some studies suggest that those who have received the BCG vaccination believe that they are at low risk for developing TB disease; that a positive TST result is false; and LTBI treatment is unnecessary.(102) In Shukla et al.'s prospective study of hospital employees, those who had prior BCG vaccination, mostly foreign-born health care workers, were less likely to initiate LTBI treatment ($p=.02$) and adhere to treatment (OR=3.5, 95%CI 1.8 to 7.1) compared to those who did not have BCG vaccination and were mostly US-born health care worker.(103) In a study by Shieh et al. looking at predictors of non-completion of LTBI treatment in a clinic in Boston, Massachusetts, 94% of 217 participants believed the BCG vaccination would protect them from developing active TB disease in the future. However, this view alone did not predict failure to complete treatment; those who perceived that they were at a low risk to progress to TB disease were most likely not to complete treatment. But in other studies, BCG did not seem to influence treatment decisions. In a large-scale prospective study conducted at 12 sites across the United States of mostly foreign-born persons, only 3.9% of participants (n=233) self-reported that

BCG was the reason they declined treatment.(95) Furthermore, in Hirsch-Moverman et al.'s study looking at factors related to LTBI completion in both the United States and Canada (n=1513), BCG was not found to be associated with treatment non-completion.(104)

Interpersonal Factors- Conditions and Influences based on Relationships.

Family

In a systematic review of qualitative literature, Munro et al. identified the role of the family and community as an influence on TB treatment-taking behavior. This influence can be bi-directional. Families and communities often serve in a supportive role in TB treatment adherence. (105) In Jimenez-Fuentes's prospective cohort study looking at LTBI treatment in an immigrant population in Spain, lack of family support was associated with non-adherence (OR=3.7, 95%CI 2.5–5.4). (89) Additionally, in another ethnographic study looking at LTBI treatment adherence (for the 12-month INH regimen) in Vietnamese refugees in California (n=24), it was noted that family support was the most relevant factor that helped patients get through treatment, particularly when experiencing side-effects. Forty-five percent of those who completed treatment stated that a family member encouraged them to complete treatment compared to 20% who do not complete treatment. The study also suggested that family and friends could influence patients to stop taking treatment. Eight of the 10, non-adherent participants reported direct or indirect peer pressure to discontinue medication.(106) In Goswami et al.'s study, in the multivariable analysis, participants planning to tell friends/ family about their positive TST was independently and significantly associated with treatment completion (RR=2.0, 95% CI 1.0-3.9), suggesting that interpersonal relationships and support may influence treatment decisions.(98)

Contact to TB Case

Some studies looking at LTBI treatment reported that those who were a known contact to a TB case or a have a family member who has TB are more likely to get tested and initiate LTBI treatment. In Goswami et al.'s study in North Carolina looking at predictors for treatment initiation, they found that being a close contact to an infectious TB case (RR=2.5, 95%CI 1.8-3.6) was associated with treatment initiation.(98) Horsburgh et al, cross-sectional survey of 32 clinics also found that those were contacts to a TB case were more likely to accept treatment compared to those who were not (OR=.19; 95CI .07-.50,

p=.001).(107) Truax's mixed-method dissertation on Vietnamese immigrants living in the United States also found that being a recent contact to an infectious TB case was a significant predictor for treatment acceptance (p≤0.001). One participant in her study indicated that she was offered LTBI treatment but was initially reluctant to take it until years later when her husband became sick with TB disease. It was after seeing him go through TB treatment that she willingly accepted LTBI treatment.(93) It is unclear from these studies whether those who are contacts to a TB case are more likely to accept treatment because of personal concerns of progressing to TB disease, having a family or close friend with TB, or if they receive more support and attention from health care workers who may influence their decision.

Structural and Environmental Factors- Influences such as policies, access, transportation

Clinic accessibility: Travel distance, time, and mode

In a qualitative study conducted by Weiland et al. in an adult learning center in the United States, 54 immigrants from diverse backgrounds, participated in focus groups to understand immigrant perceptions about TB. In this study participants mentioned that barriers to LTBI testing included transportation, cost, and work schedule conflicts. Because of the convenience sample of members of the adult learning center, the findings may not be applicable for other populations or settings.(108) However, other studies have noted similar barriers to testing and treatment for immigrant populations.(109) When specifically looking at literature on Vietnamese immigrants, in Ito's ethnographic study of Vietnamese refugees in California and LTBI treatment adherence, 40% of the treatment non-completers (n=10) had cited transportation to the clinic as problem and barrier to finishing treatment. (106) Populations that are in the process of relocation also have had challenges with completing TB treatment. In a study by Bennet et al. looking at LTBI treatment in newly arrived refugees in San Diego County, California, 28 of 37 of persons did not complete treatment because they had moved. (110)

Employment or Enrolled in School

In their systematic review of qualitative literature on TB and adherence, Munro et al. found that several studies indicated that fear of losing a job due to stigma associated with the disease or missing time off of work for treatment had an impact TB adherence.(105) However, in Jimenez-Fuentes study of LTBI treatment, unemployment (n=590) was

associated with poor treatment adherence (OR=1.9, 95%CI 1.3–2.9).(89) Similarly, Truax's study in Vietnamese immigrants in California, current employment was a significant predictor for both treatment acceptance (p=0.01), and for treatment completion (p=0.007). She posited that study participants who were concerned about their careers did not want to get sick so they were more likely to initiate and complete treatment.(93)

Summary

The exploration of the literature suggests that there is much heterogeneity in factors that are associated with LTBI testing and treatment among foreign-born/migrant populations. Additionally, there are inconsistent findings across studies on the role demographic factors, such as age and gender, play in testing and treatment acceptance, suggesting that findings may be unique to study populations and settings. There was significant heterogeneity in study quality, design, multivariable models and methodologies, making it challenging to compare risk factors across studies and to make general conclusions on predictors for testing, treatment initiation, or treatment completion for foreign-born/migrant populations. However, the studies all point to the utility of understanding factors for particular interventions and populations to understand how to improve uptake and completion.

3.5 Overall Conclusions for Background and Narrative Literature Review

The rationale for conducting a narrative review compared to a systematic review of the literature is that the aim of my study was to implement and assess an innovative approach of offering pre-arrival, voluntary LTBI testing and treatment to immigrants as a strategy to help the United States advance towards its TB elimination goal. As this approach has never been implemented before, empirical evidence to date is lacking on the strategy's feasibility, acceptability, effectiveness, or impact. The narrative approach, compared to a systematic approach, allowed for a more comprehensive understanding of the LTBI situation in the United States, what has been previously accomplished to address TB and LTBI in migrant/foreign-born populations, and how I can build upon this previous work. In terms of the *Implementation Research* framework used to guide this study, the narrative review also served the purpose of providing evidence and support to fulfill the objective of determining *appropriateness* of the study intervention as described in the *Conceptual Framework.*

The narrative review of the literature consisted of three separate topics that have informed the *appropriateness* and design of my study intervention. The first topic on US TB epidemiology and modeling studies demonstrated that strengthening efforts to address LTBI in immigrants has the greatest potential to move the United States further towards TB elimination. The TB surveillance and prevalence studies identified that Vietnam ranks in the top five countries of birth of persons with TB. Additional studies identified Vietnamese immigrants as having high rates of LTBI and high reactivation rates resulting in TB disease.

The review of existing migrant TB screening programs suggested that there were mixed results on their effectiveness as whole and that the provision and acceptance of LTBI testing and treatment was rare or suboptimal. The US pre-arrival screening process, on the other hand, has been considered a high-yield activity for detecting and treating TB in US-bound immigrants and refugees. The post-arrival process plays an important role for the further identification of TB but suffers from significant losses throughout the LTBI care cascade.

The review of the literature on factors associated with LTBI testing, treatment initiation, and completion identified some potential predictors (i.e, age, clinic distance or time to travel to clinic, shorter treatment regimens) for LTBI testing and treatment acceptance for migrant populations, but results were mostly inconsistent across studies and populations suggesting that findings maybe unique to study populations and settings. Nevertheless, understanding these factors for specific target populations could offer insight on how to improve an intervention.

Strengths and Limitations of the Narrative Review

The strength of this narrative literature review is that the method allowed for the exploration of more than one question relevant to understanding the need, current efforts, challenges, and gaps for addressing the burden of LTBI in immigrant populations as part of a TB elimination strategy. The inclusion criteria for the studies were purposefully kept wide in terms of study design, populations, interventions, controls, and outcomes. Compared to a systematic review, which generally has a narrow focus, this narrative approach allowed for a more comprehensive understanding of the many different complex factors that needed to be considered to justify my study and to help inform the

development of the study intervention, design, conceptual framework, and methods for analysis.

Although, systematic search criteria were used for each question of the literature review, a key limitation is that the narrative approach is subject to potential biases in terms of which literature I more heavily focused on to present in the review. There was significant variation in the quality and types of the studies included. Many studies had a small sample size, were observational (cross-sectional or cohort studies) in single settings, did not include a comparison group, and often did not include information on potential confounders. Study settings and context also varied greatly.

While the review focused on studies on immigrants with LTBI, it is important to note that migrant populations are heterogenous. Risk factors findings for LTBI testing and treatment were inconsistent across studies suggesting results are not generalizable across migrant populations or are more dependent on study context. The specific population for my study is US-bound Vietnamese immigrants, however, only a few articles were located with this same target population. Many studies did not include disaggregated data on migrant type or country of origin making it difficult to determine if findings would be generalizable and applicable to my study population. Additionally, there was much heterogeneity in study implementation, design, and analysis. Studies used different diagnostic tests, treatment regimens, definitions and measures for treatment adherence and completion, measures of associations, and reference groups. As such caution is necessary when interpreting results of the review.

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4. Chapter 4: Study Methods and Procedures

An overview of the study methods and procedures is provided in this chapter. Additional information on methods is provided in each stand-alone manuscript (Paper 1) and (Paper 2).

4.1 Study Design and Overview

The *Preventing Tuberculosis Overseas Pilot Study (PTOPS)* is a prospective observational cohort study that was conducted between September 2018 and October 2019. As implementation research, the study was implemented in a real-world setting, the Cho Ray Hospital Visa Medical Department (CRH VMD) in Ho Chi Minh City (HCMC), Vietnam where medical examinations occur for US-bound immigrants. Voluntary LTBI testing by an IGRA, the QuantiFERON Gold in Tube Test (QIAGEN GmbH, Hilden, Germany), and 3HP treatment, if indicated, was offered to eligible participants during the required pre-arrival overseas medical examination for US-bound immigrant visa applicants. IGRA positive participants were offered 12 doses of 3HP by DOT at CRH VMD. For those leaving for the United States prior to treatment completion, a minimum of 8 doses by DOT at CRH VMD was required and up to a minimum of 4 doses by SAT was allowed to be taken. Participants taking doses SAT in the United States received a weekly follow-up call by a US-based Vietnamese-speaking study coordinator. During the consent process and throughout the study, immigrant visa applicants were informed that acceptance or decline at any point would not impact their visa applications Those who declined to participate at any step of the LTBI care cascade were asked if they would be willing to provide their reasons for decline. Those who accepted were followed through the LTBI care cascade (testing, treatment initiation, and treatment completion), to determine uptake, acceptability, and effectiveness of the intervention (*Figure 4.1: Study Schematic*).

4.2 Ethics and Protection of Participants

Prior to implementing the study, ethics approval was sought and received by the institutional review boards of the CDC, UCSF, Vietnam NTP, CRH VMD, and LSHTM.

4.3 Orientation and Training for Study Staff and the Minimization of Observer Bias

Prior to study implementation, site study staff were provided with an orientation training that I developed. At this orientation, an overview of the Global, US, and Vietnam TB and LTBI epidemiology; diagnosis, treatment, and management of LTBI using 3HP were covered. Information on these topics were obtained from WHO and CDC guidelines. An overview of my proposed study protocol was also provided which included the study rationale and objectives. All study principal investigator partners were present at this first in-person meeting in Vietnam to go over the proposed protocol and roles and responsibilities. At this meeting, study staff were able to ask questions and to provide input on how best they thought the study could be integrated into their operating environment. Based on their feedback and input, the protocol was revised to ensure that study procedures were compatible with the regular operations of the CRH VMD.

After the initial orientation, all study personnel (including clinical investigators, data managers, and interviewers) were provided the standardized *Good Clinical Practice* training developed to prepare and certify study staff in research ethics and the conduct of clinical trials with human participants. The training was translated in Vietnamese and certificates were provided to participants at the end of completion and used as part of the IRB approval process. All personnel were also required to sign a staff confidentiality agreement.

A third onsite training and piloting of the data collection tools was conducted for all study staff after the protocol was revised. Standard operating procedures (SOPs) were also developed for all aspects of the project, from study recruitment and enrollment, data collection and data management and storage. At the training, we conducted a review of the revised protocol and staff were trained on the following topics to implement the study: recruitment, obtaining consent, enrollment, ethics, avoiding biases, confidentiality, offering testing and treatment, interviewing participants, and data collection and management.

Multiple efforts were undertaken to minimize observer bias and to ensure consistency in the administering of consent and study questionnaires. Each CRH VMD study staff had specified roles based on their skills: two study nurses were responsible for conducting recruitment, obtaining consent, and completing data questionnaires; two additional study staff were responsible for managing the database; three physicians were responsible for

determining patient eligibility for treatment and managed and assessed participants for side effects; one study nurse was responsible for conducting DOT and maintaining DOT treatment records. Each staff was given the opportunity to role-play and practice recruiting participants, obtaining informed consent, completing data collection forms, and conducting mock interviews and using probes for qualitative questions. During the training, study staff were taught to emphasize to visa applicants that study participation was voluntary and that their decision would not affect their visa applications. Case studies were developed for study staff to think through how they should respond to different scenarios. This interactive training format allowed for input and consensus by study staff on effective ways to ask each question, thereby helping to standardize the delivery of the interviews across the study. Study staff were further trained on determining participant eligibility for 3HP treatment and assessing for adverse events. Study staff practiced completing data collection forms and provided input on the formatting of the questionnaires.

Since study implementation was delayed due to drug importation challenges, a fourth refresher training on recruitment, obtaining consent, data collection, qualitative interviewing, and patient management was conducted right before the start of the study. In this training, role-plays, mock interviews, and case studies were used again.

While most of the staff understood English, all training materials were translated into Vietnamese to ensure comprehension. Additionally, all trainings at CRH VMD were attended by a dual English/Vietnamese speaker who assisted with communication between study staff and principal investigators.

The two US-based Vietnamese study coordinators responsible for following-up participants completing treatment in the United States also received similar trainings with opportunities to practice and role-plays following-up with participants and completing DOT data collection forms. They were also given copies of the study SOPs and an opportunity to discuss status of follow-ups and any challenges with study implementation during the weekly conference calls.

4.4 Monitoring and Supervision of Study Implementation

Several different approaches were taken to monitor study implementation to ensure scientific integrity and to protect the rights of study participants. At the launch of the study, UCSF/Vietnam partners observed and provided feedback to CRH VMD study staff on the recruitment and consent process as well as the study flow and data collection and storage. During study enrollment, daily debriefing meetings among CRH VMD study staff occurred to discuss recruitment status updates and any challenges with study implementation or data collection. Weekly calls were established between all partners to discuss the study and any challenges with recruitment, treatment, or data collection. The weekly calls allowed the opportunity to address any challenges as they arose and to ensure that the study was implemented as intended. Data collected from the study were uploaded weekly to a FTP site, allowing me to perform routine data audits remotely to check for logical errors, accuracy of information, omissions, transcription errors, inappropriate abbreviations, and illegible entries. Upon inspection, errors were minimal. Every quarter, UCSF/Vietnam conducted site visits to observe study implementation, the consent process, and the collection of data. I participated in two of these site visits and observed the study recruitment, delivery of DOT and assessment of side effects, and data collection and entry. The site visits allowed me to also verify data in the database with the paper records. I conducted random spot checks of the paper forms and the database. Any missing data or discrepancies in the database were checked against the paper records and immediately corrected as needed. I also visited the site at the end of the study to finalize and validate the database prior to data analysis.

4.5 Study Population

The study population consisted of immigrant visa applicants undergoing the medical screening process at CRH VMD for residency in the United States. Only applicants living in HCMC Province and surrounding areas, aged ≥12 years, and not known to be pregnant were eligible to take part in the study. The study was limited to those living in HCMC province as travel to CRH VMD for weekly directly observed therapy (DOT) for LTBI treatment (for up to 8 doses) was required for those initiating treatment. Additional inclusion and exclusion criteria were based on the CDC guidelines the 2011 *Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium Tuberculosis Infection*.(1) Since this study marked the first time use of the 3HP treatment regimen in Vietnam and involved immigrants who may be traveling during treatment, a more conservative approach was taken for determining eligibility for treatment than is generally recommended. Exclusion criteria included those who were found to have liver disorders or hepatitis B or C despite this not being a contraindication for the treatment.

Inclusion criteria

- Willingness to provide signed informed consent
- Males and non-pregnant, non-nursing females
- Age ≥12 years
- Live in HCMC Province, Binh Duong, Dong Nai, and Long An

Exclusion criteria

- Women who are pregnant, breastfeeding, or planning to get pregnant within 120 days of study start.
- Age <12 years
- Live outside of HCMC Province and surrounding area
- Have confirmed or suspected active TB (pulmonary or extrapulmonary)
- Previously completed treatment for TB disease or LTBI
- Has any condition, based on medical examination, that requires sputum smears and cultures be obtained per CDC TB TIs (chest radiograph suggests TB, other TB

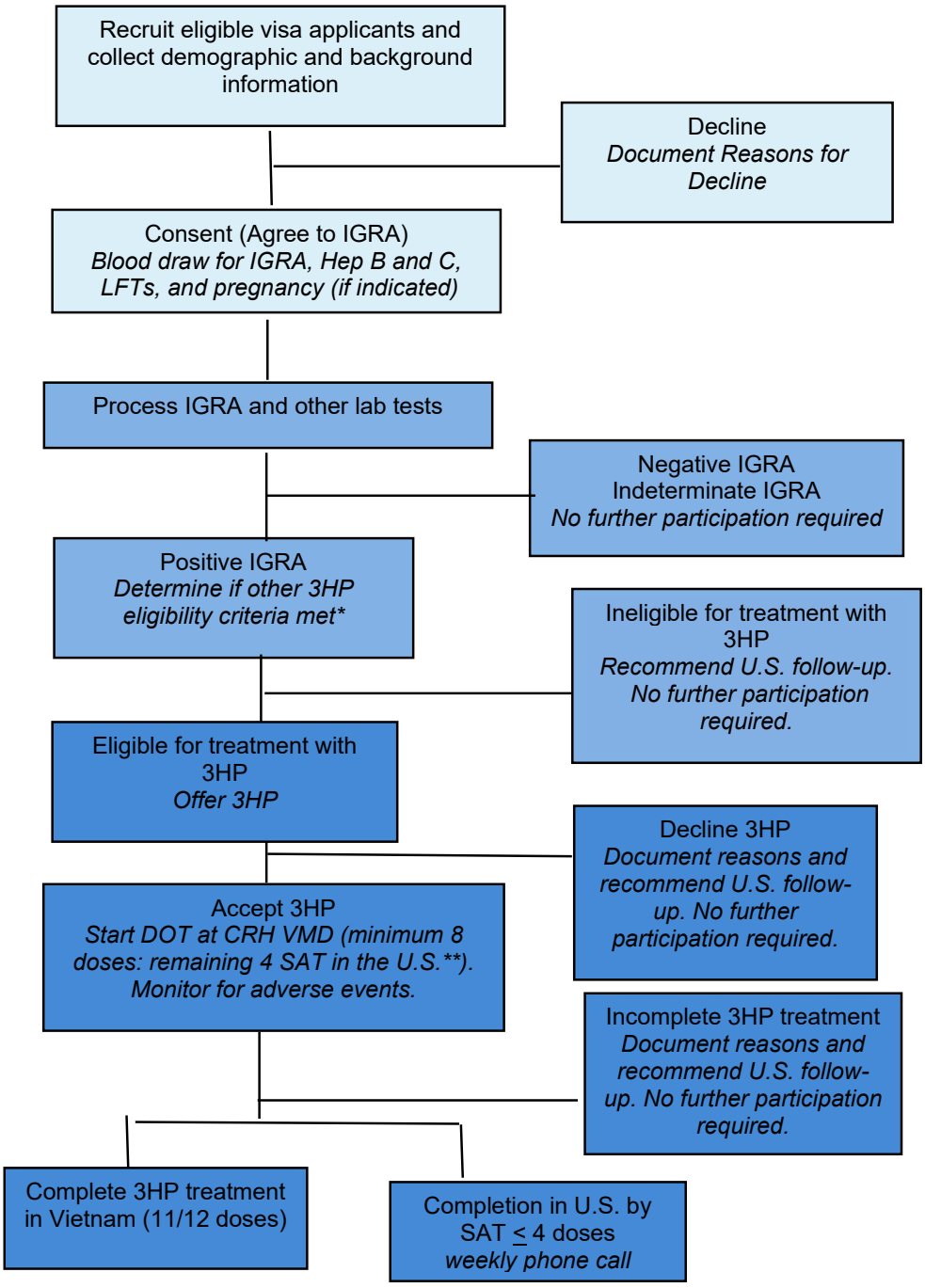
signs and symptoms, known HIV infection, or evidence of extrapulmonary TB)

- Has any condition, based on medical examination, of substance use or mental disorder
- Contacts to a source case with known resistance to isoniazid or rifampin
- History of sensitivity or intolerance to isoniazid or rifamycins.
- Has either Hepatitis B virus (HBV) or Hepatitis C (HCV)
- Serum alanine aminotransferase ALT (SGPT) > 5x upper limit of normal
- For participants with known liver disease or at risk of liver disease, ALT >3x upper limit of normal, or total bilirubin is >2x upper limit of normal

Late Exclusion

- Anyone who is diagnosed with active TB (confirmed or suspected)
- Pregnancy
- Confirmation of being a TB contact to a source case with INH or rifampin resistance.

Figure 4. 1: Study Procedures Schematic



Note: IGRA=Interferon gamma release assay, HEP=hepatitis, LFT-liver function tests, DOT-Directly observed therapy, SAT= Self-administered therapy
* Study eligibility criteria for 3HP described in inclusion/exclusion criteria section
**Participants who completed 8 or more doses of 3HP by DOT in Vietnam were given the option of taking the remaining four or less doses by SAT after arrival in the US

Related Study Documents and Data Collection Forms in Appendix

- **A** Study Information
- **I** Treatment flyer
- **B, C** Informed Consent (Adult and Adolescent)
- **D.** Data Collection Form 1: Enrollment, Background,

Related Study Documents and Data Collection Forms in Appendix

- **E,F,G** Official Medical Examination form used to abstract treatment eligibility data: DS-3026, DS-3030, and DS-205
- **H.** Form 2: Lab Results, Treatment Eligibility, and

Related Study Documents and Data Collection Forms in Appendix

- **I.** For all eligible: LTBI treatment information
- **J.** For decliners: U.S. Treatment options
- **L.** For acceptors: DOT clinic and treatment side-effects information
- **P.** LTBI test and treatment status card
- **K.** Form 3: Participant Contact/Travel Information
- **M.** Form 4: DOT and Patient Monitoring,
- **N.** Form 5: Treatment Completion Questionnaire Vietnam
- **O.** Form 6: Treatment Completion Questionnaire Vietnam
- **T, U** Form 7 and 8: Adverse Events Reporting Forms

4.6 Study Procedures

Study Timeline

The study was implemented at the CRH VMD from September 2018 to October 2019 with participant enrollment being completed in July 2018 to allow for 3 months for treatment completion follow-up. Any necessary translations and the finalization and validation of the study database was completed in December 2019.

Recruitment, Sampling Strategy, and Consent

As the study was implemented in a real-world setting, recruitment and enrollment were incorporated into the regular medical examination process for immigrant visa applicants applying for residency in the United States as specified by the *CDC TB Technical Instructions.*(2). Figure 4.1 above depicts the study procedures with the affiliated study forms. Figures 4.2 and 4.3 below depict the flow of visa applicants throughout their entire CRH VMD medical examination and the points at which study procedures were incorporated. The medical examination can last from 1-3 days; however, all examination procedures generally occur on Day 1 and, if needed, Day 2 and 3 are reserved for receiving and reviewing lab results and any additional patient follow-up if required. To ensure that visa applicants were able complete the multiple steps of the medical examination process on Day 1 and the lengthy study consent process (30 – 45 minutes); study recruitment only occurred in the morning hours of operation. While this approach meant that a few eligible visa applicants with appointments in the afternoon may have missed the opportunity to learn about and participate in the study, as a practice the vast majority of immigrant visa applicants schedule their appointments in the morning hours.

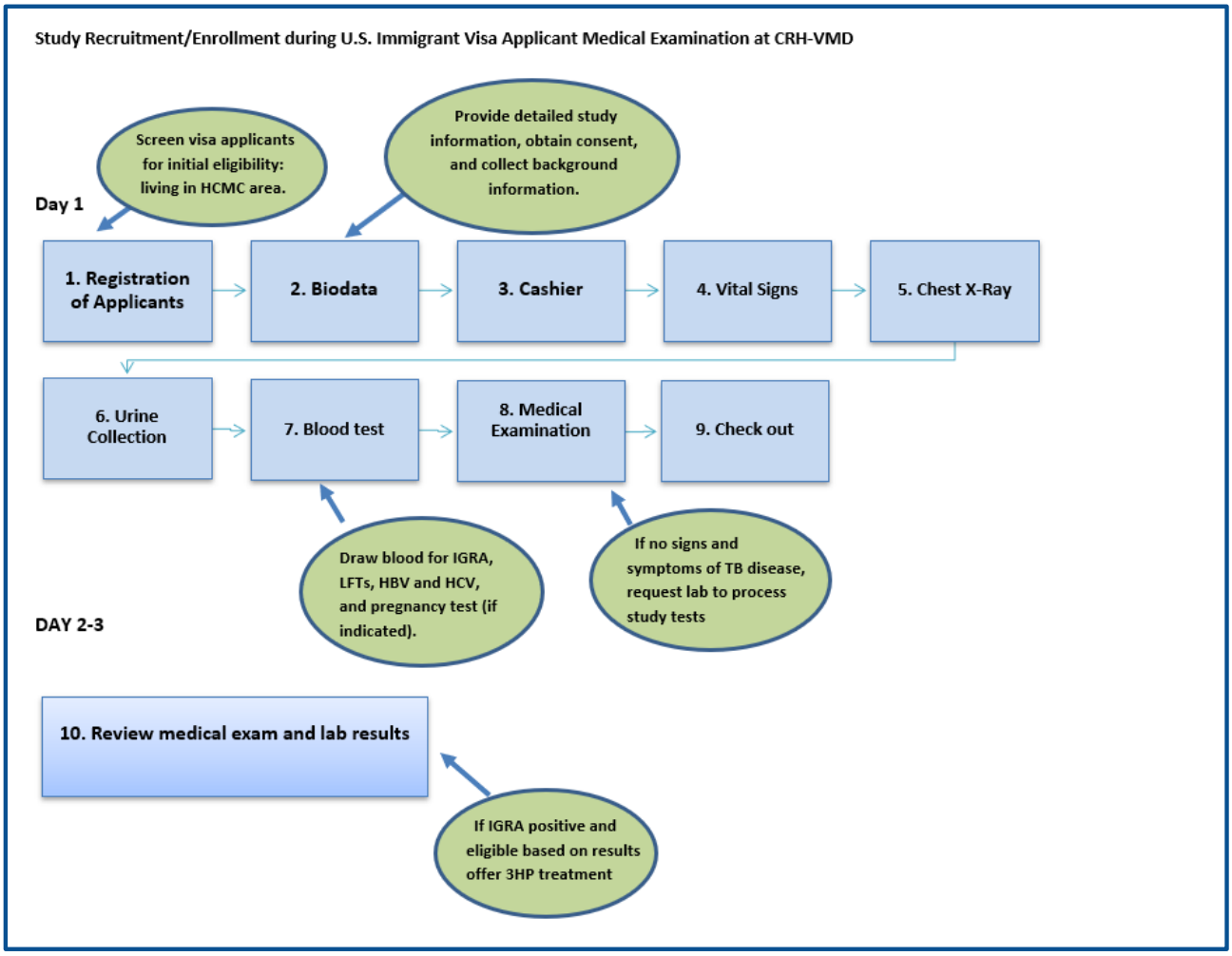
During the study time frame, all visa applicants registering for the medical examination during the morning shift were screened for recruitment. Those who met the initial eligibility criteria of living in the HCMC province area were provided an information sheet about the study that they could read as they waited (Appendix A). These applicants proceeded to the Biodata step where their name, gender, age, and additional background information were confirmed with their official paperwork. These applicants were then escorted to a private room where they were provided additional written and verbal information on the

study and the consent process by one of two study nurses responsible for overseeing enrolment (Appendices B, C, and I). All recruited applicants were given an opportunity to ask questions about the study. All applicants were informed that consenting to fully participate in the study meant that they would receive an IGRA as the first step of the study to test for infection and if they were IGRA positive that they would have the opportunity to take 3HP treatment by DOT if they chose. They were also informed that they could decline to participate at any time during the study and that their decisions on participation would not affect their visa application. All recruited visa applicants, whether they accepted or declined to participate (consent to an IGRA), were asked if they would be willing to respond to 10 questions regarding their demographics and background. Collecting this background data at the recruitment stage for those willing to consent to participate in the study (i.e., those willing to have an IGRA) and those not willing to consent to participate in the study (not willing to have an IGRA) allowed for systematic comparisons to be made between the two different groups. Additionally, recruited immigrant visa applicants who declined to participate were asked if they would be willing to provide their reasons for decline(Appendix D, Form 1).

Procedures for Participants Enrolled in Study

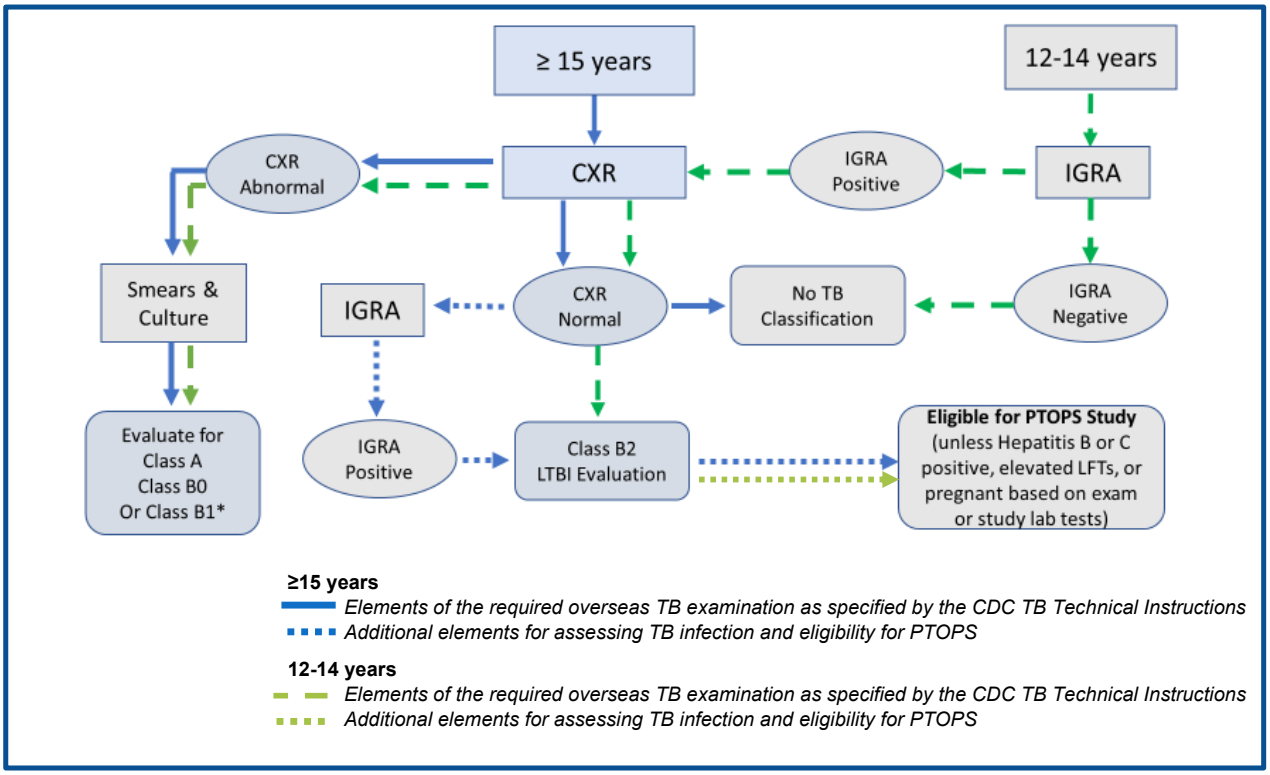
Those who consented to participate received an IGRA for the study during their medical examination (children 12-14 years of age, already receive an IGRA as part of the medical examination). Other study laboratory tests for those who consented include hepatitis B and C serology, liver function tests [LFTs], and pregnancy test, if indicated (Appendix H, Form 2). The overseas medical examination for all immigrant applicants ≥15 years of age includes a detailed medical and vaccination history; a physical examination; a chest radiograph; and sputum and cultures for TB if indicated because of signs or symptoms of TB, abnormal chest radiograph, or known HIV infection. As part of their TB screening, all child applicants (2-14 years of age) receive a medical history, physical examination, IGRA; and if they have a positive IGRA result they receive a chest radiograph and, if indicated, sputum and cultures for TB. Figure 4.3 depicts the required medical examination algorithm for immigrants as specified in the *CDC TB Technical Instructions* with addition of the LTBI test and other lab tests for the study.

Figure 4. 2 Visa Applicant Study Recruitment and Enrollment Steps during Medical Examination



Note: IGRA=Interferon gamma release assay, LFT-liver function tests, HBV=hepatitis B virus; HCV=hepatitis C virus

Figure 4. 3: TB Overseas Medical Examination and PTOPS Study Pathway



**TB Classifications for Overseas Medical Examination Outcomes: No Class- No TB disease or infection; Class A: TB disease, treatment completion required; Class B0 TB, TB disease, completed treatment by DOT; Class B1 TB, clinical signs and symptoms of TB, CXR suggestive of TB, or known HIV infection, but negative sputum smears and culture; Class B2 TB: LTBI*

***CDC TB TIs require a TST or IGRA for applicants 2-14 years of age living in countries with a World Health Organization (WHO)-estimated tuberculosis incidence rate of ≥20 cases per 100,000 population. The IGRA provided by this study fulfills this requirement, and children who receive an IGRA as part of the study will not be subjected to the TST or IGRA that is otherwise routinely provided during the overseas medical examination in Vietnam. CDC TB TIs do not require a TST or IGRA for applicants ≥15 years (except for TB contacts) so, for adults, the IGRA provided by this study represents an added test.*

Those who were IGRA positive and eligible for 3HP, as described by inclusion/exclusion criteria, were offered 3HP by DOT at CRH VMD for a minimum of 8 doses and up to maximum of 4 doses by SAT in the United States if they immigrated before treatment completion.

Those who declined were asked for their reasons why. Those who initiated treatment were assessed for side-effects at weekly DOT sessions. (Appendix M, Form 4) Those taking treatment by SAT, received weekly follow-up calls from US coordinator to determine if dose was taken and if participant experienced any side effects. The local health departments were also alerted of the participants' arrival through the established CDC Electronic Disease Notification (EDN) system for immigrants and refugees. In turn,

the participants were also given the US-based coordinator's contact information and the local health departments contact information in case they were experiencing any treatment-related serious side effects or if they had any other questions, concerns, or a needed to report a change in contact information.

Participants who did not show-up for regularly scheduled DOT visit (or respond to a phone call in the US) were contacted by study staff to reschedule their DOT visit/call. If study staff were not able to reach participant through contact information provided, study staff contacted relatives (contact information was provided by the participant) to help locate participant to reschedule DOT. At least 3 attempts were made by the study staff to locate the participants. Late or missed doses were given as soon as possible and then regularly scheduled visits resumed. As per CDC guidance, doses were not given within 72 hours of each other.

Measuring Acceptance of Test, Treatment initiation, Adherence, and Treatment Completion

- Acceptance of IGRA was defined as receiving a blood draw for the IGRA.
- Treatment initiation was defined as the taking of at least one dose of 3HP treatment.
- Adherence to and completion of treatment were defined by the taking of medication during regularly scheduled directly observed therapy (DOT) appointments.
- DOT was defined as study staff observing the participant ingesting treatment dose.
- SAT was defined as participant taking dose on their own with a US-coordinator calling to follow-up to ask if dose was taken.
- Treatment completion was defined as the taking of 11 of 12 doses within 16 weeks after the first study dose. Participants who did not complete a minimum of 11 doses within 16 weeks were considered to have failed to complete treatment for study purposes.

If doses were not taken within the definition above, participants' treatment outcome was deemed as did not complete treatment. Other than late exclusion, reasons for incomplete treatment were collected and included:

- Discontinuation due to an adverse drug reaction
- Discontinuation of drugs for any reason
- Death
- Loss to follow-up
- Withdrawal of consent
- Pregnancy
- Any completion that was not in accordance with 11 of 12 doses within 16 weeks

4.7 Sample Size Calculations

Paper 1 (Objective 2) Sample Size

For the primary analysis, described in *Paper 1,* the sample size was calculated to produce an estimate with a desired margin of error and confidence level. The below formula was used to calculate the sample size needed to estimate the proportion who complete treatment with a 5% margin of error and 95% confidence level.

When I wrote this study protocol in 2016, there was limited data on the use of 3HP in programmatic settings, particularly with immigrant populations. Thus, to estimate sample size data from CDC and available published programmatic data were used. Based on CDC data from 2003-2012, estimates of the proportion of persons with LTBI in the United States who initiate treatment, if asked, was approximately 70%.(3) Therefore, for the purpose of sample size estimation, it was assumed 70% of those asked, will initiate treatment. A 2016 published study using 3HP in New York City in a programmatic setting was used for the basis for estimating treatment completion. The programmatic study found that of those who initiated 3HP treatment for LTBI, 65% completed treatment. (4) Therefore, it was assumed that 65% of those who start treatment would complete treatment.

$$n = (Z^2 \times P(1 - P))/e^2$$

where

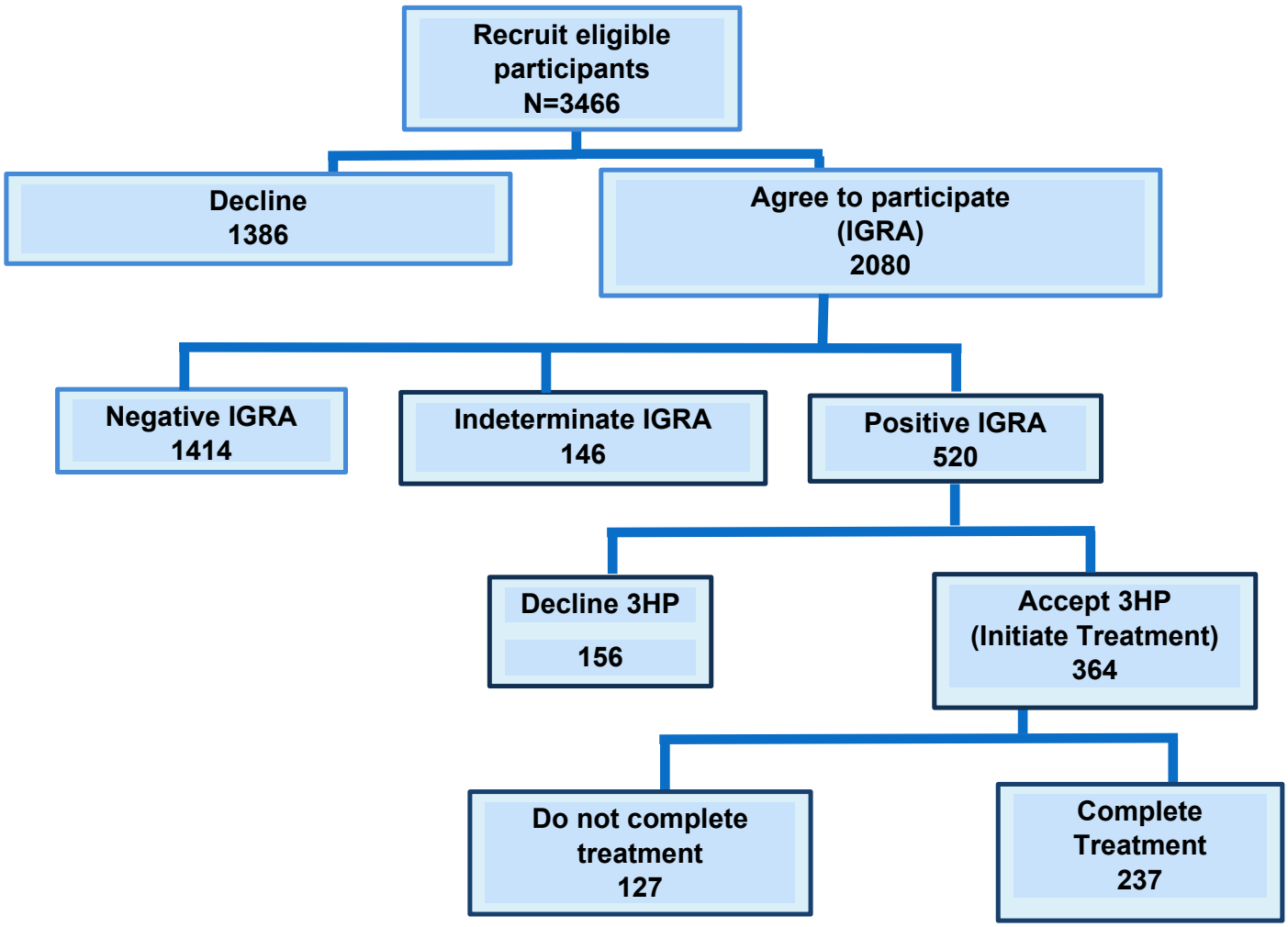
Z = value from standard normal distribution corresponding to desired confidence level (Z=2 for 95% CI)

P is expected proportion of eligible persons who complete treatment=0.65
e is desired precision (half desired CI width) or 0.1/2=0.05.
n = number of persons who start LTBI treatment
$n = (2^2 \times 0.65(1 - 0.65))/(0.05)^2$

n=364

To achieve a sample size of 364 persons who start LTBI treatment, it was estimated that at least 3466 eligible persons would have to be recruited. A study on adherence to 3HP had 60% of eligible recruited persons participate in their study.(5) Therefore, it was estimated that approximately 2080 persons would be willing to be tested for LTBI. Based on studies conducted by Chuke et al. and Powell et al., it was assumed that approximately 25% of the Vietnamese population has LTBI.(6,7) Thus, it was estimated that 520 of the LTBI tested immigrants will be LTBI positive and 70% (364) of these will accept LTBI treatment. Figure 4.4 depicts sample estimates for each step of the study.

Figure 4.4: Study Procedures Schematic with Sample Size Estimates



Paper 2 (Objective 3) Sample Size

For the secondary analysis further described in Paper 2, I conducted three power analyses to calculate the sample size needed to examine key predictors (Table 4.1) for each of the three outcomes of interest: 1. test for LTBI, 2. initiate LBTI treatment, and 3. complete LTBI treatment.

While no previous study specifically looking at the uptake and completion of 3HP LTBI treatment among Vietnamese immigrants prior to moving to the United States exists, there is one recent unpublished doctoral student thesis that explored factors associated with LTBI testing and treatment (9H) adherence among Vietnamese immigrants living in the United States. Although the treatment regimen was longer, because of the similarities in study population, I used data from this study and the other similar studies included in the literature review to provide an estimated effect size needed for key risk factors for the different outcomes. The odds ratios for the key risk factors (age, gender, BCG vaccination, family member with TB, employed/in school, travel time to clinic, TB contact) positively associated with LTBI testing ranged from 1.7 to 4.8; for treatment initiation ranged from 1.9 to 56.2; and with treatment completion ranged from 2.7-4.4. (5,8–12)

To calculate the sample sizes, I used CDC's software, *Epi Info Stat Calc.* The calculations were made using Fleiss's formula for an unmatched cohort or cross-sectional study with dichotomous exposure variable.(13)

The minimum sample size needed to provide 80% power to detect differences for each key predictor and each outcome, based on calculations with a significance level of 0.05, confidence level 95%, is as follows:

Outcome 1: Agree to LTBI test (IGRA), the minimum sample size needed = 460
Outcome 2: Initiate LTBI treatment, the minimum sample size needed =346
Outcome 3: Complete LTBI treatment, the minimum sample size needed =118.

The primary study's sample size for outcome 1 (3466: 2080 accept /1386 decline test); outcome 2 (520: 364 initiate/156 decline treatment); and outcome 3 (364: 237 complete/127 incomplete treatment) should be sufficient to conduct the secondary analyses (Figure 4.4).

Table 4.1: SEM Levels and Factors Associated with LTBI Testing and Treatment

SEM Level	***Factors Investigated in this Study for association with LTBI testing and treatment acceptance***
Individual	-Sex -Age -Employment or in school -BCG vaccination
Interpersonal	-Family member with TB -TB contact -Immigrating with family
Structural and Environmental	-Planned immigration date to the US -Travel time to the clinic -Mode of transportation (personal or public)

4.8 Data Collection, Management, and Analysis

Data Collection

For the study, I developed standardized data collection tools using existing TB programmatic tools and findings from the literature review. The data collection forms along with the recruitment and educational materials were pilot tested with study staff and visa applicants after translation into Vietnamese and prior to study implementation to ensure that the questionnaires and educational information were understood by both study staff and immigrant visa applicants. All data collection forms and accompanying educational materials can be found in the Appendices. Figure 4.1, Appendix 8.1, and Appendix 8.2 list all of the study forms and at which step of the study they were used.

Study Form 1: Enrollment, Background, Demographics, and Reasons for Decline Questionnaire (Appendix D)

All immigrant visa applicants who were approached to participate in the study were asked if they would be willing to respond to a set of demographic and background questions asked by the study staff, in Vietnamese, to assess factors associated with their decision to accept or decline testing or treatment (Factors listed in Table 4.1). Immigrant visa applicants were told that they could decline to respond to any questions that made them uncomfortable.

Immigrant visa applicants who declined to participate/ receive an IGRA were asked if they would be willing to provide reasons why. Reasons were collected using a checklist. An open-ended field was available to record the reason provide for decline if it was not included in the checklist.

Study Form 2: Lab Results, Treatment Eligibility and Reasons for Acceptance or Decline (Appendix H)

Study Form 2 allowed for the abstraction of data by study staff from the official CDC/State Department medical examination forms used at the panel sites (Appendix E, F and G, Forms DS-3026, DS-3030, and DS-2054) during the required medical examination. This data helped the study staff determine the medical eligibility for 3HP treatment for IGRA positive visa applicants.

Additionally, the form was used to indicate if IGRA positive visa applicants accepted or declined treatment. Those who declined treatment were asked by study staff to provide their reasons for why they declined treatment. Responses were recorded in an open-ended format.

Study Form 3: Participant Contact/Travel Information (Appendix K)

Contact and travel information for immigrant visa applicants accepting 3HP treatment were collected on Study Form 3. This information was accessible and used only by study staff who had direct clinical management with the visa applicant on treatment. The information was used to contact those who missed treatment or had side effects that the clinician wanted to follow-up with. The information was also shared with the US study coordinators who followed-up with immigrant visa applicants completing their treatment in the United Stated. Information from this study form was not shared with me as it included patient identifiers.

Study Form 4: DOT and Patient Monitoring (Appendix M)

Study Form 4 was completed by study staff each time an immigrant visa applicant took their weekly dose of 3HP treatment. During each DOT visit or SAT call, using a checklist, study staff inquired and recorded if the visa applicant experienced any side-effects from the previous 3HP dose.

Study Form 5 (Vietnam) and Form 6 (United States): Treatment Completion Outcome and Questionnaire (Appendix N and O)

Study Form 5 (completed in Vietnam) and Form 6 (completed in the United States for those taking doses by SAT) includes the final treatment outcomes for immigrant visa applicants who initiated treatment. Immigrants visa applicants who did not complete

treatment were also asked by study staff to provide their reasons why. Responses were recorded in an open-ended format.

Data Management

Each recruited visa applicant received a unique identification number (study id) that was included on all forms. Only Study Form 3 had patient identification and contact information. This form was only accessible to those who were involved with direct patient management. Data from the forms (with the exception of Study Form 3) were entered into the study database housed at CRH VMD for each participant using their unique identification number. For data collected on participants who moved to the United States during treatment, a separate but similar database was used to capture participant doses taken, side effects, and perceptions on treatment completion/incompletion.

The CRH VMD on-site study coordinator was responsible for the accuracy, completeness, and secure storage of records and study-related data collection forms (collectively referred to here as study forms). All hard copies of study forms were stored in a secured locked file at the study site, CRH VMD in Vietnam. Data were entered into the password protected *PTOPS* database (*MS Access, 2016*) housed on a secure site at the CRH VMD. The electronic files were transmitted to an encrypted CDC FTP site accessible by the US-based study coordinator and the CDC DGMQ Investigator. The US-based study coordinator used the data to monitor treatment completion and follow-up for participants completing treatment in the US. Access to study forms and data files without identifiers were shared with me, the Principal Investigator, through the CDC FTP site. UCSF staff based in Vietnam conducted onsite quarterly reviews of the data forms to ensure that consent was properly taken and that the forms were filled out correctly on paper and in the database. I conducted quarterly monitoring reviews of the data that was submitted electronically through the CDC FTP site and I additionally conducted two data monitoring missions onsite at CRH VMD with UCSF Vietnam staff looking at both the paper-based forms and the electronic database for any data discrepancies.

Data Analysis

For the study objectives, below is a brief description of the data analysis.
Data analysis is further described in the separate manuscripts.

Paper 1: (Objective 2)

Determine the uptake (adoption) of LTBI testing and treatment among Vietnamese US-bound immigrants, if offered during the pre-immigration medical screening exam

a. *Estimate the prevalence of LTBI among US-bound Vietnamese immigrants participating in the study*.
b. *Estimate the proportion of US-bound immigrants at CRH VMD (following the LTBI Care Cascade): who agreed to be tested for LTBI; who initiated 3HP treatment if indicated; and who completed treatment.*
c. *Describe the reasons for declining LTBI testing, treatment initiation, or treatment completion among Vietnamese US-bound immigrants.*

Demographic characteristics of study participants are presented for at each study stage. The prevalence of LTBI was calculated by the number of immigrant visa applicants who were IGRA positive among all immigrant visa applicants who had an IGRA result. Uptake of testing, treatment initiation and treatment completion were recorded as the proportion accepting testing, treatment and completing treatment for LTBI among US-bound Vietnamese immigrants approached and recruited into the study. The frequency of reasons for declining LTBI testing, treatment initiation and completion were summarized. Reasons reported by the immigrant visa applicants for declining testing, were translated, if needed, and categorized using a standardized checklist and quantified. All IGRA positive and medically eligible visa applicants choosing not to initiate treatment were asked to provide a reason why. For those willing to provide a reason, an open-ended question was asked. Responses to open-ended questions were exported to MS Excel and synthesized by categories. Frequencies for each theme that emerged were calculated. Frequencies and proportions were calculated for reasons for treatment incompletion including those due to serious side-effects that required a treatment regimen change or discontinuation as well as for other reasons provided by the participant or provider.

Paper 2 (Objective 3)

To determine individual, interpersonal, and structural and environmental factors significantly associated with Vietnamese US-bound immigrants' willingness to (1) be tested for LTBI, (2) initiate LTBI treatment, and (3) complete LTBI treatment.

Data was retrieved from the PTOPS database to determine participants' responses to the ten questions representing potential predictors, categorized by SEM levels, for the different steps of the LTBI care cascade. Analysis was conducted using R statistical software (version 3.6.1) to determine factors significantly associated with three different models created for the following outcomes of interest: (1) accepted an IGRA, (2) initiated LTBI treatment, and (3) completed LTBI treatment. Univariate analyses to estimate crude odds ratios to assess the relation between each individual factor and each of the three outcomes was conducted. Factors with an associated p value of <0.05 were considered significant. Three separate multivariable logistic regression analyses loaded with all independent factors using a backwards elimination method to create the most parsimonious model for each of the outcomes was conducted. Variables were assessed for multicollinearity for each model prior to conducting the regression by computing the variance inflation factor.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1405964	**Title**	Ms
First Name(s)	Amera		
Surname/Family Name	Khan		
Thesis Title	Preventing TB Overseas Pilot Study (PTOPS): Voluntary LatentTuberculosis Infection Testing and Treatment for US-Bound Immigrants from Vietnam		
Primary Supervisor	Lucy Platt		

If the Research Paper has previously been published please complete Section B, if not please moveto Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose anitem.	Was the work subject to academic peerreview?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include thiswork.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to bepublished?	JAMA or Lancet
Please list the paper's authors in the intended authorship order:	Amera Khan1,7, Christina R. Phares2, Hoang Lan Phuong3,Dang Thi Kieu Trinh3, Ha Phan4,5, Cindy Merrifield4,5, Phan Thi Hong Le3, Quach Thi Kim Lien3, Sooc Ngoc Lan3, Phan Thi Kim Thoa3, Le Tran Minh Thu3, Tiffany

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Stage of publication	**In CDC clearance- Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details ofyour role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I led and designed the study and data collection forms. I analyzed the data and wrote the manuscript. I revised manuscript based on feedback from other authors.

SECTION E

Student Signature	[redacted]
Date	January 7, 2021

Supervisor Signature	Lucy Platt
Date	Feb 25 2021

5. **Chapter 5: *Paper 1* The Preventing TB Overseas Pilot Study: The pre-arrival offering of voluntary LTBI testing and treatment to US-bound Vietnamese Immigrants**

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8. Vietnam National TB Program

Abstract

Background. Seventy percent of tuberculosis (TB) cases in the United States occur in non-US-born persons, usually from reactivation of latent TB infection (LTBI) acquired prior to US arrival. Strengthening efforts to address LTBI in newly arriving immigrants can contribute to US TB elimination goals.

Methods. We conducted a prospective cohort study among US immigrant visa applicants aged ≥12 years undergoing the required overseas medical examination at Cho Ray Hospital, Vietnam, from September 2018–October 2019. Consenting participants aged ≥15 years received an interferon-gamma release assay (IGRA); those 12-14 years received an IGRA as part of the required examination. Eligible participants with a positive IGRA were offered LTBI treatment with 12 doses of weekly isoniazid and rifapentine (3HP). Participants accepting treatment received at least 8 directly observed doses in Vietnam and, if needed, up to 4 self-administered doses with weekly follow-up calls in the United States.

Results. Of 5311 immigrant visa applicants recruited, 2438 (46%) consented to participate; 2276 had an IGRA processed and 484 (21%) had a positive result. Among 452 participants eligible for 3HP treatment, 304 (67%) initiated treatment and 268 (88%) completed treatment: 192 (72%) completed treatment in Vietnam and 76 (28%) in the United States.

Conclusions. Testing identified a high proportion of US-bound immigrants in Vietnam with LTBI. The proportion of those initiating treatment overseas was similar to that found in analyses conducted for immigrant populations in the United States. Among those who started treatment overseas, the proportion who completed treatment was very high (88%), with the majority of participants completing treatment prior to US arrival. We demonstrated that using the overseas medical examination to provide voluntary testing for, and treatment of, LTBI should be considered as a viable strategy to address LTBI in US-bound immigrants to advance TB elimination efforts in the United States.

Introduction

In 1989, the US Advisory Council on the Elimination of Tuberculosis declared a goal to eliminate tuberculosis (TB) in the United States by 2010.(1) TB elimination is defined as <1 case per million population;(1) in 2018, the United States reported 28 TB cases per million population. While US TB incidence has been declining for the past 20 years, with an all-time low of approximately 9,000 reported cases in 2018, the TB elimination goal is still far from reality. (2)

US TB epidemiology can be summarized as a dwindling overall incidence with an increasing proportion of cases diagnosed among non-US–born persons. In 2018, 70.2% of TB cases were diagnosed among non-US–born persons.(2) Molecular studies suggest the majority of TB cases occurring among non-US–born persons are due to reactivation of latent TB infection (LTBI) acquired prior to US arrival.(3,4) LTBI treatment has been demonstrated to significantly reduce the risk of progression to TB disease.(5) Modeling studies suggest further progression towards TB elimination in the United States requires strengthening efforts for diagnosing and treating LTBI among non-US–born persons.(6,7) Treating LTBI in refugees overseas, and in newly arriving immigrants and refugees in the United States, has been shown to be cost effective.(8,9) However, US post-arrival strategies to increase LTBI testing and treatment have had some challenges in stateside follow-up evaluation and treatment completion.(10–13) In a recent analysis of data on newly arriving immigrants and refugees at risk for TB, the authors found that 35.5% did not complete a US post-arrival evaluation for TB and LTBI. Among those who did and were recommended for LTBI treatment, 69% initiated treatment and 40.0% completed treatment.(13)

Immigrant visa applicants abroad are required to undergo a medical examination prior to US arrival conducted by panel physicians who are under agreement with the US Department of State. The purpose of the overseas medical examination is to screen for communicable diseases of public health significance as required by the US Immigration and Nationality Act (8 US Code 1182 and 1222) and the Public Health Service Act (US Code 252). Because TB is transmissible, screening and treatment for TB disease are essential components of the examination and are performed in accordance with the CDC *Technical Instructions for Tuberculosis Screening and Treatment Using Cultures and Directly Observed Therapy, 2018*.(14) Improvements in TB screening and treatment in the overseas medical examination have been associated with a temporal decline in TB cases among non-US–born persons in the United States since 2007.(15–17)

The availability of the short course LTBI treatment regimen, 3HP (3 months of isoniazid and rifapentine) given once weekly, provides an opportunity to explore the feasibility of using the overseas medical examination to allow for immigrants to start and complete a safe and effective LTBI regimen before or during travel to the United States. Thus, one strategy is to expand the overseas medical examination to include the use of IGRAs to identify persons with TB infection, and to offer voluntary 3HP treatment to applicants diagnosed with LTBI.(17,18) To date, empirical evidence on the feasibility and effectiveness of such a pre-arrival testing and treatment approach is lacking. Therefore, we conducted a prospective study to assess voluntary uptake of LTBI testing and 3HP treatment initiation and completion among US-bound immigrant visa applicants in Vietnam while following them through the LTBI cascade of care.

Study Setting

Vietnam is one of the top five countries of birth for non-US–born persons with TB in the United States.(2) According to the World Health Organization (WHO), Vietnam has a high TB burden, with an incidence of 182 per 100,000 (116–263).(19) Studies report approximately one-third of the adult population in Vietnam has LTBI.(20,21) Vietnam has three panel physician sites: one in Hanoi and two in Ho Chi Minh City. The main panel physician site is the Cho Ray Hospital Visa Medical Department (CRH VMD) in Ho Chi Minh City. CRH VMD screens approximately

1500 US-bound immigrant visa applicants per month and was therefore was selected as the study site.

Methods

From September 2018 to October 2019, we conducted a prospective study, the *Preventing Tuberculosis Overseas Pilot Study (PTOPS*), at the CRH VMD to assess the voluntary uptake of LTBI testing and treatment initiation and completion by US-bound immigrant visa applicants.

Study Eligibility Criteria

Study eligibility included US-bound immigrant visa applicants attending their required medical exam who were ≥12 years of age, not pregnant or breastfeeding, and living in the Ho Chi Minh City province area. If during the medical examination or at any time during the study, participants were found to have any of the following conditions they were excluded from participation: signs or symptoms of TB disease; HIV infection; close-contact with someone with isoniazid- or rifampin-resistant TB; previous treatment for TB disease or LTBI; substance use or mental disorder; sensitivity to isoniazid or rifamycins; hepatitis B or C; liver disease or risk of liver disease, or elevated liver functions tests, including serum alanine aminotransferase ALT (SGPT) > 5x upper limit of normal, ALT >3x upper limit of normal, or total bilirubin >2x upper limit of normal.

Study Process

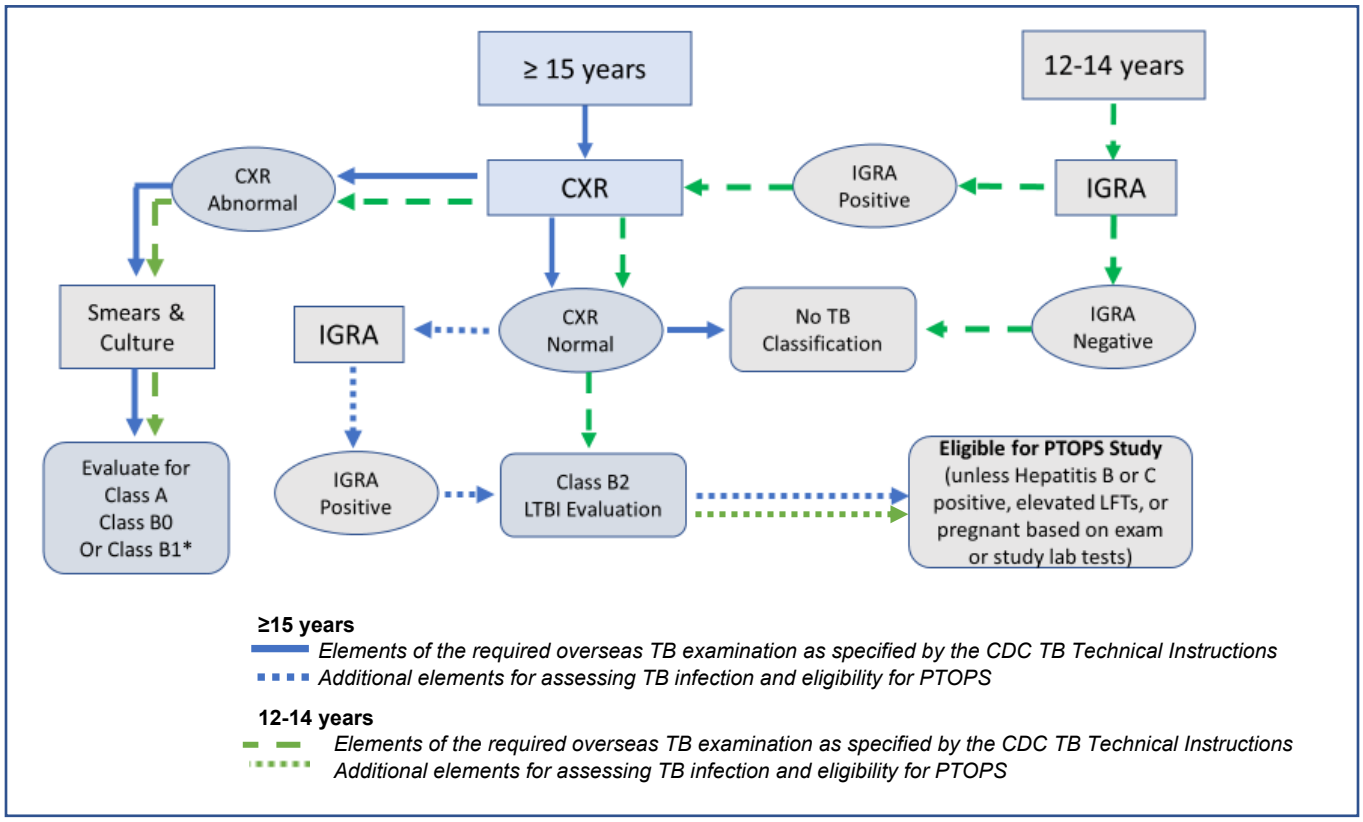
During recruitment, eligible immigrant visa applicants were provided study information in Vietnamese and an opportunity to ask questions. Applicants were informed that participation was voluntary and accepting or declining to participate would not impact their immigrant visa application. They were also informed that LTBI testing and treatment are available in the United States post-arrival, if preferred. To provide insight into reasons for losses in the LTBI care cascade, those who declined to participate were asked if they would be willing to provide their reasons for nonparticipation. Immigrant visa applicants who consented to participate were enrolled, and those ≥ 15 years of age were administered an interferon gamma release assay (IGRA), the QuantiFERON Gold in Tube Test (QIAGEN GmbH, Hilden, Germany), to test for TB infection. Those 12-14 years of age were already required to receive an IGRA as part of

the medical examination. Additional laboratory tests for participants included liver function tests; hepatitis B and C serology; and pregnancy tests, if indicated. All laboratory tests were processed unless participants withdrew from the study or were determined to be ineligible because of an abnormal chest radiograph (CXR) or any other signs or symptoms of TB disease discovered during the medial examination. Figure 1 depicts the overseas medical examination flow and the points where additional study laboratory tests were incorporated.

For IGRA-negative participants, no further participation in the study was requested. For participants who were IGRA-positive, but were also hepatitis B or C positive, pregnant, or otherwise ineligible, no further participation in the study was requested. However, as part of the immigration process, these IGRA-positive participants were categorized with a “Class B2 TB, LTBI Evaluation” classification, which triggers an alert to US health departments through the Electronic Disease Notification (EDN) system of the arrival of persons with LTBI. The classification additionally comes with the recommendation for immigrants to complete a post-arrival follow-up evaluation at a US health department where LTBI treatment can be provided if indicated.(14)

The remaining IGRA-positive participants were offered 3HP (12 weekly doses) by directly observed therapy (DOT) at the CRH VMD. For those emigrating to the United States prior to treatment completion, an option was provided for completing at least eight doses of DOT at CRH VMD with the remaining four or fewer doses by self-administration therapy (SAT) in the United States. Thus, a minimum of eight weeks stay in Vietnam prior to immigration was required for participation in the treatment portion of the study. IGRA-positive participants who declined treatment were asked to provide their reasons for declining and were additionally educated about the signs and symptoms of TB. They received a B2 classification with the recommendation to have a follow-up evaluation visit in the United States post arrival. Participants who accepted treatment were given 3HP weekly by DOT for a minimum of eight doses at the CRH VMD. At these DOT visits, participants were assessed for treatment side effects. Those who took the last four or fewer doses by SAT in the United States received a weekly follow-up call by a US-based Vietnamese-speaking study coordinator to document whether treatment was taken and to assess for any side effects. Treatment completion was defined as taking at least 11 out of 12 doses of 3HP within 16 weeks.

Figure 5.1: Overseas tuberculosis (TB) medical examination pathway and TB classifications for immigrant visa applicants, and modifications for the Preventing Tuberculosis Overseas Pilot Study (PTOPS), Vietnam 2018-2019



Note: CXR=chest radiograph, IGRA=interferon-gamma release assay, LFTs=liver function tests, TB=tuberculosis, LTBI=latent TB infection, PTOPS=Preventing TB Overseas Pilot Study

**TB Classifications for Overseas Medical Examination Outcomes: No TB Classification- No TB disease or infection; Class A: TB disease, treatment completion required; Class B0 TB, TB disease, completed treatment by DOT; Class B1 TB, clinical signs and symptoms of TB, CXR suggestive of TB, or known HIV infection, but negative sputum smears and culture; Class B2 TB: LTBI*

Ethical Approvals

Ethical approvals were obtained by the Centers for Disease Control and Prevention (#7029), London School of Hygiene & Tropical Medicine (#15663), University of California, San Francisco (#17-23654), and the Vietnam National Lung Hospital (IRB# 2053/QD-BYT).

Results

The Study Flow and LTBI Cascade of Care

Figure 2 and *Table 5.1* illustrate the proportions tested, initiating treatment, and completing treatment along the LTBI care cascade. In summary, of 5311 eligible US-bound immigrant visa applicants, 2438 (46%) applicants consented to participate in the study and receive an IGRA to

test for LTBI. Among those who consented, 2276 (93%) received an IGRA and additional study laboratory tests; the remaining 7% who had consented either withdrew from the study or were found to be ineligible during the medical examination, prior to the processing of the IGRA. Among all participants who received an IGRA, 484 (21%) were positive and of those 452 participants were eligible for 3HP. Of these, 304 (67%) initiated treatment and 268 (88%) successfully completed treatment with 192 (72%) persons completing treatment in Vietnam and 76 (28%) completing treatment by SAT within the United States.

LTBI Positivity Among Participants

Of the 2276 participants who had an IGRA processed (Table 5.2), a total of 21% were positive for LTBI. Although a slightly higher proportion of male participants (22%) were IGRA positive compared to female participants (21%), no significant differences among the sexes were found. Higher rates of LTBI were associated with increasing age. For example, for children and adolescents aged 12-14 and 15-18, only 6.3% and 9.4% of the participants, respectively, were IGRA positive. For adults, proportion positive increased with age with 14.6% of those aged 19-34; 27.2% of those aged 35-49; and 32.5% of those 50-64% being positive for LTBI.

Losses along the LTBI Cascade of Care

Each point along the LTBI cascade of care demonstrated losses in participation. Reasons for losses are listed in Tables 3-5*;* 2873 (54%) immigrant visa applicants approached for participation in PTOPS declined. Among eligible visa applicants who declined to participate, 881 (31%) noted they were too busy or stressed due to their impending move; 723 (25%) noted the study and/or IGRA were not requirements for the medical examination; 641 (22%) noted their belief that they were not infected with *M. tuberculosis*; 407 (14%) reported family advised against enrollment; 178 (6%) reported concerns about blood draws; 37 (~1%) noted concerns around delaying or impacting the visa application process; and 27 (~1%) noted their belief that prior bacille Calmette-Guérin (BCG) vaccination would protect them against TB disease.

Of those who consented, 162 (7%) did not have their IGRA processed for the following reasons identified during the medical examination: 119 (73%) had an abnormal CXR or another condition requiring further TB disease screening; 25 (15%) reported they were

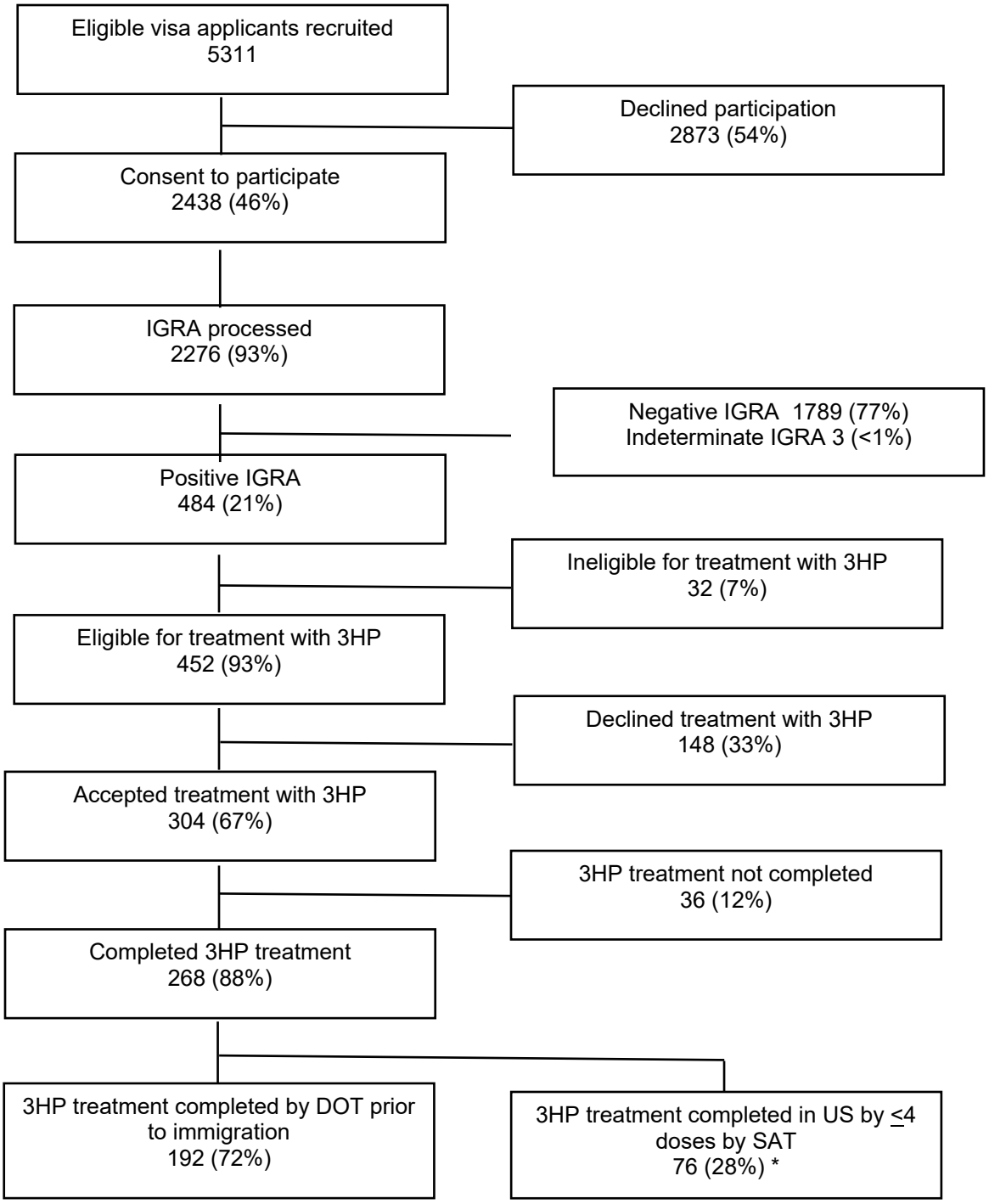
hepatitis B positive; 3 (2%) had a prior history of extrapulmonary TB disease; 2 (<1%) were applying for a visa type that was not included in the study; 1 (<1%) previously completed LTBI treatment; 1 (<1%) was breastfeeding; 1 (<1%) had recently received a live virus vaccine; and for 10 (6%) persons, consent was withdrawn or the reason was not specified.

Of the 484 participants who were IGRA positive, 32 (7%) were identified to be ineligible for continued participation based upon additional screening or laboratory results. Eighteen of those (56%) had hepatitis B and 5 (16%) hepatitis C; 3 (9%) had previously received LTBI treatment; 1 (3%) had liver disease; 1 (3%) had a substance addiction; 1 (3%) was planning to get pregnant in the next 4 months; 1 (3%) had an abnormal CXR; and 2 (6%) participants did not specify the reason.

Of the 452 participants who were IGRA positive and eligible for treatment, 148 (33%) declined treatment. Of these, 99 (67%) did not have enough time for treatment as they were immigrating within 2 months; 23 (16%) preferred taking treatment in the United States; 22 (15%) thought weekly DOT at CRH VMD was inconvenient because of time or distance; 7 (5%) were concerned about side-effects; and 3 (2%) did not feel sick and therefore believed they did not need treatment.

Thirty-six (12%) persons who initiated treatment did not complete treatment for the following reasons: 18 (50%) did not want to continue because of Grade 1 or 2 side effects; 5 (14%) suffered a serious adverse event or a Grade 3 side effect resulting in treatment discontinuation; 5 (14%) were too busy to continue treatment or had to move earlier than anticipated; 5 (14%) were identified as contacts to persons with MDR or INH-resistant TB or were diagnosed with extrapulmonary TB after initiating LTBI treatment; and 3 (8%) were lost to follow-up after US arrival.

Figure 5. 2: Proportions who consented to a test, initiated treatment and completed treatment along the LTBI Cascade of Care: The Preventing Tuberculosis Overseas Pilot Study, Vietnam, 2018-2019



Note: LTBI= latent TB infection, IGRA= interferon-gamma release assay, 3HP= 3 months isoniazid and rifapentine, DOT= directly observed therapy, SAT= self-administered therapy.

*Participants who completed 8 or more doses of 3HP by DOT in Vietnam were given the option of taking the remaining four or less doses by SAT after arrival in the United States

Table 5. 1: Characteristics of Study Participants in the Preventing Tuberculosis Overseas Pilot Study, Vietnam, 2018-2019

Participant Characteristics (n=5311)		Recruited	Enrolled	IGRA Processed	IGRA Positive	3HP Eligible	Initiate 3HP	Complete 3HP
Total		5311	2438	2276	484	452	304	268
Sex								
	Female	2888 (54%)	1350 (55%)	1304 (57%)	272 (56%)	259 (57%)	170 (56%)	152 (57%)
	Male	2423 (46%)	1088 (45%)	972 (43%)	212 (44%)	193 (43%)	134 (44%)	116 (43%)
Age (years)								
	12-14	298 (6%)	143 (6%)	142* (6%)	9 (2%)	9 (2%)	4 (1%)	4 (1%)
	15-18	580 (11%)	294 (12%)	287 (13%)	27 (6%)	26 (6%)	21 (7%)	19 (7%)
	19-34	1307 (25%)	667 (27%)	651 (29%)	95 (20%)	90 (20%)	55 (18%)	50 (19%)
	35-49	1552 (29%)	708 (29%)	648 (28%)	176 (36%)	160 (35%)	103 (34%)	93 (35%)
.	50-64	1391 (26%)	577 (24%)	510 (22%)	166 (34%)	156 (35%)	113 (37%)	95 (35%)
	≥65	183 (3%)	49 (2%)	38 (2%)	11 (2%)	11 (2%)	8 (3%)	7 (3%)

Note: IGRA= interferon-gamma release assay, 3HP= 3 months isoniazid and rifapentine
****IGRA required as part of medical examination for those aged 12-14; 1 IGRA not processed for study due to recent MMR vaccination***

Table 5. 2 Characteristics of IGRA Positive Participants in the Preventing Tuberculosis Overseas Pilot Study, Vietnam, 2018-2019 (n=2276 for total IGRAs processed)

Participant Characteristics	IGRA Processed	IGRA Positive	LTBI Prevalence per characteristic % (row)	(95% CI)
Total	2276	484	21.3%	(19.6-23.0)
Sex				
Female	1304	272	20.9%	(18.7-23.1)
Male	972	212	21.8%	(19.3-24.5)
Age (years)				
12-14*	142	9	6.3%	(3.4.-11.6)
15-18	287	27	9.4%	(6.5-13.3)
19-34	651	95	14.6%	(12.1-17.5)
35-49	648	176	27.2%	(23.9-30.7)
50-64	510	166	32.5%	(28.6-36.7)
≥65	38	11	28.9%	(17.0-44.8)

Note: LTBI= Latent TB Infection; IGRA= interferon-gamma release assay; CI=confidence interval

Table 5. 3 Self-reported reasons for declining to participate in the Preventing Tuberculosis Overseas Pilot Study, Vietnam, 2018-2019 (N=2873)

Self-Reported Reasons, n=2940*	Respondents (n=2873)	%
Too busy or too much stress currently	881	31%
Study/IGRA not required for medical exam	723	25%
Did not believe infected	641	22%
Family advised against enrollment	407	14%
Worried about blood draw	178	6%
Worried that participation could delay immigration process	37	1%
Believed BCG would protect them from TB	27	1%
Worried about enrolling in research	11	<1%
Worried that IGRA results may affect immigration status	7	<1%
Concerned about taking medication	6	<1%
Worried about stigma	5	<1%
Inconvenient to return to CRH VMD	5	<1%
Did not understand study	1	<1%
Undecided	1	<1%

*More than one reason could have been provided by respondents.

Table 5. 4: Reasons IGRA not processed or 3HP not offered to participants in the Preventing Tuberculosis Overseas Pilot Study, Vietnam, 2018-2019

Reasons IGRA not processed for participants who consented to be tested (N=162)	**Total**	**%**
Previous TB or abnormality on CXR	119	73%
Hepatitis B	25	15%
History of extrapulmonary TB	3	2%
Previous treatment	1	1%
Breastfeeding	1	1%
Applying for visa type not included in study	2	1%
Recent receipt of live virus vaccine	1	1%
Unknown, may have withdrawn consent	10	7%
Reasons for not offering 3HP to IGRA-positive participants (N=32)	**Total**	**%**
Hepatitis B	18	56%
Hepatitis C	5	16%
Previous TB or abnormality on CXR	1	3%
Liver disease	1	3%
Planning to get pregnant in next 4 months	1	3%
Substance addiction	**1**	3%
Previous LTBI treatment	3	9%
Unknown	2	6%

Note: IGRA= interferon-gamma release assay, TB= tuberculosis, CXR= chest radiograph, 3HP= 3 months isoniazid and rifapentine, LTBI= latent TB infection

Table 5. 5. Reasons for declining to initiate 3HP and treatment discontinuation among participants in the Preventing Tuberculosis Overseas Pilot Study, Vietnam, 2018-2019

Reasons for declining to initiate 3HP (N=148)	**Total**	**%**
Not enough time, planned to depart for US immediately after receiving visa	99	67%
Preferred to take medicine in the US	23	16%
Inconvenient to go to hospital for treatment (distance and/or time)	22	15%
Concerned about medicine side effects	7	5%
Did not feel sick	3	2%
Reasons for treatment discontinuation (N=36)	**Total**	**%**
Participant decided on own to stop due to Grade 1 or 2 side effects	18	50%
Participant decided on own because too busy or moving to US earlier	5	14%
Identified as contact to a person with MDR or INH resistant-TB or diagnosed with EP TB after treatment initiation	5	14%
Serious side effect, Grade 3 and/or elevated liver function tests	5	14%
Lost to follow up in US	3	8%

Note: 3HP= 3 months isoniazid and rifapentine, TB= tuberculosis, MDR-multidrug-resistant, INH=isoniazid

Discussion

Our study found providing overseas (*pre-arrival)* LTBI testing and voluntary treatment with 3HP during the required visa medical examination should be considered as a viable strategy to further US TB elimination efforts. Approximately, 21% of all participants were IGRA-positive. The proportion positive increased with age, suggesting that expanding IGRA testing to adults can identify a high proportion of immigrants who have LTBI. We were able to achieve similar results for the proportion initiating LTBI treatment and a higher proportion for completion compared to current US *post-departure* efforts.(22–24) In our study, 67% of eligible IGRA-positive participants initiated treatment and 88% of those completed treatment, resulting in 59% of all eligible participants completing treatment. These results can be compared with a recent assessment of the recommended US *post-arrival evaluation* for immigrants at risk for TB (2013-2016). Overall, 35.5% of immigrants and refugees at risk for TB did not complete a US post-arrival evaluation for TB and LTBI, and among those who did and were recommended for LTBI treatment, 69% initiated treatment and 40% completed treatment.(13)

Currently most countries with a low incidence of TB, like the United States, focus on *post-arrival* strategies to address LTBI in immigrant populations.(25–27) While a few countries provide LTBI testing for immigrants *pre-arrival*,(26) our study is the first we are aware of that evaluates offering voluntary LTBI testing and treatment to immigrants *pre-arrival*. A major challenge with post-arrival screening for newly arriving immigrants and refugees is the lack of resources required to follow up and engage with recent arrivals to initiate and complete LTBI treatment.(28) Rates of post-arrival follow-up have ranged from 60%-75% over the years despite improvements including an electronic notification system that alerts health departments to immigrants with a TB condition arriving in their jurisdictions.(29,30) Currently only children 2-14 years are routinely assessed for TB infection as part of the overseas medical exam so most immigrants 15 years or older with LTBI will be missed and not receive a domestic evaluation. However, expansion of just IGRA testing overseas could potentially overwhelm the system and result in additional workload for already challenged health departments to follow up and evaluate additional arriving immigrants with a Class B2 notification. Moreover, immigrants themselves may experience challenges seeking care post-arrival, due to language barriers, transportation issues, and competing priorities with employment and educational commitments.(29) These challenges and limitations underscore the need to maximize the use

of the overseas medical examination process to improve the proportion of those tested and who initiate and complete treatment among US-bound and arriving immigrants and refugees.

While our pre-arrival intervention demonstrated a high proportion of treatment completion, for this approach to reach maximum effectiveness, three points along the cascade must be improved.

First, participation and IGRA testing was low at 46%. Reported reasons for non-participation suggest that this was due to the perceived time commitment to participate in a study during a stressful time preparing for immigration to the United States (31%). Moreover, since this project was conducted as a research study, coupled with a lengthy consent process, it is unclear if this deterred participation. Many visa applicants who declined to participate reported doing so because the study/IGRA was not a requirement for immigration (25%). Thus, a decline for an IGRA was not necessarily due to lack of interest in knowing one's LTBI status. Currently, an IGRA is not a required element in the overseas medical examination for visa applicants ≥15 years of age and is not offered routinely to this group. Consideration of routinely offering or requiring a pre-arrival IGRA to this group could potentially inform immigrants of their TB infection status and give them an opportunity to take LTBI treatment.

Second, among those who learned they were IGRA positive, treatment acceptance was 67%. While this is similar to the proportion initiating treatment observed in the post-arrival evaluation of immigrants and refugees with a B2 classification(13) in the United States and other studies evaluating 3HP**,** (23) this proportion could be improved. Sixty-seven percent of participants who declined 3HP did so because they felt they did not have enough time to complete treatment prior to immigration. PTOPS participation required a minimum of 8 weekly DOT doses, meaning participants needed to remain in Vietnam for at least 2 months prior to immigrating to the United States. An additional 15% of participants declined treatment due to distance and time required to travel to CRH VMD for DOT. Reducing the number of required DOT visits could theoretically increase the proportion of those initiating and completing treatment. A minimum requirement of 8 weekly doses for DOT was included in this study because, at the time, CDC recommended administration of 3HP by DOT.(30) These data

underscore the need for a strategy for LTBI testing and treatment that is person-centered, convenient, and not perceived by immigrants as interfering with travel to the United States.

Third, while the proportion completing treatment was relatively high,12% (n=36) of people did discontinue treatment. Fifty percent of discontinuations were due to minor side effects and 28% were due to severe side effects or other medical conditions resulting in treatment suspension. Fourteen percent of participants who discontinued treatment did so because they were too busy with their move to continue DOT. These data underscore the need for a strategy for LTBI testing and treatment that is person-centered, convenient, and not perceived by immigrants as interfering with travel to the United States. Reducing the number of DOT visits may increase the proportion initiating and completing treatment and should be easily implemented now that WHO and CDC have revised recommendations to support SAT for 3HP.(31,32) Additionally, this may be the least burdensome option for both staff and participants in terms of time and financial costs. However, while a SAT only approach may increase treatment acceptance and completion for some persons, it may also result in more early treatment discontinuations due to concerns over minor side effects without the benefit of further support and education from health care workers during DOT visits. Since a high proportion of LTBI treatment completion is needed to be impactful towards elimination (33,34) and because missed appointments early in the course of treatment have been associated with completion failure, (35,36) an approach worth considering is providing the first month of doses as DOT and/or the use of digital adherence tools to allow participants to take their medicine and be monitored without having to visit the clinic.(37)

Recommendations for expanding overseas LTBI testing and treatment have been suggested and discussed for decades (18); however, to date no empirical evidence of how this approach would work existed prior to PTOPS. Prior to the advent of the IGRA and the 3HP, the strategy was considered potentially burdensome, particularly if made mandatory.(38) Until recently diagnosis of LTBI relied upon the tuberculin skin test (TST) which cross-reacts with BCG antigens. Thus, there were concerns about testing for infection because of the potential of false positives in BCG-vaccinated populations. Additionally, the standard LTBI treatment regimen, until recently, was 9 months of isoniazid, a lengthy regimen prone to side effects. The PTOPS approach relies on an IGRA, which is more specific than the TST, for diagnosis, reducing the potential for false positive results in a BCG-vaccinated population.(39) Moreover, PTOPS relies on voluntary acceptance of

3HP treatment. While there are concerns that visa applicants may feel the need to comply with testing and treatment for immigration purposes, our data suggest that visa applicants understood testing (for those ≥ 15 years) and treatment were voluntary and declining had no impact on immigration status (54% of applicants declined participation and 33% declined treatment). For the immigrant visa applicants, the PTOPS approach can be advantageous because it allows for the provision of testing and treatment in a familiar environment and language, and they do not have to navigate the unfamiliar US health care system upon arrival.

The overseas medical examination is an important opportunity to prevent importation of TB and contribute to elimination goals. This process has already been proven to be a high-yield intervention for identifying and treating TB disease in US-bound immigrants and refugees.(15) Moreover, the recent successful implementation of the updated TB Technical Instructions (which includes mycobacterial cultures and DOT for TB diagnosis and treatment) at the overseas panel physician sites (15) suggests that overseas panel sites have, or can acquire, the necessary expertise to provide testing for TB infection and voluntary LTBI treatment.(40) Indeed, a cost-benefit analysis modelling implementation of LTBI testing and treatment at overseas refugees panel physician sites hypothesized that this approach, could save millions of dollars compared to the current strategy of relying on health departments for post-arrival follow-up evaluations for LTBI and lead to a reduction of TB cases in the United States (41); however, a detailed evaluation of the actual costs and the benefits of this approach is needed.

In summary, our study demonstrated that using the overseas medical examination to provide voluntary testing and treatment of LTBI in a high-burden country yields the identification of those with infection and high initiation and completion and should be considered as a viable strategy to address LTBI in US-bound immigrants and to advance TB elimination efforts in the United States. The use of this strategy should be further evaluated as an addition and/or potential replacement for post-arrival testing and treatment for LTBI and as a complement to other domestic strategies to address LTBI in immigrant populations. Our study was implemented only in Vietnam, a high-TB burden country, additional studies in different settings should be conducted to determine if this approach will yield similar results.

It has been over thirty years since the declaration of the US TB elimination goal and twenty years since the Institutes of Medicine published the report *Ending Neglect: The Elimination of Tuberculosis in the United States*; however, the basic question put forth in the report still remains:

“[will] the renewed opportunity that now presents itself to move toward the elimination of tuberculosis be seized or [will] tuberculosis be subject to another period of neglect until the next resurgence”?(18)

Disclaimer

The findings and conclusions of this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

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Surname/Family Name	Khan		
Thesis Title	Preventing TB Overseas Pilot Study (PTOPS): Voluntary LatentTuberculosis Infection Testing and Treatment for US-Bound Immigrants from Vietnam		
Primary Supervisor	Lucy Platt		

If the Research Paper has previously been published please complete Section B, if not please moveto Section C.

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Journal of Immigrant and Migrant Health
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Stage of publication	**CDC Cleared -in process of submission**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I led and designed the study and data collection forms. I analyzed the data and wrote the manuscript. I revised manuscript based on feedback from other authors.

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Date	January 7, 2021

Supervisor Signature	Lucy Platt
Date	Feb 25, 2021

6. Chapter 6 *Paper 2* Factors Associated with Acceptance Along the LTBI Care Cascade among US-bound Vietnamese Immigrants, a Prospective Cohort Study

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Background

Tuberculosis (TB), a disease for which preventive treatment exists, is a global leading cause of death by infectious disease.(1) Estimates suggest that up to one quarter of the world is latently infected by *M. tuberculosis,* the bacterium that causes the disease.(2) If left untreated, approximately up to 10% of this pool of people with latent tuberculosis infection (LTBI) will progress to TB disease, thereby rendering the WHO *End TB Strategy* goal to reduce worldwide TB deaths by 95% and incidence by 90% by 2035 a serious challenge.(2,3) Achieving this ambitious goal requires a massive scale-up of efforts to identify and treat people with LTBI to prevent the development and further transmission of TB disease. A key component of the US national strategy to eliminate TB is the targeted testing and treatment of LTBI in high-risk groups for TB.(4) Since most cases of TB in the United States are in the non-US-born population and likely result from reactivated LTBI that was acquired prior to US-arrival, those born in countries with a high prevalence of TB are considered to be a high risk group.(5,6)

Past efforts to address LTBI have produced suboptimal results with treatment initiation rates ranging from (26-99%) and completion rates ranging from (39–96%).(7) Many of these poor outcomes were associated with lengthy treatment regimens such as nine months (9H) or six months of isoniazid (6H).(7,8) The recent availability of shorter treatment regimens such as four months of rifampicin (4R) and three months of isoniazid and rifapentine (3HP) has been associated with improved completion rates.(7,9)

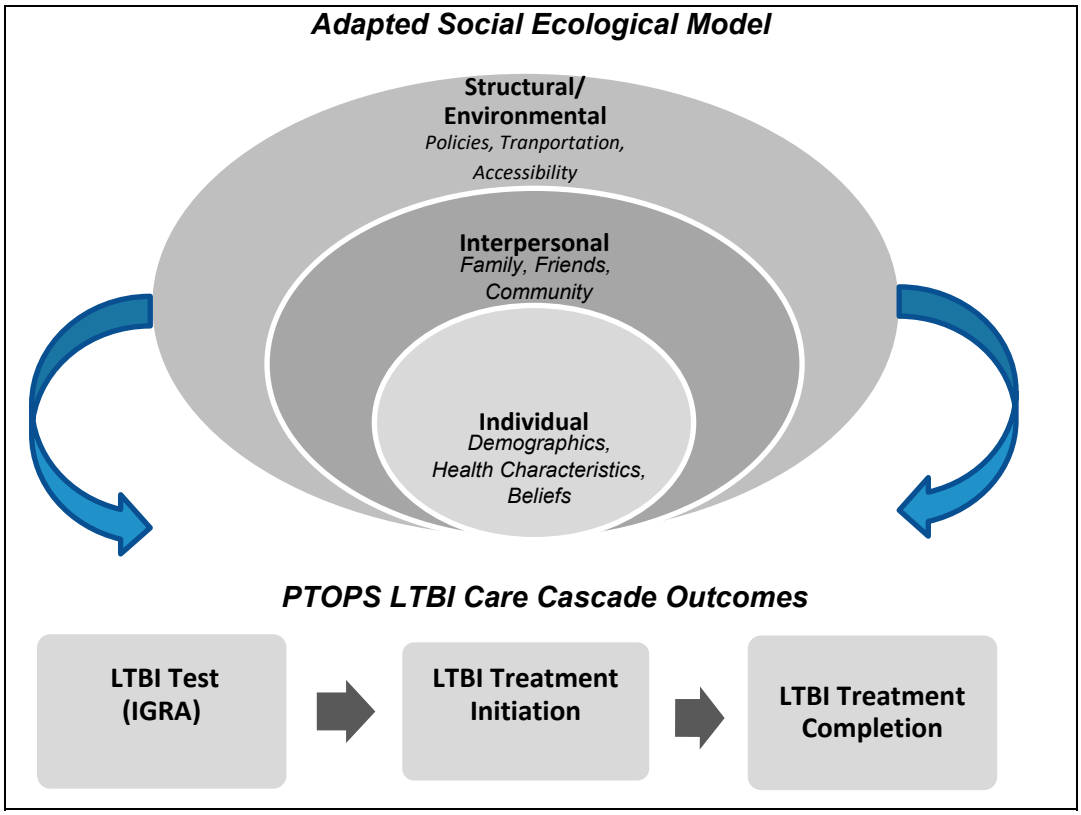
Despite these recent successes, other challenges remain in getting people at risk for TB disease through completion of the LTBI care cascade. The LTBI care cascade consists of several critical steps, namely testing, treatment initiation, and treatment completion (*Figure 1).*(10) Losses can occur at any step of the cascade due to a variety of demographic, social, behavioral, structural, economic, or clinical factors which can influence an individual's decision or ability to start and adhere to LTBI treatment.(8,11) Several systematic reviews have examined factors associated with LTBI testing and treatment. One systematic review found heterogeneity in predictors of adherence and treatment completion across studies, suggesting that context matters and that a 'one-size-fits-all' approach will not work for improving LTBI treatment completion rates.(8) Two more recent systematic reviews suggest that understanding acceptance and decline at each step of the cascade is also important and could provide insight into designing and modifying interventions to improve retention of people through the cascade.(10,12)

In addition to assessing where and why losses occur in the cascade, using a theoretical framework or model to contextualize factors associated with those losses or retention can further help guide interventions. The Social Ecological Model (SEM) considers the complex interaction between personal and interpersonal factors, as well as structural and environmental forces that can influence behavior and decision-making. Traditionally, the SEM identifies five hierarchical levels of influence: individual, interpersonal, community, organizational, and policy/enabling environment.(13) However, the model is adaptable.(14)

Our study is a component of a larger project, the *Preventing TB Overseas Pilot Study* (*PTOPS)* which aimed to assess the feasibility and acceptability of a new strategy to improve the uptake and completion of the care cascade for immigrants diagnosed with LTBI prior to their arrival to the United States. In *PTOPS*, US-bound immigrant visa applicants in Vietnam were offered a voluntary test for TB infection (an IGRA- interferon gamma-release assay) and, if diagnosed with LTBI, voluntary LTBI treatment using 3HP (3 months of 12 once-weekly doses of rifapentine [RPT] and isoniazid [INH]) during their required overseas medical examination for immigration. As part of this larger project, this study aims to make several theoretical and practical contributions for immigrant screening programs aimed at improving uptake and completion of LTBI treatment. *PTOPS* documents the first time offering of voluntary LTBI

testing and 3HP treatment as part of a pre-arrival immigrant screening program. Our study provides benchmarks with respect to implementing the *PTOPS* strategy. Using an adapted three-level (individual, interpersonal, and structural/environment) version of SEM, our study examines and categorizes factors to understand their influence and association with three outcomes along the LTBI care cascade: testing, treatment initiation, and treatment completion (Figure 1). To our knowledge, this is the first study we are aware of that uses SEM to identify and categorize independent factors significantly associated with the different steps articulated in the LTBI care cascade. Identifying and understanding these factors offers insight for where to implement modifications to increase the success of the strategy in this and other similar settings. Moreover, there is a gap in the research literature on identifying critical factors across the cascade; most previous research has focused on treatment initiation and treatment completion stages, and less is known about which factors are critical to the first step of the cascade: testing.(12,15) Through this study, a better understanding of acceptance of LTBI testing and treatment will be gained as well as the fruitfulness of using this particular framework for TB prevention programs of this kind in the future.

Figure 6. 1 Adapted Social Ecological Model levels of influence on three outcomes of the LTBI care cascade for PTOPS



Note: LTBI=latent TB infection; PTOPS=the Preventing TB Overseas Pilot Study; IGRA=interferon-gamma release assay

Study Setting

This study was conducted in Vietnam at a panel site designated to medically screen US-bound Vietnamese immigrant visa applicants. According to the World Health Organization (WHO), Vietnam is considered a high TB burden country with an incidence of 182 per 100,000 (116–263).(1) Estimates suggest approximately 30% of the adult population is latently infected with TB.(16) Vietnam is one of the top five countries of birth that contributes to TB cases in the United States.(6)

The Cho Ray Hospital Visa Medical Department (CRH VMD) in Ho Chi Minh City is the main panel physician site where US-bound immigrants undergo a required medical examination as part of their visa application. The medical examination is conducted in accordance with the CDC Technical Instructions which mandates the screening and treatment of TB disease.(17)

Diagnosing and treating LTBI is not mandatory because LTBI is a noninfectious condition. However, in Vietnam and other countries with a WHO-estimated tuberculosis disease incidence rate of ≥20 cases per 100,000 population, an IGRA is performed on children (2- 14 years of age) as part of the TB disease screening algorithm. CRH VMD screens approximately 1500 US-bound immigrant visa applicants per month for TB (*unpublished CDC data)*. This study marks the first time use of the 3HP regimen in Vietnam.

Methods

From September 2018 to October 2019, we conducted a prospective study at the CRH VMD to determine factors associated with acceptance across three points of the LTBI care cascade. Participants recruited for the study included immigrant visa applicants attending CRH VMD for their required medical examination.

For our study, eligibility criteria included immigrant visa applicants aged 12 years or older, non-pregnant, not breastfeeding, and living in Ho Chi Minh City province area as weekly clinic visits were required for direct observation for those who initiated treatment. During registration for the medical examination, eligible immigrant visa applicants were provided information about the *PTOPS* study and the benefits and risks for the IGRA and 3HP LTBI treatment. Visa applicants were informed that participation was voluntary; accepting or declining to participate at any point would not impact their visa application process or status; and testing and treatment for LTBI was also available in the United States. All immigrant visa applicants approached for recruitment were administered a short-structured questionnaire designed to help determine factors associated with their acceptance or decline of the IGRA or treatment.

Individuals who consented were provided an IGRA, the QuantiFERON Gold in Tube Test (QIAGEN GmbH, Hilden, Germany), liver function tests (LFTs), hepatitis B and C test, and a pregnancy test if indicated, during their required medical examination. Participants who were IGRA positive and did not have any signs or symptoms of TB, or any other condition (i.e., abnormal chest x-rays or HIV) requiring sputum smear and cultures to further assess for TB disease according to the required CDC algorithm(18), liver disorders, hepatitis B or C, were provided information on LTBI treatment and offered 3HP (12 weekly doses) by directly observed therapy (DOT) at the CRH VMD. For those immigrating to the United States prior to treatment completion, an option was provided for completing at least 8 doses of DOT at CRH

VMD with the remaining 4 or fewer doses by self-administration (SAT) in the United States. Acceptance of the test was defined as receiving a blood draw for the IGRA. Treatment initiation was defined as the taking of at least one dose of 3HP. Treatment completion was defined as the taking of 11/12 doses within 16 weeks as per CDC guidelines.(19)

Potential Predictors, Social Ecological Model, and the LTBI Care Cascade

Based on the review of the literature, we, *a priori,* identified independent potential predictors that previously demonstrated importance along points in the LTBI care cascade and were relevant within the context of the immigrant visa applicant medical examination. We additionally solicited input from experts overseeing TB immigrant screening programs to identify other factors potentially associated with the outcomes of uptake of LTBI testing or treatment initiation or completion.

We used an adapted version of SEM to systematically characterize and operationalize the selected factors. For this study context, the SEM was modified to accommodate 3-levels of influence: *individual, interpersonal, and structural or environmental* (Table 1).

At the individual level we included sex, age, employment or school enrollment, and prior bacille Calmette–Guérin (BCG) vaccination as potential factors.(8,20–22) The interpersonal level factors included being a identified as a contact with someone who had TB, knowing a family member with TB, and immigrating with family members. (11,22–26) The structural and environmental level factors included departure date for immigration to the United States as the study required a minimum of the first eight doses (2 months) to be completed by DOT in Vietnam and visa applicants for whom sputum smears and cultures are not required, including PTOPS participants, have up to six months to use their official medical clearance certification to immigrate to the United States. Travel time to the clinic, and travel mode were also included as structural and environmental factors.(11) We chose to measure travel time instead of distance to the clinic, as we had already controlled for distance through the eligibility criteria by limiting study participation to those living in Ho Chi Minh City province to ensure that DOT at the clinic was accessible. The time spent in travel to the clinic due to traffic can vary for participants In Ho Chi Minh City, and may influence decision-making. These independent factors are listed in Table 1 below. The factors were incorporated in a structured questionnaire

to assess their association with the three outcomes of interest. The questionnaire was administered to immigrant visa applicants by study staff at the time of recruitment.

Table 6. 1: SEM Levels(13) ***and Independent Factors Investigated in this Study for Association with LTBI Testing, Treatment Initiation, and Treatment Completion***

SEM Level and Description of type of factors that may influence decision making at each level	Independent Factors Investigated in this Study by SEM Level
Individual Knowledge, attitudes, beliefs, psychological, physical, or health characteristics, economic and/or education status.	-Sex -Age -Employment or in school -BCG vaccination
Interpersonal Formal and informal social relationships such as family, close friends, or community	- Identified contact with person with TB - Family member with TB -Immigrating with family
Structural and Environmental Government of organizational policies, accessibility to services including transportation, clinic hours	-Planned immigration date to the US -Travel time to the clinic -Mode of transportation (personal or public)

Note: SEM=Social-Ecological Model, BCG= bacille Calmette-Guérin

Data Analysis

All data were entered into the *PTOPS* database (*MS Access, 2016*) at the CRH VMD and shared with study investigators after removing participant identifiers. Participants' responses to the ten questions representing different SEM levels were analyzed using *R statistical software* (version 3.6.1) to determine factors significantly associated with three different models: (1) accepted an IGRA, (2) initiated LTBI treatment, and (3) completed LTBI treatment. Factors with an associated p value of <0.05 were considered significant. We used univariate analyses to estimate crude odds ratios to assess the relation between each individual factor and each of the three outcomes. We then conducted three separate multivariable logistic regression analyses loaded with all independent factors using a backwards elimination method to create the most parsimonious model for each of the outcomes. Because this was an exploratory analysis of independent variables, we did not adjust for multiple comparisons. Variables were assessed for multicollinearity for each model prior to conducting the regression.

Ethical Review

This study was approved by the Institutional Review Boards and Ethical Committees of the US Centers for Disease Control and Prevention, the Vietnam Ministry of Health, the University of California San Francisco, the Cho Ray Hospital, and the London School Hygiene and Tropical Medicine.

Results

Of 5311 immigrant visa applicants recruited to participate in PTOPS, 2438 (46%) and agreed to receive an IGRA to test for TB infection. A total of 452 participants tested positive and were eligible for LTBI treatment; among these, 304 (67%) initiated treatment, and 268 (88%) completed treatment (Table 2). These results are further described in *Paper 1 (Unpublished Manuscript)* and below for each of the outcomes of interest.

Table 6. 2: Characteristics of Study Participants in the Preventing Tuberculosis Overseas Pilot Study, Vietnam, 2018-2019*

Participant Characteristics (n=5311)		Recruited	Agreed to an IGRA**	IGRA Processed±	Eligible for 3HP	Initiated 3HP LTBI Treatment**	Completed 3HP LTBI Treatment**
Total		5311	2438	2276	452	304	268
Sex							
	Female	2888 (54%)	1350 (55%)	1304 (57%)	259 (57%)	170 (56%)	152 (57%)
	Male	2423 (46%)	1088 (45%)	972 (43%)	193 (43%)	134 (44%)	116 (43%)
Age (years)							
	12-17	729 (14%)	369 (15%)	365 (16%)	27 (6%)	18 (6%)	17 (6%)
	18-35	1527 (29%)	773 (32%)	749 (33%)	109 (24%)	69 (23%)	62 (23%)
	≥36	3055 (58%)	1296 (53%)	1162 (51%)	316 (70%)	217 (71%)	189 (71%)

Note: LTBI=latent TB infection; IGRA=interferon-gamma release assay

** Main outcomes of the PTOPS study presented in Paper 1: Unpublished Manuscript*

***Represents the three outcomes of interest in the cascade*

±Not all participants who received an IGRA had results available as some participants were excluded from the study because of a medical ineligibility or they withdrew from the study before their IGRA was processed by the lab

Table 6. 3: Characteristics of Study Consenters and Non-Consenters in the Preventing Tuberculosis Overseas Pilot Study, Vietnam, 2018-2019*

Participant Characteristics	Recruited	Consented n (%)	Not Consented	*p value*
Total	5311	2438	2873	
Sex				
Female	2888	1350 (47%)	1538 (53%)	*p=.18*
Male	2423	1088 (45%)	1335 (55%)	
Age				
12-17**	729	369 (51%)	360 (49%)	*p<.001*
18-35	1527	773 (51%)	754 (49%)	
≥36	3055	1296 (42%)	1759 (58%)	
Currently employed/ in school				
Yes	3352	1629 (49%)	1723 (51%)	*p<.001*
No	1959	809 (41%)	*1150 (59%)*	
BCG vaccination				
Yes	4984	2316 (46)	*2668 (54%)*	*p=.001*
No/Do Not Know	327	122 (37)	205 (63%)	
Know someone with TB				
Yes	231	139 (60%)	*92 (40%)*	*p<.001*
No/Do Not Know	5080	2299 (45%)	*2780 (55%)*	
Immigrating with family				
Yes	4301	1962 (46%)	2339 (54%)	*p=.39*
No	1010	476/ (47%)	534 (53%)	
Anticipated date for immigration to the United States				
≥2 months/Do Not Know	3914	1964 (50%)	*1950(50%)*	*p<.001*
<2 months	1397	474 (34%)	*923 (66%)*	
Travel time to the clinic				
≤45 min	3712	1696 (46%)	*2016 (54%)*	*p=.63*
>45 min	1599	742 (46%)	*857 (54%)*	
Transport mode (private vehicle)				
Yes	3444	1641/ (48)	*1803 (52%)*	*p<.001*
No	1867	797/ (43)	*1070 (57%)*	

Comparison of Study Consenters and Non-Consenters

In this study, those who consented to participate agreed to the first step of the study to receive an IGRA. Table 6.2 depicts the differences between study consenters and non-consenters. 47% of all females and 45% of all male visa applicants recruited for the study agreed to consent to participate in the study. Adult visa applicants aged 35 years or younger were more likely to consent compared to those older than 35 years of age (p <.001). Those who were

currently enrolled in school or had a job were more likely to consent to the study than those who were not in school or employed. Those who were BCG-vaccinated (p=.001) and those who knew someone with TB (p<.001) were more likely to agree to participate in the study compared to those who were not BCG-vaccinated or did not know someone with TB. Those who did not know when they were immigrating to the US or were planning to immigrate after two months were more likely to participate (p<.001) than those who were planning to immigrate within two months of their visa application medical examination. Additionally, those who had their own private mode of transportation were more likely to consent to the study (p<.001) compared to those who had to take private transportation.

Step 1: Agreed to an IGRA to test for LTBI, N= 5311

For the first step of the cascade, 2438 (46%) of 5311 immigrant visa applicants recruited agreed to receive an IGRA to test for TB infection. One hundred and forty-three (6%) of these participants, aged 12-14 years, would have received a routine IGRA as part of their required medical examination but they were included in the analysis because they agreed to receive an IGRA as the first step of the LTBI care cascade in this study. More females (n=1350, 55%) than males (n=1088, 45%) and more people ≥36 years of age (n=1296, 53%) compared to those 12-17 years of age (n=369, 15%) and those 18-35 years of age (n=773, 32%) agreed to an IGRA.

<u>Univariate analyses with individual, interpersonal, and structural/environmental predictors</u>

In the univariate analysis, *individual* level predictors significantly associated with receiving an IGRA include: those 18- 35 years of age compared to those ≥36 years of age (odds ratio (OR)=0.7; 95% confidence interval (CI) 0.6-0.8); current employment or school enrollment (OR =1.3; 95%CI 1.2-1.5); and having been vaccinated with BCG (OR=1.5; 95%CI 1.2-1.8). Knowing a family member or close friend who had TB (OR=1.8; 95%CI 1.4-2.4), was the only *interpersonal* factor significantly associated with agreeing to having an IGRA. *Structural and environmental* factors significantly associated with agreeing to a test include having a private mode of transportation (OR=1.2; 95%CI 1.1-1.4) and planning to immigrate to the United States in ≥2 months (or dates not determined) (OR=2.0; 95%CI 1.7-2.2).

Sex (an individual factor), being a contact to someone with TB, immigrating with family

members (interpersonal factors), and travel time to the clinic (a structural/environmental factor) were not significantly associated with receiving an IGRA in the univariate analyses.

Multivariable analyses with individual, interpersonal, and structural/environmental predictors

For *individual* level factors in the adjusted model, the odds of accepting the test were 1.1 times greater for females compared to males (95%CI 1.0-1.3) and 1.3 times higher for those aged 18-35 compared to those ≥36 years of age (95%CI 1.3-1.7). For those currently employed or enrolled in school, the odds were 1.2 times greater for receiving an IGRA than for those who were not (95%CI 1.1-1.4). The odds for test acceptance were also 1.3 times higher for those who reported having the BCG vaccination compared to those reporting not having had the BCG vaccination (or not knowing if they did) (95%CI 1.1-1.7).

In terms of *interpersonal* factors, the odds of having an IGRA were 2 times higher for those who had a family member or close friend with TB compared to those who did not (95%CI 1.5-2.7); and 3.3 times higher for agreeing to an IGRA for those who reported not being a contact of someone with TB compared to those who did report being a contact to someone with TB (95%CI 1.6-10). Immigrating with family members was removed from the adjusted model as it was not significantly associated with agreeing to having an LTBI test at $p<0.05$.

For *structural and environmental* factors, the odds were 2 times higher for agreeing to an IGRA for those who planned to immigrate to the United States after two months compared to those who planned to immigrate in less than two months (95%CI 1.7-2.2). Additionally, the odds for agreeing to an IGRA were 1.2 times higher for those who had a private mode of transportation in Ho Chi Minh City compared to those who did not (95%CI 1.1-1.4) Travel time to the clinic was not significantly associated with test acceptance.

Table 6. 4 Factors associated with LTBI testing, n=5311

Independent Variable	*Received IGRA n (%)*	Crude Odds Ratios (OR)		Adjusted* Odds Ratios (aOR)	
		OR 95% CI	*p value*	*aOR 95% CI*	*p value*
Individual Level Factors					
Sex					
Female	1350/2888 (47)	1.1 (1.0-1.2)	*p=.18*	1.1 (1.0-1.3)	*p=.03*
Male (Ref.)	1088/2423 (45)				
Age					
12-17**	369/729 (51)	1.0 (0.8- 1.2)	*p=1.0*	1.0 (0.8-1.2)	*p=.65*
18-35 (Ref.)	773/1527 (51)				
≥36	1296/3055 (42)	0.7 (0.6- 0.8)	*p<.001*	0.8 (0.6-0.8)	*p<.001*
Currently employed/ in school					
Yes	1629/3352 (49)	1.3 (1.2-1.5)	*p<.001*	1.2 (1.1-1.4)	*p=.001*
No (Ref.)	809/1959 (41)				
BCG vaccination					
Yes	2316/4984 (47)	1.5 (1.2-1.8)	*p=.001*	1.3 (1.1-1.7)	*p=.02*
No/Do Not Know (Ref.)	122/327 (37)				
Interpersonal Level Factors					
Know family member with TB					
Yes	139/231 (60)	1.8 (1.4-2.4)	*p<.001*	2.0 (1.5-2.7)	*p<.001*
No/Do Not Know (Ref.)	2299/5080 (45)				
Contact of someone with TB					
Yes	9/28 (32)	0.6 (0.3-1.2)	*p=.15*	0.3 (0.1-0.6)	*p=.003*
No (Ref.)	2426/5283 (46)				
Immigrating with family*					
Yes	1962/4301 (46)	0.9 (0.8-1.1)	*p=.39*		
No (Ref.)	476/1010 (47)				
Structural and Environmental Level Factors					
Anticipated date for immigration to the United States					
≥2 months/Do Not Know	1964/3914 (50)	2.0 (1.7-2.2)	*p<.001*	2.0 (1.7-2.2)	*p<.001*
<2 months (Ref.)	474/1397 (34)				
Travel time to the clinic					
≤45 min	1696/3712 (46)	1.0 (0.9-1.1)	*p=.63*	0.9 (0.8-1.0)	*p=.07*
>45 min (Ref.)	742/1599 (46)				
Transport mode (private vehicle)					
Yes	1641/3444 (48)	1.2 (1.1-1.4)	*p<.001*	1.2 (1.1-1.4)	*p=.002*
No (Ref.)	797/1867 (43)				

Note: LTBI=Latent TB Infection; IGRA=Interferon-Gamma Release Assay; CI= Confidence Interval; Ref.=Reference

**Immigrating with family not significantly associated and removed from the model.*

*** Participants age 12-14 routinely receive an IGRA as part of the medical examination; those who consented and received the IGRA for the additional purpose of participating in this study were included in this analysis*

Step 2: Treatment Initiation, n=452

For step 2, treatment initiation, of 452 IGRA positive participants eligible for 3HP, 304 (67%) initiated treatment (took at least one dose of 3HP treatment). Of these more females (n=170, 56%) initiated treatment compared to males (n=134, 44%). More people aged ≥36 years and older (n=217,71%) initiated treatment than those aged 12-17 (n=18, 6%) and 18- 35 (n=69, 23%).

Univariate analyses with individual, interpersonal, and structural/environmental predictors

In the univariate analysis, no *individual* level predictors were significantly associated with 3HP treatment initiation.

Immigrating with family members was the only *interpersonal* factor significantly associated with initiating treatment (OR=2.1; 95%CI 1.3-3.6) and planning to immigrate to the United States in ≥2 months (or dates not determined) (OR=3.7; 95%CI 2.3-6.0) was the only significant *structural or environmental* factor associated with initiating treatment.

Multivariable analyses with individual, interpersonal, and structural/environmental predictors

In the multivariable analysis both immigrating with family members (Adjusted OR (aOR)=2.0; 95%CI 1.2-3.4) and immigrating to the United States in ≥2 months (aOR=3.6; 95%CI 2.2-5.8) remained significantly associated with treatment initiation.

Table 6. 5: Factors Associated with Treatment Initiation, n=452

Independent Variable	*Initiated LTBI Treatment n (%)*	Crude Odds Ratios (OR)		Adjusted* Odds Ratios (aOR)	
		OR 95% CI	*p value*	*aOR 95% CI*	*p value*
Individual Level Factors					
Sex					
Female	170/259 (66)	0.8 (0.6-1.3)	*p=.40*		
Male (Ref)	134/193 (69)				
Age					
12-17	18/27 (67)	1.2 (0.5-2.8)	*p=.75*		
18-35 (Ref.)	69/109 (63)				
≥36	217/316 (69)	1.3 (0.9-2.0)	*p=.31*		
Currently employed/ in school					
Yes	190/282 (67)	1.0 (0.7-1.5)	*p=.95*		
No (Ref.)	114/170 (67)				
BCG vaccination					
Yes	286/424 (67)	1.2 (0.5-2.6)	*p=.73*		
No/Do Not Know (Ref.)	18/28 (64)				
Interpersonal Level Factors					
Know family member with TB					
Yes	25/32 (78)	1.8 (0.8-4.3)	*p=.17*		
No/Do Not Know (Ref.)	279/420 (66)				
Contact of someone with TB					
Yes	0/1 N/A	1.0 (1.0-1.0)	*p=.15*		
No (Ref.)	304/451 (67)				
Immigrating with family					
Yes	268/383 (70)	2.1 (1.3-3.6)	*p=.004*	2.0 (1.2-3.4)	*p=.01*
No (Ref.)	36/69 (52)				
Structural and Environmental Level Factors					
Anticipated date for immigration to the United States					
≥2 months/Do Not Know	265/361 (73)	3.7 (2.3-6.0)	*p<.001*	3.6 (2.2-5.8)	*p<.001*
<2 months (Ref.)	39/91 (43)				
Travel time to the clinic					
≤45 min	236/347 (68)	1.2 (0.7-1.8)	*p=.53*		
>45 min (Ref.)	68/105 (65)				
Transport mode (personal vehicle)					
Yes	227/332 (68)	1.2 (0.8-1.9)	*p=.40*		
No (Ref.)	77/120 (64)				

Note: LTBI=Latent TB Infection; IGRA=Interferon-Gamma Release Assay; CI= Confidence Interval; Ref.=Reference

**Sex, age, employment/school, BCG vaccination, family member with TB, household TB contact, travel time to clinic, and transport mode were not significantly associated and removed from the model*

Step 3: Treatment Completion, n=304

For Step 3, treatment completion, of 304 participants who initiated treatment, 268 (88%) completed treatment. More females (n=152, 57%) completed treatment compared to males (n=116, 43%). More people ≥36 years of age (n=189, 71%) completed treatment compared to those 12-17 years of age (n=17, 6%) and those 18-35 years of age (n=79, 26%).

In both the univariate and multivariable analysis no factors assessed were significantly associated with treatment completion.

Table 6. 6: Factors Associated with Treatment Completion, n=304

Independent Variable	Treatment Completion *n (%)*	Crude Odds Ratios (OR) *OR 95% CI*	*p value*	Adjusted* Odds Ratios (aOR) *aOR 95% CI*	*p value*
Individual Level Factors					
Sex					
Female	152/170 (89)	1.3 (0.7-2.6)	*p=.45*		
Male (Ref.)	116/134 (87)				
Age					
12-17	17/18 (94)	1.9 (0.2-16.7)	*p=.62*		
18-35 (Ref.)	62/69 (90)				
≥36	189/217 (87)	0.8 (0.3-1.8)	*p=.56*		
Currently employed/ in school					
Yes	166/190 (87)	0.8 (0.4-1.7)	*p=.58*		
No (Ref.)	102/114 (90)				
BCG vaccination					
Yes	253/286 (89)	1.5 (0.4-5.6)	*p=.51*		
No/Do Not Know (Ref)	15/18 (83)				
Interpersonal Level Factors					
Know family member with TB					
Yes	20/25 (80)	0.5 (0.2-1.4)	*p=.19*		
No/Do Not Know (Ref.)	248/279 (89)				
Contact of someone with TB*					
Yes	NA 0				
No (Ref.)					
Immigrating with family					
Yes	236/268 (88)	0.9 (0.3-2.8)	*p=.89*		
No (Ref.)	32/36 (89)				
Structural and Environmental Level Factors					
Anticipated date to immigrate the United States					
≥2 months/Do Not Know	236/265 (89)	1.8 (0.7-4.4)	*p=.21*		
<2 months (Ref.)	32/39 (82)				
Travel time to the clinic					
≤45 min	208/236 (88)	1.0 (0.4-2.3)	*p=.98*		
>45 min (Ref.)	60/68 (88)				
Transport mode (private vehicle)					
Yes	202/227(89)	1.3 (0.6-2.9)	*p=.44*		
No (Ref.)	66/77 (86)				

Note: LTBI=Latent TB Infection; IGRA=Interferon-Gamma Release Assay; CI= Confidence Interval; Ref.=Reference

**Household contact with someone with TB excluded in analysis*

No variables were significantly associated with the Outcome 3; all were removed from the model.

Discussion

In this study, we prospectively observed participants and determined key factors associated with acceptance of different steps of the LTBI care cascade in the context of an official medical screening program for immigration. The proportion of acceptance across the cascade varied with 46% of those approached agreeing to receiving an IGRA; 67% of those eligible initiating 3HP LTBI treatment; and 88% completing the treatment. In the multivariable models, *individual level factors* including female sex, age 18-35 years, BCG vaccinated, and currently employment or enrolled in school enrollment status were only significantly associated with Step 1, acceptance of the IGRA to test for LTBI. *Interpersonal level factors* were significantly associated with both steps 1 and 2 of the cascade. For step 1, knowing a family member with TB and reporting not being a contact to a TB case influenced the acceptance of the test. For Step 2 (initiating treatment), immigrating with family members was the only significantly associated interpersonal factor. For both step 1 and step 2, one *structural and environmental level factor,* planning to immigrate after 2 months, was significantly associated. Additionally, having a private mode for transportation was significantly associated with agreeing to an IGRA, but not the other outcomes. Travel time to clinic was not significantly associated with any of the outcomes of interest across the LTBI care cascade.

Our study provides several unique practical and theoretical contributions. It marks the first time offering of voluntary LTBI testing and 3HP treatment to US-bound immigrant visa applicants undergoing the pre-arrival overseas medical examination. It is also the first study we are aware of which uses SEM to identify and categorize independent factors significantly associated with the different steps of the LTBI care cascade. Guided by SEM, we chose potential predictors that were expected to vary across the three steps of interest in the cascade. Overall, our results showed using the SEM framework was useful in delineating which factors were most critical at each step of the cascade. Through this approach, we see individual, interpersonal, and structural factors were most critical in the first stage of the cascade, testing, and less so moving to the second stage of treatment initiation, to no factors in these domains emerging as predictors for the treatment completion stage. Most studies focus on identifying factors

associated with treatment initiation and treatment completion, missing the important first step of the cascade, testing, where the greatest losses occur. In fact, through the SEM framework, we demonstrated that the first step which experiences the greatest losses is also the most sensitive to individual, interpersonal, and structural factors that determine losses or acceptance in the cascade.

Individual Factors

When looking across the cascade in this study, the point where the greatest loss of participants occurred is at the first step of IGRA acceptance (47%). This first step is also the only one where we found *individual level factors* significantly associated with acceptance of testing. Systematic reviews have pointed to the inconsistencies of demographic and individual level factors in predicting LTBI testing and treatment outcomes across studies.(8) These inconsistent findings perhaps suggest that individual level predictors are study and context specific. Many TB studies have pointed to the differences in health seeking behaviors of males compared to females and of different age groups.(27,28) It is unclear if and how these differences influenced the acceptance of the test in our study. However, it is important to note that although females and those under the age of 35 were more likely to accept a test for LTBI in our study, epidemiologically men are more likely to have TB disease and LTBI prevalence is more likely to be associated with increasing age.(1,16)

Current employment or school enrollment was also found to be significantly associated with agreement to have an IGRA. One possible explanation is that a test for TB infection is a requirement for some organizations and institutions and thus may be a motivation for those with a job or in school to receive a test and certification.

BCG vaccination status was significantly associated with consenting and acceptance for a test for LTBI.(20,29) However, our study found those who reported having BCG vaccination were more likely to accept the test compared to those who did not have or recall having the BCG vaccine. This is contrary to other studies which have reported that those with a BCG vaccination were less likely to accept a test result or initiate treatment as they felt protected from TB (although protection from the vaccine wanes over time).(30,31). While further assessment is required to understand the rationale behind this finding, it is important to consider that the immigrant visa applicant's primary goal for the medical examination is to

receive clearance to immigrate to the United States. There is a possibility that those who were not BCG vaccinated may have perceived that they were at higher risk for TB and perhaps concerned that additional screening could lead to a potential delay in their medical clearance (although participants were repeatedly informed that their IGRA result would not affect their visa application process). Alternatively, BCG vaccination may be associated with a higher acceptance of medical interventions in general.

We found no individual level factors associated with testing or treatment initiation or completion, suggesting individualized targeted messaging about LTBI might be more necessary at the first step of the cascade of identifying TB infection in this context. Targeted messaging towards men and those ≥35 years of age may be warranted to ensure that those who would benefit from treatment are included in the critical initial step of the cascade. Additionally, improved messaging about the medical examination process and on BCG may help increase uptake of the IGRA.

Interpersonal Factors

In terms of *interpersonal factors,* knowing a family member or close friend with TB was significantly associated with the receiving the IGRA. This finding is compatible with other LTBI studies potentially suggesting those who are directly impacted or who have witnessed the consequences of TB disease are more likely to be concerned with their infection status.(32) However, counterintuitive to this finding is that those who additionally reported being a contact with someone with TB were less likely to agree to receive an IGRA. The number reporting to be a household contact was small (n=28), but this may be due to underreporting as immigrant visa applicants may be reluctant to admit to being a TB contact since it is a reportable condition as part of the official medical examination for US immigration. Although, the ‘TB contact’ classification does not prohibit one from immigrating, immigrant visa applicants may still be concerned that it comes with a recommendation for a follow-up visit with the health department in the United States. While our study was not able to further assess why this factor influenced the uptake of testing, similar to those without a BCG vaccination, one potential explanation is that these people may perceive that their risk for LTBI is actually high and this may have a deterrent effect on the acceptance of the IGRA, particularly in the context of immigrant screening. While further assessment of perceptions is required to draw conclusions,

it is interesting to note that Lévesque et al.'s study among refugees in Canada found similar results that those who perceived TB to be a severe disease were less likely to accept a test for TB infection.

Immigrating with family members was the only *interpersonal* factor significantly associated with initiating treatment. In a systematic review of qualitative literature on TB treatment, Munro et al identified the role of the family and community as an influence on TB treatment-taking behavior. The influence of family in TB treatment decision-making has also been reported in other qualitative literature specifically focused on Vietnamese populations.(27,33) This influence can be bi-directional. Families often serve in an encouraging and supportive role for treatment or are influential in declining or discontinuing treatment.[10] Persons immigrating with their families may be concerned about protecting against future cases of TB. Our study was not able to capture the reasons why those immigrating without family members were less likely to initiate treatment, but often these people are waiting to be reunited with family members in the United States and perhaps are concerned about potential delays in traveling to the United States.

Additional messaging on how TB is transmitted and how preventive treatment can protect the individual as well as their families and communities could be stressed to improve uptake of both testing and treatment.

Structural and Environmental Factors

The *structural and environmental level* factor, having a private mode for transportation was significantly associated for agreeing to an IGRA, but not the other outcomes. It is unclear why this was associated with testing, but one potential reason may be that those who had to take public transportation were concerned about the additional time required for enrolling in the study and being screened for the LTBI which could have conflicted with their transportation schedule. Travel time to the clinic was not significantly associated with any of the outcomes of interest across the LTBI care cascade, this may have been because we controlled for travel distance in the study inclusion criteria by limiting participation to those living in Ho Chi Minh City province.

Planning to immigrate after two months, was the most significantly associated predictor of both testing and treatment initiation. This comes as no surprise as our study required a minimum of 8 weekly DOT doses of 3HP at the CRH VMD prior to immigrating to the United States. When we developed our study, CDC recommended weekly DOT for 3HP. However, since then, SAT for 3HP is now recommended as a treatment option by both WHO and CDC. Shortening the requirement of DOT doses can potentially increase the number of people willing to get tested and subsequently initiate and complete treatment. This may remove barriers for those who have to take public transportation to the clinic as well as for those who plan on immigrating to the United States in less than two months after receiving their medical clearance.

No predictors in our model were found to be significantly associated with treatment completion. The small sample size (n=304) and the high rate of treatment completion and the subsequent limited variation in the outcome (88% completion v 12% non-completion) could potentially explain the challenges in finding significant predictors for completion that were measured in our study.

Constraints and Limitations

Despite the contributions of this study, there were some logistical constraints and limitations. First since the overall goals for PTOPS were to assess the feasibility and acceptability of voluntary LTBI testing and treatment during the required visa application medical examination, this study was conducted in a real-world setting at CRH VMD where over a hundred persons are seen each day as part of their visa application process. Our study design and setting were not conducive for conducting in-depth examinations of immigrant visa applicants' perceptions around TB and LTBI. Because of the operational requirements of the clinic, there was a need to keep the study questionnaire brief to ensure that all participants were able to get through their required medical examination efficiently without disrupting the clinic flow. The scope of the questionnaire was also necessarily limited because of the intensive interviews that immigrant visa applicants are subject to as part of the official immigration process. There were concerns that immigrant visa applicants may not want to participate in the study if the questionnaire process was perceived to be long or if questions seemed sensitive in nature. For example, additional factors that have been shown to influence treatment outcomes, such as substance and excessive alcohol use, were not included as potential predictors for our study

as these are considered inadmissible conditions and could impact the immigrant visa status. Additionally, individual demographic questions about income and occupation were also not asked as they could be deemed sensitive in nature in the context of an official immigration examination setting. Therefore, we were not able to make any judgements about differences across the cascade for any other factors than the ones that were included in our models. Second, although it was stressed that acceptance of the IGRA and treatment was voluntary, there is the possibility some immigrants felt the need to accept either out of social desirability or for fear that declining might affect their visa status (although given that 54% declined an IGRA most felt free to do so). Third, the decreasing sample size moving from step 1 to 3 may have contributed to the identification of fewer predictors associated with Step 2 and then subsequently Step 3. Finally, another limitation of this study is that it was only conducted at one site, thus, the results may not be generalizable to other sites and populations; however, this is in line with the important conclusion of this study that predictors for LTBI testing and treatment may be context specific.

Conclusion

To contribute towards the END TB strategy, interventions aimed at treating LTBI require high numbers of people to first be identified with infection and then initiate and complete treatment. Understanding factors associated with each step along the LTBI care cascade can help in the design and improvement of interventions to increase uptake of LTBI testing and treatment. By incorporating the SEM to characterize potential predictors, we see that uptake of LTBI testing, treatment initiation and completion are influenced differently by individual, interpersonal, and structural factors across different points of the cascade. Understanding these differences allow for a targeted approach to improving the intervention. While our results are context and setting specific, moving forward, similar interventions conducted as part of migrant screening should consider more targeted messages to address *individual level* factors at the first step of the cascade to increase testing uptake. Improved messaging and further understanding of how interpersonal relationships influence both testing and treatment initiation should be considered. Additionally, structural barriers that address the time constraints associated with immigration travel plans and the taking of treatment can be addressed through alternative options to DOT.

Future qualitative studies to assess some of our findings could provide more in-depth insight on how to increase the numbers people at all points of the cascade. Other programs targeting immigrant populations can incorporate and improve upon this current framework and methodology to better understand how to implement LTBI test and treatment programs.

Disclaimer

The findings and conclusions of this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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7. Chapter 7: Overall Discussion and Conclusions

7.1 Overall Discussion

Despite seeing a continuing annual decline in TB cases, the United States is still far from achieving its TB elimination goal of <1 case per million. Moreover, the rate of decline has been slowing. To regain momentum towards elimination, the reservoir of LTBI in non-US-born populations must be addressed. This thesis explores the implementation of an innovative intervention designed to reduce LTBI in a non-US-born population. Taken as a whole, my thesis serves as an original contribution by providing empirical evidence on the adoption and acceptability of voluntary LTBI testing and 3HP treatment offered to US-bound immigrants during the *pre-arrival* overseas medical examination process. Using an implementation research approach my study was conducted in a real-world setting at a panel physician site in Vietnam. The study identified a high prevalence of LTBI infection, particularly with the adult immigrant visa applicant population in Vietnam aged 18 and above (24%), who would otherwise have been missed as they generally do not receive an IGRA as part of the required medical examination. This suggests that expanding IGRA testing to adults (particularly those coming from high TB burden countries) can identify a high proportion of immigrants who have LTBI. Additionally, the study achieved similar results for LTBI treatment initiation, but higher completion compared to current US *post-arrival* efforts.(1) In my study, 67% of eligible IGRA-positive participants initiated treatment and 88% completed treatment, resulting in 59% of all eligible participants completing treatment. Comparing these results with a recent assessment of the recommended US *post-arrival evaluation* for immigrants at risk for TB (2013-2016) shows that this approach is as effective, if not more. Overall, 36% of immigrants and refugees at risk for TB did not complete a US post-arrival evaluation for TB and LTBI, and among those who did and were recommended for LTBI treatment, 69% initiated treatment, and only 40% completed treatment.(1)

When looking across the LTBI cascade of care, the greatest loss of participants occurred at the first stage of testing. Using the SEM to categorize factors associated with acceptance across the LTBI care cascade, the study found that individual level factors (males, older age,

not employed or enrolled in school, and not BCG vaccinated) are significantly associated with declining the offer of the test. To improve the numbers of people who complete the LTBI care cascade targeted approaches to males, those older in age, and those not vaccinated, or employed or enrolled in school should take place. Additionally, the United States should consider routinely offering the IGRA to all immigrant visa applicants coming from high TB burden countries. Removing structural/environmental barriers such as the requirement of eight weeks of DOT which may interfere with people's busy schedules and travel plans can potentially also increase the number of people who agree to the test and initiate and complete treatment, if indicated. This was further supported by the fact that the leading reported reason for declining the test was that people 'felt too busy or stressed to take the test and participate in the study' (31%). Moreover, the leading reported reason for declining treatment if IGRA positive, was that visa applicants who declined felt there was 'not enough time and that they planned to depart for the US immediately after receiving the visa' (67%).

My study demonstrated that using the overseas medical examination to provide voluntary testing and treatment of LTBI in a high-burden country yields the identification of those with infection and can result in high treatment initiation and completion. Thus, this approach should be considered as a potential strategy to address LTBI in US-bound immigrants and to advance US TB elimination efforts. The adoption and acceptance of the testing and treatment were by the immigrant visa applicants were similar to US post arrival efforts, but treatment completion was much higher than what has been achieved by U.S. post-arrival efforts. The use of this strategy should be further evaluated as an addition and/or potential replacement for post-arrival testing and treatment for LTBI and as a complement to other domestic strategies to address LTBI in immigrant populations.

7.2 Strengths and Limitations

Strengths

The primary strength of this research project is that it is the first to provide empirical evidence on a strategy that has been repeatedly called for as a potential option to help the United States achieve its goal of TB elimination. It is also the first study to offer and use 3HP at a panel site,

as well as in the country of Vietnam. The study findings are also useful for other low TB incidence countries with migrant screening programs. Using an implementation research (IR) framework, this study was developed from start to finish with the collection of primary data for the purposes of the DrPH. IR is a relatively new field with research typically conducted in a real-world setting with the goal of providing evidence to guide policies and decisions about the implementation and the scaling up of an intervention under routine conditions. Although this thesis only focuses on a few components of the IR framework, using an IR framework allows for consideration of multiple factors that can influence the success of an intervention during the design phase as well can be used to evaluate the implementation and outcomes of an intervention. This project was incorporated in the routine operations of the CRH VMD during the overseas medical examination for US-bound immigrants. This real-world setting allowed for an understanding of the acceptability of this intervention and what barriers and challenges would need to be addressed if scaled-up.

Another strength of this study is that unlike most of other studies looking at the uptake and completion of LTBI treatment, this study starts at the beginning of the LTBI care cascade, testing. Many studies just focus on the end of the cascade, reporting on LTBI initiation and completion. While these studies offer insight into factors associated with treatment initiation and completion, just focusing on the end misses the earlier part of the cascade where a substantial number of losses begin with those not willing to be tested.(2,3) As shown by this study, the early phase is where most of the losses occurred, intervening at this phase may result in an increase of the numbers of people completing the entire cascade. Moreover, the study also marks the first use of SEM, that I am aware of, to categorize potential predictors across the LTBI care cascade. Categorizing factors according to SEM levels allows for understanding how to target and improve the intervention across the different steps of the cascade to potentially increase the numbers of people who complete treatment. This study was also able to capture reasons for decline at each step of the cascade from all visa applicants who were approached for the study, allowing for understanding on how best to modify the intervention to improve uptake. Further studies are required to see if targeted messaging and modification of the intervention based on this study’s findings will actually result in improvements in total number of people completing treatment.

Limitations

There are several limitations to this research. As mentioned, the intent of the study was to evaluate the implementation of voluntary LTBI testing and 3HP treatment in a new and "real-world" setting, the required overseas immigrant visa application medical examination. However, because of the first time use of the 3HP treatment regimen in Vietnam, the project was still considered a research study and not programmatic implementation. As such, certain aspects required for a research study (i.e., eligibility; recruitment and consent; and data collection) could have potentially influenced some visa applicants' decisions to participate in the study.

Eligibility. Study eligibility was limited to those in the HCMC area to control for distance being a participation barrier for those outside of the HCMC area since attending weekly DOT at the clinic was required for those who accepted treatment. This potential selection bias also might suggest that results may not be generalizable to other Vietnamese communities that may be from rural or other geographical areas of the country which may have different cultural practices and or potential risks for exposure to TB.

Recruitment and Consent Process. Because of the first time use of 3HP, a lengthy and very time-consuming consent process (ranging from 30-45 minutes depending on participant questions) was required for participation in the study. This process potentially impacted the study in two ways. First, because of the lengthy consent process coupled with the need for visa applicants to complete their required medical examination in a timely fashion, study recruitment was conducted only in the morning shift of the clinic operations. While the vast majority of visa applicants arrive at the clinic in the morning hours, this meant that visa applicants who arrived at the clinic in the afternoon were not represented in the sample. This recruitment strategy potentially could have contributed to selection bias. There may be differences, such as occupation or access to transportation, between those who arrived in the morning hours compared to those in the afternoon hours. These differences in occupation and

transportation access could be associated with socioeconomic differences which in turn have implications for study participation, LTBI positivity rates, and willingness to accept and complete LTBI treatment. Secondly, the actual length of the consent process could have also been a deterrent to study participation. The study design included a shorter consent process which mostly focused on the IGRA and LTBI testing and treatment in general, with more information on 3HP provided later only for those who were IGRA positive. However, because of the numerous partners involved in the study, multiple IRB reviews occurred with one suggesting providing all testing and 3HP treatment information in the beginning; this request made the consent process lengthy. Additionally, because of the consent process, it was challenging to discern if recruited visa applicants who declined to participate did so because they were not interested in receiving an IGRA or if they were just not interested in participating in a lengthy study. Conversely, because the study was conducted during the official required visa application medical examination, some participants may have felt that their visa application could be negatively impacted if they did not agree to a LTBI test or treatment despite being told that participation was voluntary and their willingness to participate would not affect their visa status. Thus, in this case there was a chance that participation in the study and acceptance of the test or treatment could have been impacted by social desirability bias such that those who participated may have felt that it was “advantageous” to do so in the context of their visa application.

Data Collection. For the study objective looking at factors associated with acceptance across the LTBI care cascade, there were limitations to the type of questions asked and length of the questionnaire used to elicit information from the study participants. Reasons for the limitations were because of the study setting, a busy panel site, and the target population, immigrant visa applicants. The CRH VMD panel sees approximately 80-100 visa applicants per day who flow through the clinic in a systematic way. The intent of the study was not to disrupt this flow, but to incorporate the study intervention within it. As such, the length of the questionnaire had to be limited to allow visa applicants a chance to complete their examination in a timely manner. Additionally, because this study was conducted as part of an official process for a visa application, considerations for questions that might be sensitive or impact the visa application were not included in assessment. For example, potential predictors for LTBI treatment initiation and completion such as substance use or excessive alcohol use were not included in the

participant questionnaire. These conditions are “inadmissible” if identified during the medical examination process and can negatively affect a visa application. Occupation, income, and education were also excluded from the variable list for this study. Prior to study implementation, in April 2017, President Trump stated his intention to institute Merit-based Immigration Reform (www.whitehouse.gov/issues/immigration). In his proposal, he suggested that immigrant visa applicants’ income, occupation, and educational backgrounds would be considered, and only highly paid skilled immigrants would receive immigration visa approval. Thus, these variables were deemed too sensitive in nature and could potentially cause undue stress and ultimately undermine participation, initiation, and/or completion of LTBI treatment, if included in the study questionnaire. Although there is some evidence of the association of the excluded factors with uptake and completion of LTBI treatment, my study attempted to identify a significant portion of the variance, not all of it.

Information Bias. In addition to the limitation to the types of questions that could be asked, there is always the possibility of information bias for the data collected, although attempts were made to minimize this type of bias. Information bias can include *missing data, recall bias, misclassification bias, and observer bias*. Because this was a prospective cohort study, we were able to ensure that there was no missing data compared to a retrospective study. Weekly uploads of data and in-depth quarterly reviews allowed for data quality assurance. Because of the self-report format for some of the study questionnaires, there is the potential recall bias leading participants to provide inaccurate responses due to misunderstanding the question or not remembering events accurately. For example, participants may not have remembered receiving a BCG vaccination as this generally occurs in childhood. Additionally, there is concern that some of the responses may also be influenced by *social desirability,* particularly since the study was implemented during the official visa application medical examination. Visa applicants may have not felt comfortable providing accurate responses as they may have thought their responses would influence their visa application status. To mitigate *misclassification bias*, where possible, data collected for the study to determine visa applicant eligibility for 3HP was obtained from extracting information from the official medical examination forms. Results from the medical examination undergo rigorous review with multiple checks to ensure that accurate information is reported. While there is still potential that visa applicants could have been misclassified as IGRA positive, the laboratory processing the

IGRA is ISO accredited and goes through continuous quality assurance reviews from both the national government and the CDC. Additionally, I reviewed the data weekly, cross-checking forms, to make sure that there were no illogical entries to minimize the potential for misclassification.

While efforts to minimize observer bias through the multiple trainings, standardized data collection tools, and monitoring and supervision were taken (as described in Chapter 4: Study Methods and Procedures) there remains the possibility that study participation, treatment acceptance, and completion could have been influenced by *experimenter bias*. Because this study was incorporated into routine operations of CRH VMD, clinical staff were included as part of the study to manage participants on treatment by design to assess the feasibility of his strategy as part of their daily operations. Moreover, despite extensive training, *experimenter bias* always remains an issue when unconscious cues are transmitted to participants. Similarly, the *Hawthorne effect* may introduce error, that is individuals alter or modify their behaviours because they know that they are under observation.

Limits to Generalizability. Findings from this study may not be generalizable across panel sites as the study was only implemented in one setting in Vietnam- one that is perceived to be a high functioning panel site by CDC. Results obtained from a high functioning site may need to be taken with some caution when inferring impacts for low functioning sites. Additionally, social and cultural influences on the uptake of testing and treatment by the Vietnamese visa applicants may be different for populations from other countries. Systematic similarities and differences between countries needs to be considered before applying these results. The study identified a high prevalence of LTBI among adult visa applicants. This is not surprising as Vietnam is considered a high TB burden country. However, it is important to note that finding a high prevalence of LTBI among adults from medium to low TB burden countries is unlikely and this type of intervention may not produce a similar yield in other settings. Thus, these results may not be replicable at other panel sites. Further implementation of the intervention at other sites in other countries should occur to provide more insight on replicability of the results.

7.3 Recommendations, Next Steps, and Considerations for Practice and Future Research

Recommendations for Policy and Practice

This study is the first step to understanding if pre-arrival voluntary LTBI testing and treatment should be considered as an option to help the United States achieve its TB elimination goal.

Recommendations from this study include for the US government to:

- Implement the routine offering of an IGRA to all children and adults at panel sites in high TB burden countries and the provision of voluntary treatment prior to US arrival.
- Continue and expand the current intervention in Vietnam to other panel sites in Vietnam and expand the inclusion criteria to allow for all immigrant visa applicants an opportunity to receive an IGRA and treatment, if indicated

However, in order for these recommendations to be implemented more information is needed to inform scale-up of this type of intervention.

Shorter Treatment Regimens and Alternatives to DOT

While the study findings underscore the potential of offering treatment with a short-course regimen during the pre-arrival period to achieve robust rates of treatment completion, there are a few things that should be considered for future implementation and assessment. As previously discussed, this study was designed with the use of 3HP by DOT for a minimum of 8 dose and up to 4 doses of SAT with a follow-up call in the United States. One reason that the study required DOT is that the protocol was written when CDC guidelines had originally recommended DOT for the use of 3HP.(4) CDC has since updated its guidelines in 2018 to allow for the use of SAT.(5) DOT and SAT with a follow-up was also part of the study, as this was the first time use of 3HP in Vietnam. This approach allowed for careful monitoring of drug intake as well as an assessment for adverse events. Additionally, since this study was conducted among visa applicants potentially traveling during treatment, a conservative approach was taken and visa applicants who had hepatitis B or C, were excluded, although these conditions are not necessarily contraindications for 3HP. If this strategy is further implemented reducing DOT visits may be more convenient for the visa applicants and perhaps

more people would be willing to initiate and complete treatment. This would also be less of a burden on the panel site staff. Digital adherence technology (DAT) tools have been approved for use by WHO and should be considered as well to reduce the burden on health care workers and to offer the immigrant visa applicants the opportunity to take their medicine in a place that is convenient for themselves. (6)

Another important consideration is to address challenges associated with the follow-up of immigrants who are taking SAT doses after immigrating to the United States. My study used coordinators who spoke the same language as the arriving immigrants. While the immigrant appreciated the support from persons who spoke their language, this approach may be resource intensive and a challenging if this strategy is further scaled-up and expanded to other countries. Solutions on how best to manage the stateside treatment follow-up needs to be thought through in collaboration with the state health departments.

This study used the 3HP regimen; however, there currently is a shortage of rifapentine (P). In August 2020, the U.S. Food and Drug Administration (FDA) published a statement regarding impurities identified in rifapentine and steps it is taking to mitigate shortages of these drugs (www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications). To avoid issues of shortages, future implementation of this strategy should look at other short course treatment regimens such as 3HR and 4R, and if and when approved for general use, 1HP.

Ethical considerations

LTBI treatment has both individual and public health benefits. For the individual, the benefit is the prevention of a disease that can be difficult to treat and result in death. For public health, large numbers of people completing LTBI treatment can contribute to a reduction in TB incidence. Despite these benefits, there are several ethical concerns that need to be considered for offering testing and treatment in the context of a migrant screening program, some of which have been previously discussed in the literature.(7–9)

First, in terms of testing for infection, because there is no gold standard test, ethical concerns regarding the testing of immigrants for LTBI have previously been raised. These concerns

were especially relevant with the widespread use of the TST which lacks specificity, particularly in populations that have been BCG-vaccinated.(9,10) However, because of this and other concerns the CDC has recommended the use of IGRAs over the TST for immigrant populations since they do not cross-react with BCG antigens.(11) My study offered an IGRA on a voluntary basis and we were able to identify high proportion of infection (21%) among our study population. In populations from high TB burden countries, it can be argued that the routine offering of IGRA would have the benefit of informing people of their status and thereby giving them an option to take treatment or not.

Second, even if the offering of the IGRA becomes routine, treatment should remain voluntary. Unlike TB disease, LTBI is a non-infectious state and thus not transmissible to others. Additionally, while treatment offers benefits to individuals and options like 3HP are safer and more tolerable than 9H, there is still a risk for adverse events. These risks must be weighed with the benefits by the individual with infection and in consultation with a medical professional. Moreover, even if treatment is voluntary there is the real concern that visa applicants may feel pressured to take treatment to receive clearance to immigrate. Although my study showed many immigrants understood treatment was voluntary by declining the offer, future efforts must continue to ensure that this is communicated and understood.

Third, if this strategy is implemented, who bears the cost of testing and treatment must be determined. Currently, the visa applicants are responsible for the cost of the overseas medical examination. Since the purpose of medical examination is to identify conditions that are considered a public health threat, and only 5-10% of people with LTBI, without additional risk factors, will progress to disease, it could be considered unfair for the immigrant to pay for LTBI testing and treatment. Additionally, if the treatment is voluntary but comes with a cost, many visa applicants may not want to take it. While both the price of the IGRA and 3HP have significantly been reduced, determining responsibility for the payment the test and treatment needs to occur.

Fourth, serious considerations on how to implement this strategy without contributing to increased stigma and fear of immigrants must be taken. Recent events and policies from the Trump administration demonstrate how this fear can be manipulated and used to develop policies to reduce or halt immigration. For example, this New York Times article from May

2020, discusses how a Trump advisor, pre-COVID-19, unsuccessfully sought to close borders using public health powers by eliciting fears that immigrants bring in diseases (www.nytimes.com/2020/05/03/us/coronavirus-immigration-stephen-miller-public-health.html).

Policy Considerations- Kingdon's Agenda Setting Framework

While this study provides empirical evidence that offering voluntary LTBI testing and treatment during the *pre-arrival* medical examination is feasible and can achieve high rates of acceptance and treatment completion, evidence alone is often not enough to implement a new policy. Understanding the current political/environmental situation is just as necessary when advocating for a policy change. Kingdon's agenda-setting framework suggests that policy changes occur when a "window" appears because of the confluence of three streams: problem, policy, and politics. (12) The *problem stream* refers to the perception by the public that an issue requires government action, such as a "focusing event". In this situation, the current focusing events in the United States are the COVID-19 pandemic and concerns that immigration and travel contribute to the spread of diseases. The *policy stream* refers to the ongoing research and evidence for the need for policy. This study, along with the US TB epidemiology, provide the basis for the evidence and need for change in how we approach TB elimination in the United States. The *politics stream* refers to the broader political context such as the national mood and/or changes in government. The movement in the political stream is currently signified by urges from the public to the government to do more to protect the public, particularly from disease transmission. The United States has just transitioned from the Trump administration to the Biden administration. While a major focus of the Trump administration was to halt and control immigration, it is too early to assess how the Biden administration will deal with immigration, even though the administration plans to reverse many of Trump's policies. However, the Biden administration has signaled that rebuilding the country's public health infrastructure will be a priority. Given that the COVID-19 crisis is still raging, and that the public and new administration are concerned with controlling airborne disease transmission that is affiliated with overseas travel, there is potentially a confluence of the three streams and an opening of a "window" for the government to consider implementing the *PTOPS* strategy. However, any presentation to US policymakers on the scientific evidence from this study and

should take into consideration some of the ethical concerns described in the section above about stigma faced by immigrants in regard to disease transmission.

Additional Future Research

While my study demonstrates that offering LTBI testing and treatment during the overseas medical examination can be a viable strategy to advance TB elimination efforts, this study was implemented in only one setting. It would be important to conduct additional studies at other panel sites to see how the intervention performs in other countries and to determine the replicability of results. Currently, my protocol has been adopted by CDC and IOM to implement in Tanzania among US-bound refugees. The study is on hold until 3HP becomes available in Tanzania. Additional sites in which to pilot this approach are currently being considered by CDC.

Although my study uncovers some reasons for decline or acceptance of LTBI testing or treatment; further in-depth qualitative interviewing can provide deeper insights into immigrants' motivations to accept or decline testing or treatment. In depth interviews can also provide additional insight into how well the intervention was implemented and how it can be improved. Additionally, qualitative interviewing with health care staff at this panel site and other sites could provide much needed information on panel physicians' current knowledge and attitudes about LTBI treatment which can help determine what type additional training and messaging is needed for panel physicians to feel comfortable offering LTBI testing and treatment.

While the PTOPS project was based on an implementation research framework, only a few components of the framework were assessed for the purposes of the DrPH. Cost benefit and cost-effectiveness of the intervention were beyond the scope of my project but are important for the CDC to assess while considering this strategy for further implementation. Tasillo et al using a Markov model found that testing and treating non-US-born persons for LTBI to be cost-effective compared to not testing and treating them for LTBI .(13) Campbell et al determined that combining pre-arrival testing with post-arrival treatment could be a cost-effective approach.(14) Porco et al determined that post-arrival LTBI treatment to be both cost-effective and cost-saving.(15) Wingate et al in a hypothetical cost-benefit analysis of overseas LTBI testing and treatment for refugees determined that the approach could potentially save the United States millions of dollars while contributing to TB elimination goals.(16) While these

cost studies based on modelling provided valuable insights, to truly determine if the PTOPs intervention is cost-effective, empirical evidence is needed to compare if the PTOPs strategy is cost-effective compared to post-arrival strategies. Moreover, if this strategy is scaled-up, it will be necessary to determine who will bear the costs of the test and treatment.

Finally, future research will need to determine the impact (i.e., long term case rate reduction) of the intervention. One possible method is to follow IGRA positive participants from this study over time and compare those who did not take 3HP treatment to those who took treatment to determine if anyone developed active TB disease. If PTOPs is continued and scaled up in Vietnam, future impact research should include using data from the US surveillance system and the EDN to see if there are differences in rates of TB among Vietnamese immigrants in the United States before and after the implementation of the intervention.

7.4 Outputs and Dissemination Efforts for PTOPS

As the United States and other high income low TB incidence countries are pushing towards achieving the World Health Organization's END TB strategy goals there has been much interest in the implementation and findings from the PTOPS project. Below are some outcomes and dissemination efforts from my thesis work.

1. US Centers for Disease Control and Prevention (CDC) PTOPS Scale-Up Workgroup: Based on preliminary findings from my study, CDC has created a cross-center PTOPS workgroup to determine next steps for scaling-up the intervention. I serve as an External Senior Advisor to the workgroup.

2. The Vietnam National TB Programme (NTP) is using PTOPS findings to help inform the development of their national Latent TB Infection (TPT) guidelines and strategy. The PTOPS study marks the first time the 3HP treatment regimen has been used in Vietnam. The results from the PTOPS study are also being used to help Vietnam acquire country approvals for importing 3HP into the country.

3. Replication of the study: My PTOPS protocol has been adapted by CDC and IOM for U.S-bound refugees from Tanzania. We are currently waiting for the availability of 3HP to implement the project. I serve as Senior Advisor on the project.

4. I, Amera Khan, presented the PTOPS project and preliminary results at the “Preventing TB to End TB”, meeting for Ministries of Health in the Gulf Countries to come up with strategies to address TB in migrants. The meeting was hosted by the Harvard Medical School Center for Global Health Delivery–Dubai on June 22-23, 2019 in Muscat, Oman.

5. I, Amera Khan, developed and presented the PTOPS study at the Late-Breaker Session of UNION World Lung Health Conference in Hyderabad, India on November 2, 2019.
Khan A, Phares C, Phuong H, Nahid P, Phan H, Merrifield C, Tran T, Nhung N, Oeltmann J, and the PTOPS Study Group. Preventing TB Overseas Pilot Study (PTOPS): latent tuberculosis infection treatment for US-bound immigrants. The Union Late Breaker (LB-3052) 2019.

6. The PTOPS UNION Abstract was cited in AJRCCM article *Narita M, Sullivan Meissner J, Burzynski J. Use of Modeling to Inform Tuberculosis Elimination Strategies. American journal of respiratory and critical care medicine. 2019 Nov 7(ja).*

7. PTOPS study coordinator, Cuc Tran, presented Amera Khan’s UNION presentation at a Regional Southeast Asia Migration Meeting in Thailand, December 2019.

8. UCSF Co-PI, Payam Nahid presented the PTOPS project at the North American Region UNION Conference on a session on immigrants and latent TB infection. Chicago, IL. Feb 2020

9. The PTOPS project was awarded the CDC National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) Honor Award for Excellence in Policy, 2020.

7.5 Conclusions

Addressing the reservoir of LTBI is necessary for eliminating TB in the United States, however, it will require millions of people to be treated for LTBI in order to reduce incidence. For example, it is estimated that among contacts, 20-52 persons with LTBI must be treated to prevent 1 case of TB within a subsequent 5-year period.(17) Therefore, in order to eliminate TB, the US TB program needs to aggressively seek any clinical encounter, such as the overseas examination to diagnose persons with LTBI and provide opportunities for treatment.

This study demonstrated that the pre-arrival offering of LTBI testing and treatment resulted in a similar proportion (67%) of treatment initiation and higher proportion of treatment completion (88%) among immigrant visa applicants compared to immigrant populations completing their post-arrival evaluation in the United States. Being female, aged 18-35, bacille Calmette-Guérin (BCG) vaccinated, and in school or employed, knowing a family member with TB, and having a private mode of transportation were associated with test acceptance. Immigrating after 2 months was associated with test and treatment acceptance. No predictors emerged for treatment completion. Overall, this study demonstrates that using the overseas medical examination to provide voluntary testing for and treatment of LTBI, with a short-course regimen, in US-bound immigrants should be considered, particularly for immigrants coming from high-burden TB countries, as a viable strategy to advance TB elimination efforts.

7.6 References

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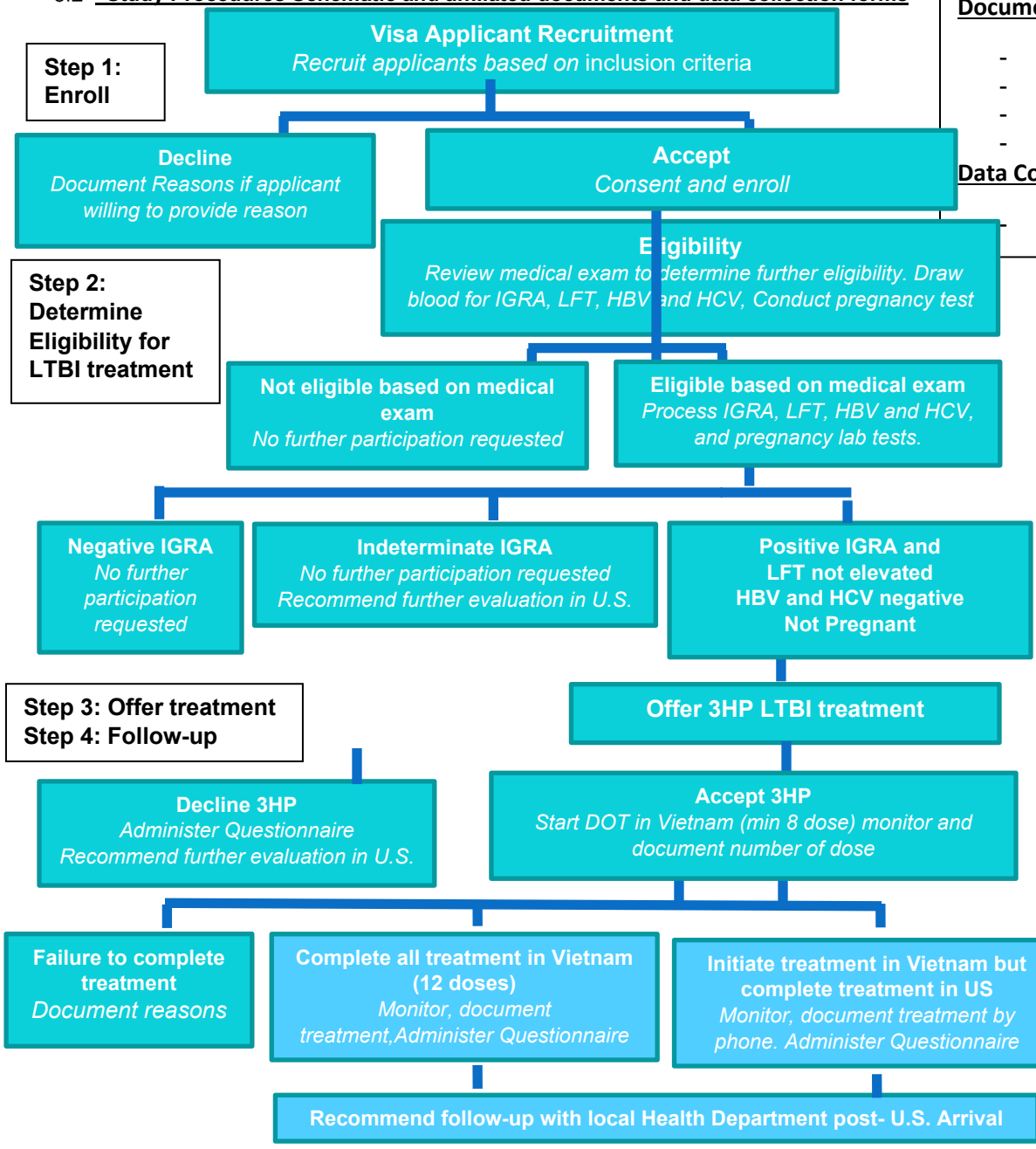
8. Appendices

8.1 List of Study Documents

App. No.	Document Description	Study Step	Information for Study Staff	Information for Patient (translate)	Data Collection	Patient Mgmt
A	Study Information Flyer (TB/LTBI benefits of test and treatment)	1		X		
B	Informed Consent (Adult)	1		X		
C	Informed Consent (Adolescent)	1		X		
D	Form 1: Enrollment Status and Decline	1			X	
E	US DS-3030	2	X			X
F	US DS-3026	2	X			X
G	US DS-2054					
H	Form 2:Treament Eligibility, Acceptance, or Decline	2, 3			X	X
I	LTBI treatment study information for all eligible	1,3		X		
J	LTBI test status card/certificate for ineligibles and decliners	3		X		
K	Form 3: Participant Contact and Travel information	3, 4	X			x
L	Taking 3HP: LTBI DOT clinic information and treatment side effects for acceptors	3		X		
M	Form 4: DOT and Patient Monitoring	3	X		X	X
N	Form 5: Treatment Completion Questionnaire-Vietnam	3, 4			X	
O	Form 6: Treatment Completion Questionnaire-U.S.	3, 4			X	
P	LTBI test and treatment status card and certificate of completion	3, 4		X		
Q	Phase 2: Focus Group Consent Form	P2	*Not Part of DrPH*			
R	Phase 2: Focus Group Guide	P2	*Not Part of DrPH*		X	
S	Study Staff Confidentiality Agreement		X			
T	Form 7: Adverse Event Reporting Form					X
U	Form 8: Adverse Event Follow-up Form					X

8.2 **Study Procedures Schematic and affiliated documents and data collection forms**



Documents for Participants

- **A.** Study Information
- **I, Treatment flyer**
- **B, C.** Informed Consent (Adult and Adolescent)
- IGRA, LFT HBV, HCV, and pregnancy blood test referral

Data Collection Forms

- **D.** Form 1: Enrollment Status and Decline Questionnaire

Documents for Study Staff

Abstract data to determine treatment eligibility using

- **E,F,G.** DS-3026, DS-3030, and DS-2054
- IGRA, LFT, HBV, HCV, and pregnancy results

Data Collection Forms

- **H.** Form 2 Treatment Eligibility, Acceptance, or Decline

Documents for Participants

- **I.** For all eligible: LTBI treatment information
- **J.** For decliners: U.S. Treatment options
- **L.** For acceptors: DOT clinic and treatment side-effects information
- **P.** LTBI test and treatment status card

Data Collection Form

- **H.** Form 2: Treatment Eligibility, Acceptance, or Decline
- **K.** Form 3: Participant Contact/Travel Information
- **M.** Form 4: DOT and Patient Monitoring,
- **N.** Form 5: Treatment Completion Questionnaire Vietnam
- **O.** Form 6: Treatment Completion Questionnaire Vietnam

Appendix A: Study Information Flyer

Protect You and Your Family

Help Us Prevent TB Disease

Join our study to help prevent TB disease and to protect you and your family's health.

What is this study about?

Tuberculosis (TB) disease is caused by a germ that can make you very sick. TB germs are spread in the air from person-to-person. Some people have TB germs in their body, but these germs are sleeping. People with sleeping germs do not feel sick and cannot spread the germs to others. This is called **latent TB infection.**

About 25% of all Vietnamese people have latent TB infection. If you have latent TB infection your body is keeping the TB germs under control. Overtime, your body can get weak and the TB germs can multiply. If this happens you can develop TB disease, get really sick, and spread the germs to your family and friends. You can prevent TB disease by taking medicine for latent TB infection.

About 25% of all Vietnamese (one in four people) have latent TB infection.

We are doing this study to find out if we can offer you a test to see if you have latent TB infection. If you do have latent TB infection, we will offer you treatment here in Vietnam to prevent you from getting sick with TB disease. This study is being offered to visa applicants 12 years and older.

Get Tested for Latent TB Infection

If you take part in this study

- You will get a test that will tell you if you have latent TB infection.
- If you have latent TB infection and are eligible, we will offer you free treatment to take here in Vietnam before you leave for the United States.
- We will offer you the same treatment medicine that doctors are using in the United States.

Taking part in this study is your choice

- If you have any questions about the study, TB disease, or latent TB infection you can ask the doctor or study staff.
- You can be treated for latent TB infection in the United States without being part of this study.
- **Taking part or not taking part in this study will NOT affect your medical exam or chances of getting a visa.**

For more information on this study talk to Cho Ray Hospital Visa Medical Department study staff

Appendix B: Informed Consent: Adult _Parent *Flesh-Kincaid Reading Level 7.5*

**CONSENT, OR PERMISSION BY A PARENT OR LEGAL GUARDIAN,
TO BE PART OF A RESEARCH STUDY**

Cho Ray Visa Medical Department

Enrolling children
If you are a parent providing permission for your child to take part in this study, the word "you" in this document means your child. Children, 12 years and older, will be able to participate in this study.

Information about this study
You are being asked to take part in a study because you are going through the medical exam process as part of your visa application to the United States. If you are breastfeeding, pregnant, or planning to be pregnant during the next four months, you will not be eligible for this study.

The purpose of this study is to evaluate if we can provide latent TB infection (LTBI) testing and treatment to visa applicants before they immigrate to the United States. This study will also ask you to share your opinions about the testing and treatment of latent TB infection. This research will also help us understand if offering LTBI testing and treatment is feasible during the U.S. visa applicant medical exam process.

As you know, all persons who apply for a visa to immigrate to the United States must be screened for active tuberculosis (TB) disease. Latent TB infection is when a person has TB germs in their body, but is not sick. The germs are sleeping. If you have latent TB infection, you can develop active TB disease at some time in your life. If you develop active TB disease, you can get very sick and spread the TB germs to your family and friends. You can take latent TB infection treatment to prevent TB disease.

Visa applicants, 15 years and older, are generally not tested for latent TB infection as part of the visa medical exam but will be tested in this study. Children 2-14 years are usually given a test for latent TB infection as part of the visa medical exam.

Depending on the results of your medical screening exam and the test to determine if you have latent TB infection you may be eligible to take latent TB infection treatment to prevent TB disease.

This consent form has more information about the study, potential risks and benefits, and what will happen if you decide to take part in the study. If you decide to take part in this study you will be asked to sign this form.

Will participating in this study affect my ability to get a visa?
No. Your participation is voluntary. Taking part in this study is your choice. If you choose to take part or not to take part, it will not help or hurt your chances of getting a visa. It also will not affect the medical exam, or your interview for immigration. If you have any questions, you can ask the Cho Ray Hospital Visa Medical Department study staff.

Who is doing this study?
This study is being done in partnership with Dr. Hoang Lan Phuong at the Cho Ray Hospital Visa Medical Department**,** the United States Centers for Disease Control and Prevention (CDC), Dr. Nguyen Viet Nhung from the Vietnam National TB Programme-National Lung Hospital and Dr. Payam Nahid from the University of California San Francisco.

Who has reviewed this study?
The role of institutional review boards (IRB) is to protect the rights, safety, and wellbeing of people in research studies. This study has been reviewed and approved by the following IRBs

- Independent Ethics Committee for Biological Medical Research- Ministry of Health, Hanoi, Vietnam
- University of California San Francisco, IRB
- The United States CDC Institutional Review Board (IRB)

What will happen if I take part in the study?
If you agree to take part in this study, the following will happen;

- We will ask you a few questions about your health.
- We will collect contact information and information on your travel plans to the United States.
- When you have your blood drawn as part of the visa medical exam, a little more blood will be drawn from your arm for the study (about 2 teaspoons (10ml) using the same needle stick). (You will not be stuck twice.)
- This blood will be held in the laboratory. Your blood samples will not be used for any other purposes. The lab will throw away any remaining blood samples one week or earlier after collection if not used.
- If you are a female, the doctor may ask for a urine sample or use your blood to test for pregnancy.
- We will review your medical examination results

For those 15 years and older, the doctor will look for signs and symptoms of TB during your regular visa medical exam.

For children, 12-14 years old, your visa medical exam will already include a test for latent TB infection. If your test shows that you have latent TB infection, then you will also have a chest x-ray as part of your regular visa medical exam.

If the doctor thinks that you have any signs or symptoms of active TB disease or need a more in depth TB investigation you will no longer be part of this study. Your blood will not be processed and the doctor will tell the lab to throw away the extra blood collected for the study. You will continue with your regular visa medical exam.

If the doctor finds that you do NOT have any signs or symptoms of TB disease:
The doctor will tell the lab to use the extra blood collected to test for:

- *Latent TB infection:* to check if you have TB germs in your body (15 years and older). (This is the same test used for children during the visa medical exam, so if you are 12-14 years, the doctor will use the test result for the visa medical exam. You will not be tested twice.)
- *Liver Function, Hepatitis B, and Hepatitis C:* These tests will let us know how your liver is working. If your liver is not working normally, it may be inflamed, or you may have an infection, such as hepatitis B or hepatitis C. Although the latent TB infection medicines are generally safe, these medicines may cause more problems and harm to your liver.
- *Pregnancy:* if you are a female of childbearing age, the doctor will use either a blood or urine test to check if you are pregnant.

The doctor will review and record the lab results on your medical exam forms. This will <u>NOT</u> affect your chance of getting a visa. This will <u>NOT</u> affect your visa medical exam.

If the latent TB infection test result is:

- *Negative*. You do not have latent TB infection. Your participation in the study will be complete.
- *Indeterminate*. We do not know if you have or do not have latent TB infection.
  The doctor will recommend that you have the latent TB infection test repeated in the United States. Your participation in the study will be complete.
- *Positive*. You have latent TB infection.
  - If you have latent TB infection but are not eligible for treatment in Vietnam, you will be given the results of your test, information on TB disease signs and symptoms and advise you to follow up with local health department when you arrive in the United States.
  - If your liver tests are normal, you do not have hepatitis B or C, your pregnancy test is negative, and your chest x-ray (from the visa medical exam) is normal, the doctor will recommend latent TB infection treatment to prevent TB disease.

Latent TB Infection Treatment in Vietnam
If you have latent TB infection and are eligible for treatment, the doctor will recommend that you take latent TB infection treatment. The treatment is called 3HP. The 3HP treatment contains the drugs rifapentine and isoniazid and is given one time per week for 3 months (12 weeks).

The 3HP treatment is approved by the U.S. Centers for Disease Control and Prevention, the U.S. Food and Drug Administration and is endorsed by the World Health Organization. The 3HP treatment is only available in Vietnam as part of this study.

If your test results show that you have latent TB infection, we will ask you to come back to the clinic to discuss treatment options. The doctor will describe the treatment and give you a pamphlet on 3HP. The pamphlet will describe how to take the medicine, the treatment schedule, possible side effects or problems you may have while taking these medicines.

After you review the treatment information, you will have a choice to take the treatment.

If you choose to take the treatment, you will take isoniazid, rifapentine and vitamin B6 one time per week for 3 months (12 weeks), at Cho Ray Hospital Visa Medical Department. The study staff will observe you taking your medicine. These visits will take about 15-20 minutes.

We hope that you will take all doses in Vietnam before you leave for the United States. At the end of your treatment, we will ask you questions about your opinions on taking latent TB infection treatment.

If you choose Not to take treatment, you will be asked questions to find out why you decided not to take treatment. We will provide you with information on TB disease signs and symptoms and future treatment options and advise you to follow up with the local health department when you arrive in the United States.

What are the risks of being in this study?
There may be some risks to taking part in this research study.

Blood Collection: When you have your blood drawn, you may feel a little pain or dizziness, or have some bruising.

Potential Side Effects from 3HP Treatment: Some participants who take latent TB infection treatment may have side effects from the medicines. All medicines have side effects. We do not know who will have side effects or who will not. Some side effects may be mild and some may be serious. If you have side effects you must tell your doctor right away. You will be evaluated and told what to do if you have side effects. If you have serious side effects, additional blood may be collected and or your doctor may decide to take you off the medicine.

Below is a list of potential side effects.

Common, not serious • All or most people taking rifapentine will have orange colored tears, sweat, saliva and urine. This can discolor contact lenses or dentures
Likely, some may be serious (4 – 20 people out of 100 may have one or more of these) • Nerves: Numbness and or tingling in your hands, arms, or legs (INH only) • General: stomach upset, heartburn, nausea • Skin: rash or itching • Poor appetite • Low blood count • Joint pain • Tiredness or weakness • Dizziness • Diarrhea • Flu-like symptoms: with or without fever, chills, sweats, body aches, red eyes, warm skin, fatigue
Rare and serious (1 - 3 people out of 100 may have one or more of these • Liver: inflammation or damage to the liver; jaundice (yellow skin and or eyes), nausea, loss of appetite, pain on right side of abdomen and dark colored urine • Blood: Platelets help the blood clot. If platelets are low this can cause bleeding and may cause purple spots on your skin. Low red blood cells can make you feel tired, and low white blood cells can affect how your body fights against infections • Allergic reaction may cause rash, fainting, low blood pressure, low body temperature, shortness of breath or wheezing, swelling of face, lips or throat

These medicines can also interact with other **prescription medicines and medicine you can buy on your own**, and with alcohol. Please tell us before you start any new medicines. Avoid drinking alcohol while you are taking treatment.

Rifapentine can cause birth control pills and other birth control methods containing hormones not work as well as usual. If you are sexually active, we will ask you take precautions using a barrier method to avoid getting pregnant. Rifapentine should not be taken if you are pregnant. If you become pregnant you ***must*** tell your study doctor or study staff right away.

Are there benefits to taking part in this study*?*
Yes. Persons at the highest risk for TB in the United States are those born outside of the United States. The benefit to you is that you will learn if you have latent TB infection and receive treatment that can prevent you from developing TB disease in the future. It might be easier for you to complete the treatment in Vietnam, a familiar place to you, as compared to the United States.

How long will my participation in the study be?
All participants will have a latent TB infection test. This test will be done during the regular 2-3 day visa medical exam process. Most participants will not have latent TB infection. If you do not have latent TB infection, you will be done with the study within those 2-3 days.

If you do have latent TB infection, you will be offered treatment. If you take the treatment, you will be in the study for at least 12 weeks to complete the treatment. If you do not take the treatment, you will be done with the study within the 2-3 days of the visa medical exam.

What other choice do you have if you don't take part in this study?
You can get tested for latent TB infection and get medicine to treat latent TB infection in the United States without participating in this study.

What if my immigration to the United States is approved before I have completed my treatment?
We think you will be able to complete treatment before you leave for the U.S. If you need to move before you complete treatment, it may be possible to complete your treatment once you arrive in the U.S. We will ask for your contact information in the U.S because it is important for us to stay in contact with you until you finish your medicine.

What if I don't want to stay in the study?
You do not have to stay in the study. If you say yes now, you can change your mind later. If you choose to leave the study early, talk to your doctor before stopping. If you do leave the study early, the health information that was collected from you will remain part of the study.

Are there costs for taking part in this study?
There is no cost to you for being in the study. You will not have to pay for any medicine or tests that are part of this study. The treatment offered is free of charge. (You will have to pay for your regular visa medical exam as part of your visa application).

Will I be paid for taking part in this study?
Yes, you will be paid for your time, effort and transportation to participate. You will only receive payment for visits you complete in Vietnam. If you do not complete a visit you will not be paid. You will receive 115,000 VND for your time to take the latent TB infection test (one visit) and 250,000 VND (12 visits) for each treatment visit you complete. There is a total of 13 visits. If you complete 13 visits you will be paid a total of 3,115,000VND.

What happens if I am injured because you took part in this study?
If you are injured because of being in this study, Cho Ray Hospital Visa Medical Clinic will offer you immediate necessary treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. Alternatively, you could be referred to another government medical facility if you do not have health insurance. The study sponsors cannot pay you for any care from study related injuries or pay your family if you are injured. You are not giving up any of your rights by signing this consent form and agreeing to be in this study.

Will my medical information be kept private?
We will check your medical exam records to get information for the study. We will not use your name in any speech or paper about the study. You will be identified only by a number. Personal information from your records will not be shared. We will keep all information from your medical records private. If you do have latent TB infection, this information will be shared with the local U.S. Health Department after you arrive in the United States. You may be contacted by them for a follow-up medical visit.

Your medical and research records may be reviewed by the:

- Independent Ethics Committee for Biological Medical Research- Ministry of Health, Hanoi, Vietnam
- Cho Ray Hospital Visa Medical Department
- U.S. Centers for Disease Control and Prevention
- U.S. Office for Human Research Protections (OHRP)
- Research staff

Who can I contact if I have questions, concerns, comments, complaints or if I think I have been harmed by being in the study?

Primary contacts	**Office Number**	**After-Hours Number**
Dr. Hoang Lan Phuong	**(84) 28 3 8565703**	**84903867678**

For questions about your rights as a research subject, contact the Ethical Committee in Biological Medical Research, Ministry of Health that reviews research on human subjects. They will answer questions about your rights as a research subject and take any comments or complaints. You can contact Dr. Nguyen Ngo Quang by calling *0985858558,* or by email to *quangbyt@yahoo.com*

STATEMENT OF CONSENT TO PARTICIPATE IN THE LATENT TB INFECTION TREATMENT STUDY

If you agree to participate in this research, please sign this section. You will be given a signed copy of this form to keep. You do not waive any of your legal rights by signing this form.

Adult Signature Section

SIGN THIS FORM ONLY IF THE STATEMENTS LISTED BELOW ARE TRUE

- You have read the above information.
- You agree to have a blood test for TB infection, liver function, and a blood or urine test for pregnancy (if female and of childbearing age)
- You have discussed the information to your satisfaction.
- You have voluntarily decided to take part in this research study.
- You know that after choosing to be in this study, you may stop at any time.
- You authorize use of your information as described in this form.

Printed Name of Participant	Signature of Participant	Date	Time

Printed Name and Title of Person Obtaining Consent	Signature of Person Obtaining Consent	Date	Time

PARENT, GUARDIAN, OR LEGAL REPRESENTATIVE SIGNATURE SECTION

- You are giving permission for your child to take part in this study.
- You have read the above information.
- You agree for your child to have a blood test for TB infection, liver function, hepatitis B and C, and a blood or urine test for pregnancy (if female of childbearing age)
- You have discussed the information to your satisfaction.
- You voluntarily agree for your child to take part and believe your child wants to take part.
- You know that after choosing to be in this study, your child may stop at any time.
- You believe being in the study is in your child's best interest.
- You authorize use of your child's information as described in this form.

Printed Name of Participant	Signature of Participant, Indicating Assent	Date	Time
Printed Name of Person Giving Permission for Participant	Signature of Person Giving Permission ☐Parent/☐Guardian/☐Legal Representative	Date	Time
Printed Name of Person Obtaining Permission	Signature of Person Obtaining Permission	Date	Time

Appendix C: Assent Form: ***Flesh-Kincaid Reading Level 6.4***

ASSENT TO BE IN A RESEARCH STUDY

12-17 years old

What is this study about?
Dr. Hoang Lan Phuong at the Cho Ray Hospital Visa Medical Department**,** together with researchers from the United States Centers for Disease Control and Prevention (CDC), Vietnam National TB Programme-National Lung Hospital and the University of California San Francisco are doing a research study.

This is a research study. You are being asked to be in this study because you are having your medical screening examination to get your visa to the United States. If you are 12-14 years old, you will find out during your medical examination if you have latent TB infection. If you are 15 years and older, you would be tested for latent TB infection as part of this study.

Latent TB infection means you have the germ that causes TB in your body, but it is not active and not making you sick. The germ is sleeping. People with latent TB infection can develop active TB disease in the future.

Why is this study being done?
If you have latent TB infection, we want to find out if you would accept taking treatment to prevent from getting active TB disease. You would take treatment in Vietnam before you move to the United States. This research will also help us understand if offering latent TB infection (LTBI) testing and treatment is feasible during the U.S. visa applicant medical exam process

What is involved in being in this study?
You will have a screening visit to see if you can participate:

- We will talk to you and your parent or guardian about the study, what will happen while you are in the study and answer any questions.
- Your parent or guardian will be asked if they give their permission for you to be in this study. If your parent or guardian don't agree, you cannot be in the study. If they do agree, and you agree too, here's what will happen next:
- You will have some blood drawn.
    - You will have a latent TB infection test to determine if you have TB germs in your body (15 years and older). (12-14 years will be done as part of the medical screening process.
    - You will have tests to check if your liver is working normally and to see if you have hepatitis B or C infection. If your liver is not working normally or if you have hepatitis, the medicines might hurt your liver.
- We will look at your medical examination results.
- If you are a female and can get pregnant, you will have either a blood or a urine pregnancy test. If you are a female and you are breast-feeding, pregnant, or planning to become pregnant in the next four months you will not be able to be in the study.

If your tests show you can be in the study and the doctor thinks it would be good for you, you will be offered latent TB infection treatment. You will be given detailed information about the treatment to help you and your parent(s) make your decision.

If you choose to take treatment, the following will happen:

You will take 2 medicines named, Rifapentine and Isoniazid*. You will also take vitamin B6.*

- You will come to the clinic one time per week for 12 times. You will take a total of 12 doses.
- We will watch you take your medicine to be sure you swallowed it.
- We will ask you for information on how we contact you in Vietnam and in the U.S. Your contact information is important because we don't want to lose contact with you.

While you are taking medicine:

- We will ask you questions about your health. You may be asked to have some blood drawn during the study if you are feeling sick or think you may be pregnant.
- If you leave for the US before you finish your medicine, we may give you medicine to finish in the US. Your doctor will tell you if this can happen.

After you complete your treatment

- The clinic staff will ask you some questions about your experiences taking the treatment. Your parent or guardian can help with the questions, if needed.
- We will give you a record that you completed your treatment. You should save this document for your records and give it to the local Health Department when you arrive in the US.

How long will I be in the study?

If you do not have latent TB infection, you will be done with the study in 2-3 days.
If you have latent TB infection and choose to take treatment, you will be in the study for about 12 weeks. If you have latent TB infection and do not take treatment, you will be done with the study in 2-3 days

Will the blood draw or medicines cause me problems?

When you have blood drawn, the needle stick may hurt or cause a bruise. All medicines can cause problems. We do not know who will or will not have problems because of the medicines. Some possible problems that you could have because of the medicines include:

- During the time that you are taking rifapentine your sweat, urine, saliva and tears may turn orange-colored. This is not harmful or painful. Orange tears can stain contact lenses.
- Liver problems, rash, upset stomach, headaches, joint pain, weakness, and numbness or tingling in your hands or feet.
- You may feel like you have the flu and have fever, chills, sweats, body aches, and red eyes and warm skin
- Rifapentine can cause some birth control to not work as well as usual. If you are sexually active, we will ask you take precautions using a barrier method to avoid getting pregnant. Rifapentine should not be taken if you are pregnant. If you become pregnant you ***must*** tell your study doctor or study staff right away.

Some side effects may be more serious. You must tell the doctor or study staff if you notice or feel anything different so they can see if you are having a side effect. We will give more information about the medicine and treatment before you start taking them.

Why should I take part in this study?

If you have latent TB infection, you will get treatment to prevent you from getting TB disease in the future. It might be easier for you to take this treatment in Vietnam, a place you are familiar with, instead of in the U.S.

What if I have some questions and I change my mind?
Your parent or guardian has said you can be in the study. But taking part in this study is your choice. It is important for you to talk with your parent or guardian about being in this study. Nobody will get mad at you if you don't want to do this.

- If you choose not to join this study, it will not change your medical examination or interview process as part of your visa application to United States.
- You can stop being in the study at any time.

What other choices do I have if I don't participate in the study?
You can get a test for latent TB infection and medicine to prevent TB in the U.S. without taking part in this study.

You and your parent or guardian can ask any question you may have about the study. You may ask now, or at any time during the study you or your parent or guardian may contact the following study staff:

Name	Office Number	After-Hours Numbers
Dr. Hoang Lan Phuong	**(84) 28 3 8565703**	**84903867678**

If you don't want to be in this study, just say so, and don't sign this form.

If you want to be in this study, please sign your name below. Your signature means you agree to participate in this study.

- My parent or guardian has agreed for me to be in this study and signed a permission form.
- My signature below means that I agree to be in this study.
- I agree to have a blood test for TB infection, liver function, and a blood or urine test for pregnancy (if female of child bearing age)
- I was given a chance to ask questions.
- I feel that my questions have been answered.
- I know that being in this study is my choice.
- I know that after choosing to be in this study, I can stop at any time.

Printed Name of Participant	Signature of Participant	Date	Time

Printed Name and Title of Person Obtaining Assent	Signature of Person Obtaining Assent	Date	Time

Appendix D: Form 1: Enrollment

Study ID [ST ID]

Place Barcode Here

Form 1: Recruitment and Enrollment Status

For all visa applicants who live in the catchment area provide study and consent information (18 years and older) or assent information (12-17 years) and complete questions below.

A. Date: *Enter date for when applicant is screened and provided consent (or assent) information*

1. Screen Date: **[SCREEN_DATE]**

M M - D D - Y Y Y Y

B. Applicant Information

2. Year of Birth **[YOB]**

Y Y Y Y

3. Gender **[SEX]**

☐ M **Male**

☐ F **Female**

C. Consent to Participate: *Provide study consent information to applicants 18 years and older. Indicate if applicant provides consent to enroll in study or not. For child applicants age 12-17, provide assent information and indicate if applicant assents to enroll in study.*

4. Do you consent to participate in study? (*for those age 12-17,* Do you assent to participate in the study?) **[ENROLL]**

☐ Y **Yes:** Applicant signed study consent form (or assent form if age 12-17) (*Skip question 5 and complete questions 6-14 in Section D. Order blood tests for study)*

☐ N **No**: Applicant declines to participate in the study *(Complete question 5 below)*

5. Are you willing to answer a few additional questions and provide reasons for why you declined to participate in the study?
[DECLINE]

☐ Y **Yes:** Applicant is willing to provide reasons for decline *(Complete question 6-14 in Section D and question 15 in Section E)*

☐ N **No:** Applicant not willing to provide reason for decline **(***STOP)*

Name of Interviewer_____

Study ID [ST ID]

Place Barcode Here

Form 1: Recruitment and Enrollment Status

D. Questions: *Ask all applicants questions 6-14. Remind all applicants that responses are voluntary. These questions are to assess applicants' perceptions. There are no right or wrong answers.*

6. Are you currently employed or in school in Vietnam? **[EMPLOY]**

☐ Y **Yes** ☐ N **No**

7. Have you had the BCG vaccination (TB vaccine)? **[BCG]**

☐ Y **Yes** ☐ N **No** ☐ DKN **Don't know**

8. Have any of your family members or close friends had or currently have TB disease? **[FAMTB]**

☐ Y **Yes** ☐ N **No** ☐ DKN **Don't know**

9. Have you shared a home or a room with someone who had or currently have TB disease? **[HOME_TB]**

☐ Y **Yes** ☐ N **No** ☐ DKN **Don't know**

10. When do you plan on moving to the U.S.? **[MOVE]**

☐ A **Less than 1 month from now**

☐ B **1 to <2 months from now**

☐ C **2 to <3 months from now**

☐ D **3 or more months from now**

☐ E **Don't know**

11. Are you immigrating with family members? **[IMMFAM]**

☐ Y **Yes** ☐ N **No** ☐ DKN **Don't know**

12. From your home, how long does it take you to get to this clinic (Cho Ray Visa Medical Department)?

_____hour(s) _____minutes **[TIME]**

13. How do you travel to the clinic *(transportation mean)?*

☐ C **Personal Car** ☐ M **Personal Motorbike** ☐ HC **Hired Car (taxi)** ☐ HM **Hired motorbike**

☐ B **Bus** ☐ T **Train** ☐ Bi **Bicycle** ☐ W **Walk** ☐ O **Other (please explain)** _____

14. What State in the U.S. are you planning to move to? _____

- For applicants participating in study, end of questions, thank applicants. (STOP)
-For applicants declining to participate, ask question 15 on next page.

Study ID [ST ID]

Place Barcode Here

Form 1: Recruitment and Enrollment Status

E. **Applicant Reasons for Decline** *Ask applicant question 15 and check all reasons provided below, but do not read the list aloud. If reason is not listed below, write response in the box below.*	
15. Why did you decline to participate in the study? **[DC_REASON]** ***Do not read list aloud. Check all reasons that applicant mentions.***	
Individual Level- Patients Belief about Research	
[DC_IN_RS]	☐ Worried about enrolling in any research studies
[DC_IN_BLD]	☐ Worried about blood draw
[DC_IN_UND]	☐ Does not understand study (even though understands the language being used for the consent process)
Individual Level- Patient Beliefs about TB	
[DC_NOTINF]	☐ Believes they are **Not** infected with TB
[DC_BCGPROT]	☐ Believes BCG will protect them from TB
[DC_LTBITEST]	☐ Believes that LTBI test will be inaccurate because of BCG
[DC_MED]	☐ Concerned that they might have to take medication
[DC_DUR]	☐ Concerned about duration of medication, if required
Intrapersonal Level- Patient lifestyle, Family, Other	
[DC_FAMILY]	☐ Family member against enrollment
[DC_STIGMA]	☐ Worried about stigmatization if LTBI positive
[DC_BUSY]	☐ Too busy or too much stress right now
[DC_FAM COM]	☐ Worried about study commitment/ family issues
Organization or Policy- Immigration Process	
[DC_MedProc]	☐ Worried that taking LTBI test will make medical screening process longer
[DC_IMMSTAT]	☐ Worried that LTBI test results may affect immigration status
[DC_TRAVEL]	☐ Worried that LTBI test results may delay travel plans
Other Reason	
[DC_OTHER]	☐ **Other Reason** *(if not listed above, please write-in below)*
	_____ _____ _____ _____ _____ _____

(End of study for applicant. Thank applicant for their time)

Name of Interviewer_____

Appendix E: U.S DS-3030

Photo

U.S. Department of State

TUBERCULOSIS WORKSHEET

For Use with DS-2054

OMB No. 1405-0113
EXPIRATION DATE: 09/30/2017
ESTIMATED BURDEN: 20 MINUTES
(See Page 2 - Back of Form)

Name *(Last, First, MI)* | Age

Birth Date *(mm-dd-yyyy)* | Passport Number | Alien *(Case)* Number

1. Test for Cell-Mediated Immunity to Tuberculosis

Required for applicants 2 through 14 years of age where WHO-estimated TB rate ≥ 20 per 100,000 and contacts; perform one type only.

☐ TST Date applied *(mm-dd-yyyy)* _____
Results *(mm)* _____

☐ IGRA Date drawn *(mm-dd-yyyy)* _____
☐ Positive
☐ Negative
☐ Indeterminate, Borderline, or Equivocal

☐ QFT Nil Value: IU _____
TB Response: TB minus nil IU/ml _____

☐ T-Spot Nil Value: Number of cells _____
TB Response: Higher of Panel A or Panel B minus nil value _____

2. Chest X-Ray Indication *(Mark all that apply)*

☐ Chest X-Ray not indicated
☐ Age ≥ 15 years
☐ Signs or symptoms of tuberculosis
☐ Known HIV infection
☐ TST ≥ 10 mm or IGRA positive
☐ Contact: TST ≥ 5 mm or IGRA positive

_____
Date Chest X-Ray Taken *(mm-dd-yyyy)*

3. Chest X-Ray Findings

☐ Normal Findings ☐ Abnormal Findings *(Indicate category and finding, checking all that apply in the tables below)*

Can Suggest Tuberculosis *(Need Smears and Cultures)*

☐ Infiltrate or consolidation
☐ Cavitary lesion
☐ Nodule(s) or mass with poorly defined margins *(such as tuberculoma)*
☐ Pleural effusion *(perform lateral or decubitus radiograph or ultrasound, if needed)*
☐ Hilar/mediastinal adenopathy
☐ Miliary findings
☐ Discrete linear opacity
☐ Discrete nodule(s) without calcification
☐ Volume loss or retraction
☐ Other

No Sputum Specimens Required

Mark as Class B Other on DS-2054

☐ Cardiac
☐ Musculoskeletal
☐ Other, specify in Remarks

Do Not Mark as Class B Other on DS-2054

☐ Pleural thickening
☐ Diaphragmatic tenting
☐ Calcified pulmonary nodule(s)
☐ Calcified lymph node(s)

Remarks

_____ _____ _____
Radiologist's Name *(Printed)* | Radiologist's Signature *(Required)* | Date Interpreted *(mm-dd-yyyy)*

4. Sputum Smears and Cultures Decision

☐ No, not indicated -Applicant has no signs or symptoms of TB, no known HIV infection, and:
- ☐ X-ray Normal or 'No specimens required' and test for cell-mediated immunity to TB negative *(if performed)*
- ☐ X-ray Normal or 'No specimens required' and test for cell-mediated immunity to TB positive *(if performed)*

☐ Yes, are indicated - Applicant has *(Mark all that apply):*
- ☐ Signs or symptoms of TB
- ☐ Chest X-ray suggests TB
- ☐ Known HIV infection
- ☐ End of treatment cultures

5. Sputum Smears and Cultures Results

Sputum Smear Results	Date specimen obtained *(mm-dd-yyyy)*	Date specimen reported *(mm-dd-yyyy)*	Positive	Negative
	1.			
	2.			
	3.			

Sputum Culture Results	Date specimen obtained *(mm-dd-yyyy)*	Date specimen reported *(mm-dd-yyyy)* *Date of exam on DS 2054	Positive	Negative	NTM	Contaminated
	1.					
	2.					
	3.					

DS-3030
09-2014

Page 1 of 4

6. Tuberculosis Classification

Applicants may have more than one TB Classification. However, they cannot be classified as both Class B1 TB and Class B2 TB. In addition, applicants cannot be classified as Class B3 TB, Contact Evaluation if they are Class A or Class B1 TB, Extrapulmonary.

☐ **No TB Classification**
CXR not suggestive of tuberculosis, no signs or symptoms, no known HIV infection, TST or IGRA negative *(if performed)*, not a contact

☐ **Class A**
Applicant has tuberculosis disease

☐ **Class B1 TB, Pulmonary**
CXR suggests tuberculosis, or signs and symptoms, or known HIV infection and sputum smears and cultures are negative and not a clinically diagnosed case.

☐ **Class B1 TB, Extrapulmonary**
Applicants with evidence of extrapulmonary tuberculosis. The anatomic site of infection should be documented.

Anatomic Site of Disease _____

- ☐ No treatment
- ☐ Current treatment
- ☐ Completed treatment

☐ **Class B2 TB, LTBI Evaluation**
Applicants who have a tuberculin skin test ≥10 mm or positive IGRA but otherwise have a negative evaluation for tuberculosis. Contacts with TST ≥ 5 mm or positive IGRA should receive this classification (if they are not already Class B1 TB, Pulmonary).

- ☐ No LTBI treatment
- ☐ Current LTBI treatment *(Indicate medications in Part 7)*
- ☐ Completed LTBI treatment *(Indicate medications in Part 7)*

☐ **Class B3 TB, Contact Evaluation**
Applicants who are a recent contact of a known tuberculosis case.

- ☐ No preventive treatment
- ☐ Current preventive treatment *(Indicate medications in Part 7)*
- ☐ Completed preventive treatment *(Indicate medications in Part 7)*

Source Case:

Name _____

Alien Number _____

Relationship to Contact _____

Date Contact Ended *(mm-dd-yyyy)* _____

Type of Source Case TB *(Mark only one and attach DST results)*

- ☐ Pansusceptible TB
- ☐ MDR TB (resistant to at least INH and rifampin)
- ☐ Drug-resistant TB other than MDR TB
- ☐ Culture negative
- ☐ Culture results not available

Remarks

7. Previous Tuberculosis Diagnosis and Treatment History for Applicants Diagnosed or Treated Through Panel Physician

Complete this section only if one of the following is true *(mark appropriate option):*

☐ Applicant was diagnosed with tuberculosis disease by the panel physician

☐ Applicant was on tuberculosis treatment at the time of presentation for their medical examination

How was the diagnosis made: ☐ Positive laboratory tests ☐ Clinical diagnosis

Diagnostic Chest Radiograph

Facility performing chest radiograph: _____

Date Radiograph obtained *(mm-dd-yyyy):* _____

Findings Present

☐ Infiltrate or consolidation
☐ Cavitary lesion
☐ Nodule or mass with poorly defined margins (such as tuberculoma)
☐ Hilar/mediastinal adenopathy
☐ Pleural effusion
☐ Miliary findings
☐ Discrete linear opacity
☐ Discrete nodule(s) without calcification
☐ Volume loss or retraction
☐ Other
☐ Normal or no findings suggestive of tuberculosis

Sputum Smear Results

Date specimen obtained *(mm-dd-yyyy)*	Date specimen reported *(mm-dd-yyyy)*	Positive	Negative
1.			
2.			
3.			

Sputum Culture Results

Date specimen obtained *(mm-dd-yyyy)*	Date specimen reported *(mm-dd-yyyy)*	Positive	Negative	NTM	Contaminated
1.					
2.					
3.					

Drug Susceptibility Test Results. Attach with DS Forms.

Method of DST:	Date specimen obtained *(mm-dd-yyyy)*	Date DST reported *(mm-dd-yyyy)*
☐ MGIT ☐ Agar ☐ LJ		

Drug		Susceptible	Resistant
Required for first-line DST	Isoniazid		
	Rifampin		
	Ethambutol		
	Pyrazinamide		
Required for multidrug-resistant cases	Ethionamide		
	Amikacin		
	Capreomycin		
	Para-aminosalycilic acid *(PAS)*		
	Fluoroquinolone, specify: _____		
	Other, specify:		

7. Previous Tuberculosis Diagnosis and Treatment History for Applicants Diagnosed or Treated Through Panel Physician, Continued

Were molecular tests used in addition to the required sputum smears, cultures, and DST:

☐ No

☐ Yes *(mark all that apply)*:

Molecular Test	Mycobacterium Tuberculosis		Rifampin Resistance		Isoniazid Resistance		Second-Line Test
	Positive	Negative	Positive	Negative	Positive	Negative	
☐ Hain Line Probe Assay							☐ Performed, attach results
☐ GeneXpert							

Tuberculosis Treatment

Treating physician or institution

☐ DGMQ-Designated DOT site: _____

☐ Non-DGMQ Designated DOT site: _____

Drug	Dosage	Start Date *(mm-dd-yyyy)*	End Date *(mm-dd-yyyy)*
Isoniazid			
Rifampin			
Ethambutol			
Pyrazinamide			
Other, specify:			

PAPERWORK REDUCTION ACT AND CONFIDENTIALITY STATEMENTS

PAPERWORK REDUCTION ACT STATEMENT

Public reporting burden for this collection of information is estimated to average 20 minutes per response, including time required for searching existing data sources, gathering the necessary documentation, providing the information and/or documents required, and reviewing the final collection. You do not have to supply this information unless this collection displays a currently valid OMB control number. If you have comments on the accuracy of this burden estimate and/or recommendations for reducing it, please send them to PRA_BurdenComments@state.gov

CONFIDENTIALITY STATEMENT

AUTHORITIES: The information asked for on this form is requested pursuant to Section 212(a) and 221(d) and as required by Section 222 of the Immigration and Nationality Act. Section 222(f) provides that the records of the Department of State and of diplomatic and consular offices of the United States pertaining to the issuance and refusal of visas or permits to enter the United States shall be considered confidential and shall be used only for the formulation, amendment, administration, or enforcement of the immigration, nationality, and other laws of the United States. Certified copies of such records may, in the discretion of the Secretary of State, be made available to a court provided the court certifies that the information contained in such records is needed in a case pending before the court.

PURPOSE: The U.S. Department of State uses the facts you provide on this form primarily to determine your classification and eligibility for a U.S. immigrant visa. Individuals who fail to submit this form or who do not provide all the requested information may be denied a U.S. immigrant visa. Although furnishing this information is voluntary, failure to provide this information may delay or prevent the processing of your case.

ROUTINE USES: If you are issued an immigrant visa and are subsequently admitted to the United States as an immigrant, the Department of Homeland Security will use the information on this form to issue you a Permanent Resident Card, and, if you so indicate, the Social Security Administration will use the information to issue a social security number. The information provided may also be released to federal agencies for law enforcement, counterterrorism and homeland security purposes; to Congress and courts within their sphere of jurisdiction; and to other federal agencies who may need the information to administer or enforce U.S. laws. More information on the Routine Uses for this collection can be found in the System of Records Notice State-24, Medical Records.

Appendix F: U.S DS-3026

Photo

U.S. Department of State

MEDICAL HISTORY AND PHYSICAL EXAMINATION WORKSHEET

For Use with DS-2054

OMB No. 1405-0113
EXPIRATION DATE: 09/30/2017
ESTIMATED BURDEN: 30 minutes
(See Page 2 - Back of Form)

Name *(Last, First, MI)*	Exam Date *(mm-dd-yyyy)*
Birth Date *(mm-dd-yyyy)*	Passport Number	Alien *(Case)* Number

1. Past Medical History

No	Yes		No	Yes	
		General			**Obstetrics and Sexually Transmitted Diseases**
☐	☐	Illness or injury requiring hospitalization *(including psychiatric)*	☐	☐	Pregnancy, current
					Estimated delivery date *(mm-dd-yyyy)* _____
		Cardiology	☐	☐	Pregnancy, birth dates *(mm-dd-yyyy)*
☐	☐	Hypertension			_____ _____ _____
☐	☐	Congestive heart failure or coronary artery disease			_____ _____ _____
☐	☐	Arrhythmia			
☐	☐	Rheumatic heart disease			**Previous treatment for sexually transmitted diseases, specify date *(mm-yyyy)* and treatment:**
☐	☐	Congenital heart disease	☐	☐	Chancroid _____
			☐	☐	Gonorrhea _____
		Pulmonology	☐	☐	Granuloma inguinale _____
☐	☐	Tobacco use: ☐ Current ☐ Former	☐	☐	Lymphogranuloma venereum _____
☐	☐	Asthma	☐	☐	Syphilis _____
☐	☐	Chronic obstructive pulmonary disease			
☐	☐	Tuberculosis history: Diagnosed *(mm-yyyy)* _____			**Endocrinology**
		Treated *(mm-yyyy)* _____	☐	☐	Diabetes mellitus
☐	☐	Fever	☐	☐	Thyroid disease
☐	☐	Cough			
☐	☐	Night sweats			**Hematologic/Lymphatic**
☐	☐	Weight loss	☐	☐	Anemia
			☐	☐	Sickle Cell Disease
		Psychiatry	☐	☐	Thalassemia major
☐	☐	Major impairment in learning, intelligence, self-care, memory, or communication	☐	☐	Other hemoglobinopathy
☐	☐	Major mental disorder (including bipolar disorder, major depression, mental retardation, post-traumatic stress disorder, schizoaffective disorder, schizophrenia)			**Other**
☐	☐	Use of drugs other than those required for medical reasons	☐	☐	HIV: if previously tested, mm-yyyy of test _____
☐	☐	Addiction (dependence) or abuse of specific substances or drugs on the CSA	☐	☐	Wears glasses or contact lenses
☐	☐	Other substance related disorders (including alcohol abuse or dependence)	☐	☐	Malignancy, specify: _____
☐	☐	Ever caused serious injury to others, caused major property damage or had trouble with the law because of medical condition, mental disorder, or influence of alcohol or drugs	☐	☐	Chronic renal disease
☐	☐	Ever had thoughts of harming yourself	☐	☐	Chronic liver disease *(including hepatitis)*
☐	☐	Ever acted on those thoughts	☐	☐	Hansen's Disease: Diagnosed *(mm-yyyy)* _____
☐	☐	Ever had thoughts of harming others			Treated *(mm-yyyy)* _____
☐	☐	Ever acted on those thoughts	☐	☐	Other medical conditions requiring treatment, specify:
					_____
		Neurology			_____
☐	☐	History of stroke	☐	☐	Disabilities *(including loss of arms or legs)*, specify:
☐	☐	Seizure disorder			_____
					_____
☐	☐	**Applicant appears to be providing unreliable or false information, specify in remarks**			_____

2. Current Medications *(List all current medications)*

_____
_____
_____
_____

3. Previous Surgeries *(List all previous surgeries)*

_____
_____
_____
_____

4. Vital Signs and Vision

Height _____ cm	BP _____ / _____	Temperature _____ °C	Visual acuity at 20 feet:
Weight _____ kg	Pulse _____ / min	Respiratory Rate _____ / min	Uncorrected L 20/ _____ R 20/ _____
BMI _____ kg/m²			Corrected L 20/ _____ R 20/ _____

5. Physical Examination *(include all findings and give details in Remarks)*

N, normal; A, abnormal

N	A		N	A	
☐	☐	General appearance	☐	☐	Inguinal region *(including adenopathy)*
☐	☐	Nutritional status *(including acute wasting and or chronic stunting malnutrition)*	☐	☐	Musculoskeletal system *(including gait)*
			☐	☐	Extremities *(including pulses, edema)*
☐	☐	Hearing and ears	☐	☐	Skin *(including hypopigmentation or anesthesia consistent with Hansen's Disease, evidence of self-inflicted injury or injections)*
☐	☐	Eyes			
☐	☐	Nose, mouth, and throat *(include detail)*	☐	☐	Hematologic *(including signs of anemia such as pallor, koilonychia)*
☐	☐	Heart *(S1, S2, murmur, rub)*	☐	☐	Lymph nodes
☐	☐	Lungs	☐	☐	Nervous system *(including nerve enlargement)*
☐	☐	Abdomen *(including liver, spleen)*	☐	☐	Mental status *(including mood, intelligence, perception, thought processes, and behavior during examination)*
☐	☐	Genitalia *(including infection(s))*			

6. Mental Health Specialist

☐ Referral made to mental health specialist. If so, attach report.

7. Syphilis Laboratory Results and Treatment

☐ Laboratory testing not done

	Test Name	Date specimen reported *(mm-dd-yyyy)*	Positive	Negative	Initial Titer
Screening					
Confirmatory					

Treated
☐ Yes
☐ No

If treated, therapy:
☐ Benzathine penicillin, 2.4 MU IM
☐ Other *(therapy, dose)*: _____

Treated by panel physician: ☐ Yes ☐ No

Stage of syphilis *(mark one)*:
☐ Primary
☐ Secondary
☐ Early latent
☐ Late latent or latent of unknown duration
☐ Tertiary
☐ Neurosyphilis
☐ Congenital

Date(s) treatment given *(mm-dd-yyyy)*
_____ _____ _____

8. Diagnosis and Treatment of Other Sexually Transmitted Infections

Infection: ☐ Chancroid ☐ Gonorrhea ☐ Granuloma inguinale ☐ Lymphogranuloma venereum

Diagnosed by panel physician: ☐ Yes ☐ No Treated by panel: physician: ☐ Yes ☐ No

Drug	Dosage	Start Date *(mm-dd-yyyy)*	End Date *(mm-dd-yyyy)*

9. Diagnosis and Treatment for Hansen's Disease

Type of Hansen's Disease

☐ Multibacillary
☐ Paucibacillary

Treatment

☐ Partial
☐ Completed

Treated by panel physician

☐ Yes
☐ No

Drug	Dosage	Start Date *(mm-dd-yyyy)*	End Date *(mm-dd-yyyy)*

If not treated by panel physician, was referral made by panel physician to another provider for treatment:

☐ Yes. Provide facility name: _____
☐ No

Diagnosis

☐ Initial diagnosis made by panel physician
☐ Initial diagnosis made by non-panel physician before medical evaluation by panel physician

If so, year of diagnosis: _____

10. Remarks

_____

_____

_____

_____

_____

PAPERWORK REDUCTION ACT AND CONFIDENTIALITY STATEMENTS

PAPERWORK REDUCTION ACT STATEMENT

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PURPOSE The U.S. Department of State uses the facts you provide on this form primarily to determine your classification and eligibility for a U.S. immigrant visa. Individuals who fail to submit this form or who do not provide all the requested information may be denied a U.S. immigrant visa. Although furnishing this information is voluntary, failure to provide this information may delay or prevent the processing of your case.

ROUTINE USES If you are issued an immigrant visa and are subsequently admitted to the United States as an immigrant, the Department of Homeland Security will use the information on this form to issue you a Permanent Resident Card, and, if you so indicate, the Social Security Administration will use the information to issue a social security number. The information provided may also be released to federal agencies for law enforcement, counterterrorism and homeland security purposes; to Congress and courts within their sphere of jurisdiction; and to other federal agencies who may need the information to administer or enforce U.S. laws. More information on the Routine Uses for this collection can be found in the System of Records Notice State-24, Medical Records.

Appendix G: U.S DS-2054

Photo

U. S. Department of State

MEDICAL EXAMINATION FOR IMMIGRANT OR REFUGEE APPLICANT

For use with DS-3030

OMB No. 1405-0113
EXPIRATION DATE: 09/30/2017
ESTIMATED BURDEN: 10 minutes
(See Page 2 - Back of Form)

Name *(Last, First, MI)*	Birth Date *(mm-dd-yyyy)*	Sex ☐ M ☐ F

U.S. Consul *(City, Country)*	Passport Number	Alien *(Case)* Number

Birthplace *(City, Country)*	Present Country of Residence	Prior Country
Present Address of Residence	**Present City of Residence**	**Present Postal Code of Residence**
Intended US Address	**Intended US City**	**Intended US State**
Intended US Postal Code	**E-mail Address**	

Date of Medical Exam (*Date of physical exam or date of final TB culture results, if cultures performed) (mm-dd-yyyy)*

Date Exam Expires *(3 months if Class A TB, or Class B1 TB, otherwise 6 months) (mm-dd-yyyy)*

Exam Place of Current Exam *(City, Country)*	Date of Prior Exam, if any *(mm-dd-yyyy)*

Panel Physician Performing Exam	Panel Site	Radiology Facility
Sputum Smear Laboratory	**Sputum Culture Laboratory**	**Syphilis Laboratory**
Drug Susceptibility Test Laboratory	**DOT Facility**	

Applicant Category *(Mark One)*	Immigrant Visa	Refugee	Asylee	Non-Immigrant Visa *(NIV)*	Parolee
	☐ Immigrant ☐ Special Immigrant *(SIV)* ☐ Diversity ☐ Adoptee	☐ Refugee ☐ Visa 93	☐ Asylee ☐ Visa 92	☐ K-Visa ☐ Other NIV	☐ Parolee

1. Classification *(Check all boxes that apply)*

☐ **No apparent defect, disease, or disability** *(See Worksheets DS-3025, DS-3026, DS-3030)*

☐ **Class A Conditions** *(See Worksheets DS-3025, DS-3026, DS-3030)*

- ☐ Tuberculosis disease
- ☐ Syphilis, untreated
- ☐ Chancroid, untreated
- ☐ Gonorrhea, untreated
- ☐ Granuloma inguinale, untreated
- ☐ Lymphogranumoma venerum, untreated
- ☐ Hansen's Disease, untreated multibacillary or paucibacillary
- ☐ Addiction or abuse of specific substance on the CSA
- ☐ Any physical or mental disorder *(including other substance-related disorder)* with harmful behavior or history of such behavior likely to recur
- ☐ Immigrant visa applicant refuses vaccinations

☐ **Class B Conditions** *(See Worksheets DS-3025, DS-3026, DS-3030)*

Tuberculosis

- ☐ B1 TB, Pulmonary
- ☐ B1 TB, Extrapulmonary
- ☐ B2 TB, LTBI Evaluation
- ☐ B3 TB, Contact Evaluation

Hansen's Disease

- ☐ Multibacillary, treated
- ☐ Paucibacillary, treated
- ☐ Syphilis, treated within last year
- ☐ Any physical or mental disorder *(excluding addiction or abuse of specific substance on the CSA but including other substance-related disorder)* without harmful behavior or history of such behavior unlikely to recur
- ☐ Sustained, full remission of addiction or abuse of specific substance on the CSA

☐ **Class B Other** *(Specify or give details from worksheets)*

2. Immunization Documentation for Immigrant Visa Applicants *(See DS-3025, mark one)*

US vaccination requirements complete:

☐ Requesting Blanket Waiver

US vaccination requirements NOT complete:

☐ Requesting Individual Waiver based on religious or moral convictions

☐ Requesting Adoptee Exemption

☐ Applicant refuses vaccinations

3. Applicant I certify that I understand the purpose of the medical examination and I authorize the required tests to be completed.	Applicant Signature	Date *(mm-dd-yyyy)*
4. Panel Physician I attest that I performed this examination and that I have an agreement with the Department of State.	Panel Physician Signature	Date *(mm-dd-yyyy)*

PAPERWORK REDUCTION ACT AND CONFIDENTIALITY STATEMENTS

PAPERWORK REDUCTION ACT STATEMENT

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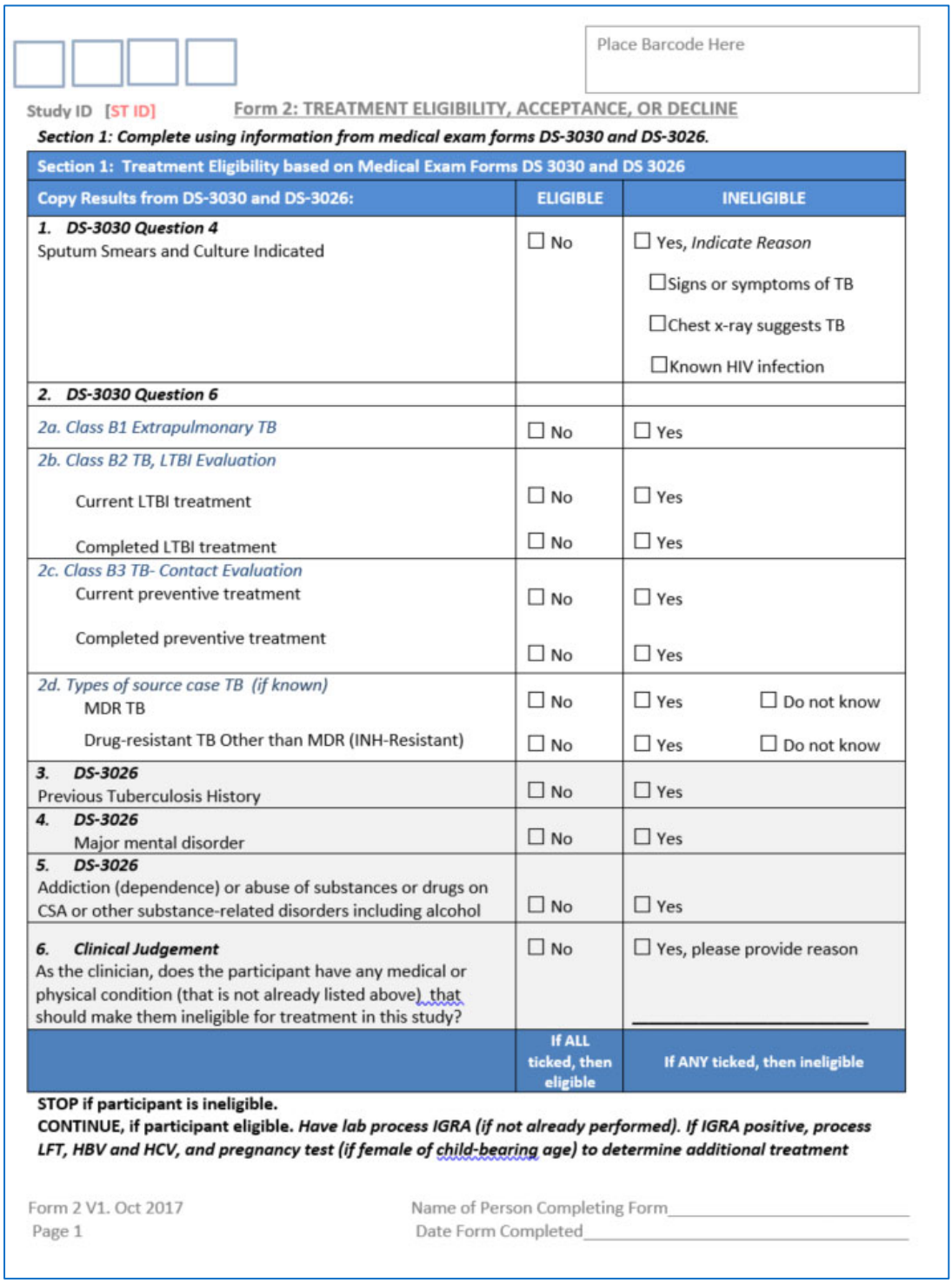
Appendix H: Form 2: Treatment Eligibility, Acceptance, and Decline



☐☐☐☐

Place Barcode Here

Study ID [ST ID]

Form 2: TREATMENT ELIGIBILITY, ACCEPTANCE, OR DECLINE

Section 1: Complete using information from medical exam forms DS-3030 and DS-3026.

Section 1: Treatment Eligibility based on Medical Exam Forms DS 3030 and DS 3026		
Copy Results from DS-3030 and DS-3026:	**ELIGIBLE**	**INELIGIBLE**
1. DS-3030 Question 4 Sputum Smears and Culture Indicated	☐ No	☐ Yes, *Indicate Reason* ☐ Signs or symptoms of TB ☐ Chest x-ray suggests TB ☐ Known HIV infection
2. DS-3030 Question 6		
2a. Class B1 Extrapulmonary TB	☐ No	☐ Yes
2b. Class B2 TB, LTBI Evaluation Current LTBI treatment	☐ No	☐ Yes
Completed LTBI treatment	☐ No	☐ Yes
2c. Class B3 TB- Contact Evaluation Current preventive treatment	☐ No	☐ Yes
Completed preventive treatment	☐ No	☐ Yes
2d. Types of source case TB (if known) MDR TB	☐ No	☐ Yes ☐ Do not know
Drug-resistant TB Other than MDR (INH-Resistant)	☐ No	☐ Yes ☐ Do not know
3. DS-3026 Previous Tuberculosis History	☐ No	☐ Yes
4. DS-3026 Major mental disorder	☐ No	☐ Yes
5. DS-3026 Addiction (dependence) or abuse of substances or drugs on CSA or other substance-related disorders including alcohol	☐ No	☐ Yes
6. Clinical Judgement As the clinician, does the participant have any medical or physical condition (that is not already listed above) that should make them ineligible for treatment in this study?	☐ No	☐ Yes, please provide reason _____
	If ALL ticked, then eligible	**If ANY ticked, then ineligible**

STOP if participant is ineligible.

CONTINUE, if participant eligible. ***Have lab process IGRA (if not already performed). If IGRA positive, process LFT, HBV and HCV, and pregnancy test (if female of child-bearing age) to determine additional treatment***

Form 2 V1. Oct 2017
Page 1

Name of Person Completing Form_____
Date Form Completed_____

eligibility criteria.
Complete Section 2 of this form.

Section 2: Record results of IGRA, LFT, HBV and HCV, and pregnancy test results to further determine eligibility.

Section 2: Treatment Eligibility based on Lab Results		
Lab Results	**ELIGIBLE**	**INELIGIBLE**
7. IGRA Results *(Record IGRA Result on DS 3030 Form Question 1)*	☐ Positive	☐ Negative ☐ Indeterminate
8. Hepatitis B (HBV) positive?	☐ No	☐ Yes
9. Hepatitis C (HCV) positive?	☐ No	☐ Yes
10. Baseline LFTs 5x elevated upper limit of normal?	☐ No	☐ Yes
11. For participants with known liver disease or disorder, ALT >3x upper limit of normal or total bilirubin is >2x upper limit of normal?	☐ No	☐ Yes
12. Pregnant based on test results?	☐ No	☐ Yes
	If ALL ticked, then eligible	**If ANY ticked, then ineligible**

STOP if participant is ineligible. ***For those who have an IGRA positive but are ineligible based on LFT, HBV or HCV, or pregnancy test results, recommend follow-up in the U.S and give information on signs and symptoms of TB disease. For those with indeterminate results recommend follow-up in the U.S.***

CONTINUE, if eligible. ***Discuss results with participants and offer LTBI treatment using 3HP.***
Complete Section 3 of this form.

Name of Person Completing Form_____
Date Form Completed_____

Place Barcode Here

Study ID [ST ID]

Form 2: TREATMENT ELIGIBILITY, ACCEPTANCE, OR DECLINE

Section 3: For participants eligible for treatment, provide all lab results and 3HP LTBI treatment information. Ask a few more eligibility questions.

Section 3: Discuss LTBI Results and Ask Participants Additional Questions		
Additional Questions for Participants to Determine Treatment Eligibility	**ELIGIBLE**	**INELIGIBLE**
13. Ask participants to list any medicines that they know that they are allergic to. *Are any listed medicines participant allergic to related to isoniazid or rifapentine/rifamycins?*	☐ No	☐ Yes
14. **IF FEMALE, ask if:**		
Planning to get pregnant in the next four months?	☐ No	☐ Yes
Breastfeeding?	☐ No	☐ Yes
Able to avoid pregnancy? (For example, if pre- or post-menopausal, abstaining from sex, willing to use condoms or IUDs, answer yes.)	☐ ***YES***	☐ ***NO***
	If ALL ticked, then eligible	**If ANY ticked, then ineligible**

STOP if participant is ineligible. ***Recommend follow-up in the U.S. and give information on signs and symptoms of TB disease.***
CONTINUE, if eligible. ***Offer 3HP LTBI treatment. Share and review "Treatment Information" factsheet with participant and address any questions or concerns participants may have about treatment.***
Complete Section 4

Name of Person Completing Form_____
Date Form Completed_____

Place Barcode Here

Study ID [ST ID]

Form 2: TREATMENT ELIGIBILITY, ACCEPTANCE, OR DECLINE

Section 4: Offer participant 3HP LTBI treatment and record participant's decision to accept or decline treatment.

Section 4: Participant's Acceptance or Decline of 3HP LTBI Treatment
15. Check the appropriate box below to indicate participant's decision to receive LTBI treatment **[TREAT]**
☐ **A Acceptance:** Participant accepts offer of 3HP LTBI treatment ○ *Provide participant with DOT schedule, clinic information and "Taking 3HP Treatment Information".* ○ *Collect participant's contact information and travel information (use Form 3).*
☐ **D Declined**: Participant declines offer of 3HP LTBI treatment ○ *Ask participant reasons for declining treatment. Write down all reasons provided by participant for decline in box below (continue on back, if needed)*

Name of Person Completing Form_____

Date Form Completed_____

Appendix I: LTBI Treatment Information

Protect You and Your Family and Prevent TB Disease
Take Latent TB Infection Treatment

Your latent TB infection test result.
Your test results shows that you have latent TB infection.

What is latent TB infection?
Latent TB infection means you have the germ that causes TB disease in your body. The reason you do not feel sick is because your body is able keep the TB germs under control. If your body becomes weak, the TB germs can become active and you can develop TB disease, feel sick, and spread the germs to your family and friends.

What can you do to prevent developing TB disease?
To prevent TB disease, you can take latent TB infection treatment. Taking treatment is **the only way** to kill the TB germs in your body.

What type of latent TB infection treatment will be provided to you as part of this study?
You will receive the 3HP latent TB infection treatment. This treatment contains two medicines, rifapentine and isoniazid. You will take a dose once a week, for 12 weeks with a vitamin B6 pill.

All the medicines used in this study are approved by the U.S. Food and Drug Administration (FDA). The U.S. Centers for Disease Control and Prevention (CDC) recommends this treatment to patients in the United States to prevent TB disease **for many years**. The World Health Organization also endorses this treatment. **In Vietnam, only rifapentine is currently available as part of this study.**

Latent TB Infection
Treatment Information

What are the possible side effects of taking the 3HP latent TB infection treatment?

All medicines can cause side effects. Some side effects may be mild and some may be serious. *Rifapetine may cause your tears, sweat, saliva, and urine to turn orange in color. If you wear contact lenses or dentures, they may become discolored.*

If you experience any of these possible side effects, call the doctor or nurse right away.

- Dizzy or lightheaded when sitting, standing, or lying down, or fainting
- Less appetite, or no appetite for food
- Stomach upset, nausea, or vomiting
- Stomach pain or stomach cramps
- Pain in your lower chest or heartburn
- Flu-like symptoms with or without fever
- Severe tiredness or weakness
- Fevers or chills
- Severe diarrhea or light colored stools (poop)
- Brown, tea-colored, or cola-colored urine
- Skin or whites of your eyes appear yellow
- Pain or tingling in your hands, arms, or leg
- Skin rash or itching
- Bruises, or red and purple spots on your skin that you cannot explain
- Nosebleeds, or bleeding from your gums or around your teeth
- Shortness of breath
- Although rare, if experiencing severe allergic reaction, seek immediate medical attention: swelling of lips, eyes, throat, arms, or legs, or difficulty breathing or wheezing

At each of your treatment visits, we will check to see if you have had any side-effects. If you have side effects, you **must** tell your study doctor, nurse, or coordinator right away, because it could mean you have liver damage.

These medicines can also interact with other **over-the-counter and prescription medicines**, and with alcohol. Please tell us before you start any new medicines. Avoid taking Tylenol (acetaminophen, paracetamol) and drinking alcohol while you are taking isoniazid and rifapentine.

Latent TB Infection Treatment Prevents TB Disease

Taking treatment prevents TB disease!

If you choose to take treatment:

- You will be given the same medicine that is used in the United States.
- You can complete treatment here in Vietnam before you leave for the United States.
- Treatment will be free at no cost to you.
- Treatment will be given once a week for 12 weeks as Cho Ray Hospital Visa Medical Department. We will ask you questions about your health and any side effects.
- You will be reimbursed for your time and travel for each clinic visit in Vietnam (250,000VND per visit)

After you complete treatment in Vietnam:

- We will ask you some questions about your experience taking treatment
- You will be given a certificate to show you completed your treatment. You can show it to the local Health Department when you arrive in the United States. Some jobs and schools in the United States may want to see the treatment completion certificate as well.

If you leave for the United States, before you finish your treatment:

- If you have completed at least 6 doses of treatment at Cho Ray Hospital Visa Medical Department, we will provide you with your remaining pills (6 doses) to take on your own in the U.S.
- You will be given instructions on how to take your medicine and what to do if you have any side effects.
- You will be asked to keep a record of when you took your medicine.
- A healthcare worker in the U.S. will call you to check that you are taking your pills and that you do not have any side effects. You will be reminded to visit your local health department in the US after you arrive for a follow-up visit.
- You can call a study healthcare worker in the U.S. if you have any questions or concerns.
- You will receive a certificate for treatment completion.

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Latent TB Infection Treatment Prevents TB Disease

If you choose NOT to take the latent TB infection treatment in Vietnam as part of this study:

- We will ask you to provide your reasons for why you do not want to take the treatment
- We will give you a record card with your latent TB infection results and recommend that you follow-up with the local health department after you arrive in the United States to discuss treatment options.
- We will provide you with information on signs and symptoms of TB disease since you have latent TB infection and the TB germs in your body may become active.

Reminders

- TB disease can be prevented by taking latent TB infection treatment.
- As part of this study, treatment will be provided free of charge here in Vietnam before you leave for the United States.
- The treatment medicine we will provide you with is the same that the doctors are using in the United States.
- You can be treated for latent TB infection in the United States without being part of this study.
- **Taking part or not taking part in this study will NOT affect your medical exam or chances of getting a visa.**

For more information on this study, TB disease, or latent TB infection, talk to Cho Ray Hospital Visa Medical Department study staff

Appendix J: LTBI Test Status Card for Ineligibles and Decliners

Name: DOB: | |

QFT: ❑ Pos ❑ Neg ❑ Indeterminate Date: | |

Chest X-Ray: Date: | | ❑ Normal ❑ Abnormal (Stable)

Treatment Started: ❑ Yes ❑ No Completed ❑ Yes ❑ No

Notes:

Provider Name:

Cho Ray Hospital Visa Medical Dept. HCMC, Vietnam

Signature: Phone: ( )

YOUR LATENT TB INFECTION (LTBI)

TEST RECORD

- Keep this card with you and take to clinic appointments
- Show this card to the doctor, so they know if you have been tested for latent TB infection but not treated
- Call your doctor if you have any signs or symptoms of TB disease for 2 or more weeks:
  - Cough
  - Chest pain
  - Coughing up blood
  - Losing weight without trying
  - Feeling weak and tired
  - Fever and chills
  - Night sweats

Appendix K: Form 3: Contact and Travel Information

Study ID [ST ID]

Place Barcode Here

FORM 3: PARTICIPANT CONTACT AND TRAVEL INFORMATION FOR 3HP LTBI TREATMENT

3HP LTBI Treatment Start Date: M M – D D – Y Y Y Y

PARTICIPANT INFORMATION

Participant Name: _____
First *Surname*

Address in Vietnam: _____

_____

Alternate Address (if applicable): _____

_____

Mobile Phone Number Vietnam: _____

Alternative (family member) Phone Number: _____ Work Phone Number: _____

Email: _____

Is patient known contact to TB case taking active TB treatment at Cho Ray Visa Medical Department?
☐ No ☐ Yes, list names below

_____

Are other persons from household participating in LTBI study?
☐ No ☐ Yes, list names below

EMERGENCY CONTACT INFORMATION FOR PARTICIPANT IN VIETNAM

Name : _____

Phone Number _____ Email: _____

_____

Name of Person Completing Form :_____

Study ID [ST ID]

Place Barcode Here

FORM 3: PARTICIPANT CONTACT AND TRAVEL INFORMATION FOR 3HP LTBI TREATMENT

U.S. Travel Date? ***Ask participant if they have a planned travel date. List below. If it is before anticipated treatment completion, please remind participant the importance completing treatment and that it is best to complete by DOT in Vietnam. But If patient completes at least 8 doses by DOT, offer the remaining 4 doses to take in U.S.***

Travel Date: ☐☐ - ☐☐ - ☐☐☐☐
M M D D Y Y Y Y

U.S Relocation Information

Address:

Phone number in U.S. where you can be reached:

Alternate phone number in U.S. where you can be reached:

Email Address:

U.S. Contact's Address: ***This should be someone in the U.S. who knows how to locate participant (such as family or friend)***

U.S. Contact's Name:

U.S. Contact's Address:

U.S. Contact's Phone Number:

U.S. Contact's Email:

Name of Person Completing Form :_____

Appendix L: Taking 3HP

Taking 3HP (Isoniazid and Rifapentine)
Latent TB Infection Treatment Information

You have been given medicine to treat your latent TB infection. This medicine will help **PREVENT** you from getting TB disease. This medicine contains Isoniazid and Rifapentine. You will also be given a Vitamin B6.

Your Latent TB Infection Medicine Schedule:

Your medicine will be given to you at the Cho Ray Hospital Visa Medical Department once a week for 12 weeks.

Treatment Place: Cho Ray Hospital Visa Medical Department Clinic												
Doctor Name **Phone Number** **Nurse Name** **Phone Number**												
Treatment Start Date:												
Weekly Appointment **DAY** **TIME**_____			☐ Monday		☐ Tuesday		☐ Wednesday		☐ Thursday		☐ Friday	
Weekly Dose Number (check box after taking dose)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ 11	☐ 12

- At the weekly visit, a nurse will watch take you the medicine and will check to see if you are having any problems with out medicine.
- You can ask any questions about the treatment at the visit or you can call the clinic
- If you cannot make your treatment appointment, call the clinic reschedule as soon as possible
- Tell your nurse and doctor about all other medicines you are taking or planning to start.
- If you see other doctors, tell them that you are being treated for latent TB infection as part of this study.
- **Let the Nurse know if you have made your travel plans to the United States**

Most people can take their TB medicines without any problems. But any medicine you take may cause problems. Turn to the next page for Tips and Side Effects you should know about while taking this medicine.

Taking 3HP (Isoniazid and Rifapentine) Latent TB Infection Treatment Information

Tips for Taking this Medicine

- Your stomach might feel upset after taking medicine. Eating something before taking your medicine, may help prevent your stomach from feeling upset
- Avoid alcohol use while on this medicine. Alcohol use may cause side effects.
- Avoid taking Tylenol (acetaminophen, paracetamol) while on this medicine
- Your urine, saliva, and tears might turn an orange-red color while on this medicine. This is normal. If you wear contact lenses or dentures worn during treatment they may become permanently stained.
    - To avoid staining during treatment, you can stop wearing your contact lenses, and wear glasses.
    - If you use dentures, take your dentures out whenever possible.
- **For Women**
    - This medication may interfere with hormone based birth control (including birth control pills, rings, and shots). During treatment, barrier forms of birth control (condoms or diaphragms) should be used to avoid pregnancy.
    - If you become pregnant or think you might be pregnant, tell the doctor or nurse right away.

CALL your doctor or nurse right away if you have ANY of these signs or symptoms:

- Dizzy or lightheaded when sitting, standing, or lying down, or fainting
- Less appetite, or no appetite for food
- Stomach upset, nausea, or vomiting
- Stomach pain or stomach cramps
- Pain in your lower chest or heartburn
- Flu-like symptoms with or without fever
- Severe tiredness or weakness
- Fevers or chills
- Severe diarrhea or light colored stools (poop)
- Brown, tea-colored, or cola-colored urine
- Skin or whites of your eyes appear yellow
- Pain or tingling in your hands, arms, or leg
- Skin rash or itching
- Bruises, or red and purple spots on your skin that you cannot explain
- Nosebleeds, or bleeding from your gums or around your teeth
- Although rare, if experiencing severe allergic reaction, seek immediate medical attention: swelling of lips, eyes, throat, arms, or legs, or difficulty breathing or wheezing

NOTE: People react differently to medicines. If you think you are having any reaction to your treatment, call the doctor right away.

Appendix M: Form 4 DOT and Patient Monitoring

Place barcode here

☐☐☐☐☐☐

Study ID [STID]

Form 4: LTBI DOT and Symptom Monitoring Log

Complete this form at all scheduled LTBI dosing visits. Record all doses taken by DOT and SAT doses dispensed to participants who have completed at least 8 doses of DOT and are leaving to the US before treatment completion.

Treatment Dose: Isoniazid _____mg, Rifapentine _____mg, Vitamin B6 _____mg (Once per week for 3months/12 doses) Weight: _____kg

Date: Dose #	__/__/__ 0 Baseline	__/__/__ 1	__/__/__ 2	__/__/__ 3	__/__/__ 4	__/__/__ 5	__/__/__ 6	__/__/__ 7	__/__/__ 8	__/__/__ 9	__/__/__ 10	__/__/__ 11	__/__/__ 12
DOT dose administered	X	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
SAT dose(s) (✓tick box only if given)	**Do Not dispense SAT doses**							☐	☐	☐	☐	☐	☐
Side Effects: *Ask participant at each visit if they are experiencing any side effects. (✓tick box for all that apply)*													
No adverse reaction	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Loss of appetite	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nausea or vomiting	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Yellow eyes or skin	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Headaches	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Rash/hives	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fever or chills	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Weak, sore muscles, or joints	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Numbness or tingling	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fatigue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dizziness/fainting	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bruising	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Abdominal pain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
(Other symptoms) _____	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Initials of person providing DOT and symptom review													

***Ask participant*: How much time does it take for you to get to this clinic? _____Minutes[F4MIN]**

Form 4 v3. Page 1

Place barcode here

Study ID ☐☐☐☐[ST ID] **Form 4: LTBI DOT and Symptom Monitoring Log**

At each visit check with patient if any changes to travel plans for U.S.

***Ask participant*: How much time does it take for you to get to this clinic?** **Hours_____Minutes_____**

Notes:

Complete Form 6: U.S. 3HP LTBI Treatment Outcome and Perceptions,
For applicants who have:

- Completed INH-RPT treatment at CHR VMD (at least 11/12 doses within 16 weeks)
- Pending Completion of Treatment in U.S
- Incomplete treatment: stopped INH-RPT treatment before completion
  (Lost to follow-up, death, serious side effect, or patient decided to stop treatment and or withdrew consent)

Appendix N: Form 5 Treatment Completion Questionnaire (Vietnam)

Place Barcode Here

Study ID [STID]

Form 5: Treatment Outcome and Perceptions (Vietnam)

Complete this form when the LTBI treatment visit at Cho Ray Hospital Visa Medical Department (CRH VMD) is known to be the last visit (for example, treatment is complete, patient declines future visits, or patient will leave country before next visit)
Section A: Indicate treatment outcome and dose information
Section B: Ask participants on their last known treatment day their perceptions about their treatment experience.
Remind participant all responses voluntary.

A. Treatment Outcome Information from CRH VMD

1. **Date of Last LTBI DOT Dose at CRH VMD: [F6Q1CREND]**

M M D D Y Y Y Y

2. **How many doses were completed at CHR VMD? (*indicate highest dose number*) [F6Q2CRDOSE]**

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐11 ☐12

3. **What is the LTBI Treatment Outcome at CRH VMD (Please mark one box) [F6Q3CROUT]**

☐ Completed INH-RPT treatment at CRH VMD and immigrating to U.S. (at least 11/12 doses within 16 weeks) A
☐ Completed INH-RPT treatment at CRH VMD but NOT immigrating to U.S. (at least 11/12 doses within 16 weeks) B
☐ Pending Completion of INH-RPT Treatment. Continue treatment in U.S. C
☐ Incomplete Treatment (stopped INH-RPT treatment before completion) D

Indicate reasons for stopping treatment before completion: [F6Q3CRINCO]

☐ Lost to follow-up A
☐ Death B
☐ Serious side effects C *(please explain)*

[F5Q3CRSSER]_____

_____

☐ Participant decided to stop treatment on their own D *(provide participant's reason for stopping treatment below)*

[F5Q3CRPDS]

☐ Other (*please explain*) E [F5Q3CROTH]_____

Form 5
Page 1 of 2

Name of Person Completing Form :_____

Place Barcode Here

Study ID [$TID] **Form 5: Treatment Outcome and Perceptions (Vietnam)**

B. Participant perceptions about treatment experience

Ask participants on their last known treatment day about their LTBI treatment experience. Let them know this information will help us to improve the experience for other immigrants who will be taking LTBI treatment.

4. Why did you decide to take latent TB infection treatment? [F5Q4CRTAKE]

5. Would you recommend taking this treatment to your friends and family who might immigrate to the U.S.? [F5Q6CRREC]

   ☐ Y Yes ☐ N No Please explain why (for yes or no)? [F5Q6CREXPL]

6. Did you experience any challenges with taking your treatment at Cho Ray Hospital Visa Medical Department? [F5Q8CRCHAL]

   ☐ Y Yes ☐ N No

   If yes, please explain why? [F5Q8CREXPL]

7. Did you have to delay your departure to the United States to take this treatment? [F5Q7CRDELAY]

   ☐ Y Yes ☐ N No

   If yes, by how many days? _____[F5Q7CRDAYS]

8. Do you have any suggestions for how we can improve the treatment experience for visa applicants? [F5Q8CRSUGG]

9. A. If these medicines were not available for free through the study, would you have been willing to pay $40 (about 935,000 VND) for this treatment? [F5Q9PAY]

   ☐ Y Yes ☐ N No

   9B. If no, what would you have been willing to pay? [F5Q9B_AMT]

   - ☐ A I would not pay (zero)
   - ☐ B 1 – 10 Dollars (about 233,00 - 233,500 VND)
   - ☐ C 11 – 20 dollars (about 256,800 – 467,000 VND)
   - ☐ D 21 – 30 dollars (about 490,400 – 700,600 VND)
   - ☐ E 31 – 40 dollars (about 723,900 – 934,000 VND)
   - ☐ F Unsure

Name of Person Completing Form :_____

Appendix O: Form 6 Treatment Completion Questionnaire (U.S.)

Place Barcode Here

Study ID [STID]

Form 6: 3HP LTBI Treatment Outcome and Perceptions (U.S.)

Complete this form at the last known 3HP LTBI treatment in the United States.
Section A: Indicate treatment outcome and dose information
Section B: Ask participants who completed their perceptions about their treatment experience. Remind participants that all responses to questions are voluntary.

A. Treatment Dose and Outcome Information for U.S.

1. Date of the last 3HP LTBI Treatment Dose in U.S.: [F6Q1USEND]

M M D D Y Y Y Y

2. Which doses were completed in the U.S.? (*indicate highest dose number*) [F6Q2USDOSE]

☐9 ☐10 ☐11 ☐12

3. What is the 3HP LTBI Treatment Outcome for those completing treatment in U.S.? (Please mark one box) [F6Q3USOUT]

☐ Completed 3HP LTBI treatment in U.S. (at least 11/12 doses) A

☐ Incomplete treatment: Stopped 3HP LTBI treatment before completion B

Indicate reasons for stopping treatment before completion: [F6Q3USINCOM]

☐ Lost to follow-up A
☐ Death B
☐ Serious side effect C (*please explain*) [F6Q3USSSER]

_____

_____

☐ Patient decided to stop treatment on their own D (*provide patient's reason for stopping treatment*)

[F6Q3USPDS]

☐ Other E (*please explain*)_ [F6Q3USOTH] _____

Name of Person Completing Form : _____

Place Barcode Here

Study ID [STID]

Form 6: 3HP LTBI Treatment Outcome and Perceptions (U.S.)

B: Participant's perceptions about treatment experience in U.S.

Ask participants who completed treatment about their 3HP LTBI treatment experience. Let them know this information will help us to improve the experience for other immigrants who will be taking 3HP LTBI treatment.

1. Why did you decide to take latent TB infection treatment? [F6Q4USTAKE]

2. Would you recommend taking this treatment to your friends/family who may immigrate to the U.S.? [F6Q5USREC]

   ☐ Y Yes ☐ N No *Please explain why?* [F6Q5CREXPL]

3. Did you experience any challenges with taking your treatment doses in the U.S? [F6Q6USCHAL]
   ☐ Y Yes ☐ N No *If yes, please explain why?* [F6Q6USEXPL]

4. Did you have to delay your departure to the United States to take this treatment? [F6Q7USDELAY]
   ☐ Y Yes ☐ N No If yes, by how many days?_____ [F6Q7USDAYS]

5. Did you complete your follow-up visit to local health department? [F6Q8USHD]
   ☐ A Yes (provide date MM/DD/YYYY) [F6Q8USHDD] _____
   ☐ B No
   ☐ C Visit planned, but has not occurred yet
   ☐ D Participant does not plan on visiting health department (provide participant's reason for not visiting health department) [F6Q8USHDD] _____

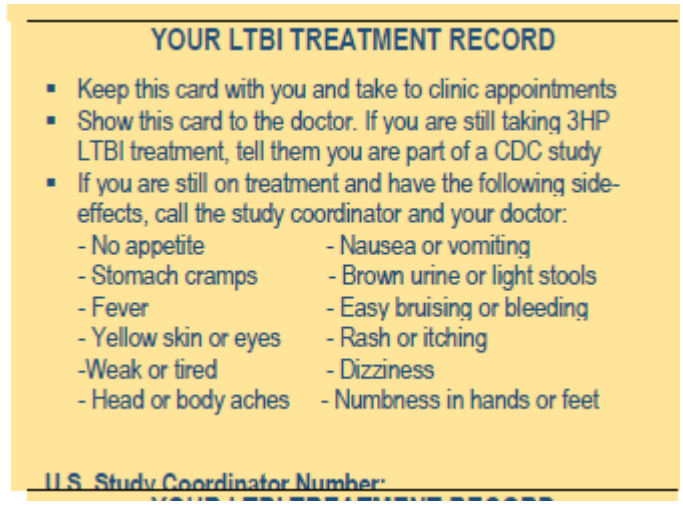
6. Do you have any suggestions on how we can improve you experience in taking latent TB infection treatment? [F6Q9USSUGG]

7. A. If these medicines were not available for free through the study, would you have been willing to pay $40 (about 935,000 VND) for this treatment? [F6Q7PAY]
   ☐ Y Yes ☐ N No

7B. If no, what would you have been willing to pay? [F6Q7B_AMT]
- ☐ A I would not pay (zero)
- ☐ B 1 – 10 Dollars (about 233,00 - 233,500 VND)
- ☒ C 11 – 20 dollars (about 256,800 – 467,000 VND)
- ☐ D 21 – 30 dollars (about 490,400 – 700,600 VND)
- ☐ E 31 – 40 dollars (about 723,900 – 934,000 VND)
- ☐ F Unsure

Name of Person Completing Form :_____

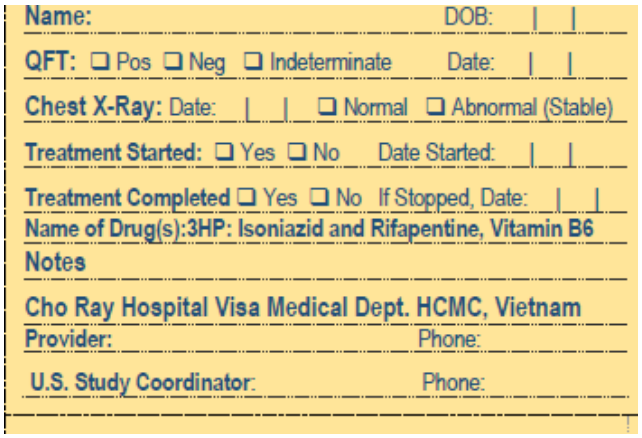
Appendix P: LTBI Test and Treatment Status Card and Completion Certificate



YOUR LTBI TREATMENT RECORD

- Keep this card with you and take to clinic appointments
- Show this card to the doctor. If you are still taking 3HP LTBI treatment, tell them you are part of a CDC study
- If you are still on treatment and have the following side-effects, call the study coordinator and your doctor:
  - No appetite
  - Stomach cramps
  - Fever
  - Yellow skin or eyes
  - Weak or tired
  - Head or body aches
  - Nausea or vomiting
  - Brown urine or light stools
  - Easy bruising or bleeding
  - Rash or itching
  - Dizziness
  - Numbness in hands or feet

U.S. Study Coordinator Number:



Name: DOB: | |

QFT: ❑ Pos ❑ Neg ❑ Indeterminate Date: | |

Chest X-Ray: Date: | | ❑ Normal ❑ Abnormal (Stable)

Treatment Started: ❑ Yes ❑ No Date Started: | |

Treatment Completed ❑ Yes ❑ No If Stopped, Date: | |

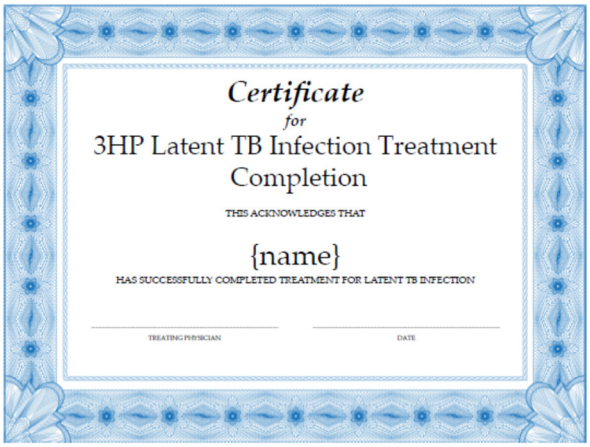
Name of Drug(s):3HP: Isoniazid and Rifapentine, Vitamin B6

Notes

Cho Ray Hospital Visa Medical Dept. HCMC, Vietnam

Provider: Phone:

U.S. Study Coordinator: Phone:



Certificate

for

3HP Latent TB Infection Treatment Completion

THIS ACKNOWLEDGES THAT

{name}

HAS SUCCESSFULLY COMPLETED TREATMENT FOR LATENT TB INFECTION

TREATING PHYSICIAN DATE

Phase 2: Feasibility Study with CHR VMD Healthcare Staff

Appendix Q: Focus Group Informed Consent-(Flesh-Kincaid Reading Level 8.6)

Informed Consent Focus Group Discussion

Study Title: *Phase 2* Preventing TB Overseas Pilot Study (PTOPS): Latent Tuberculosis Infection Testing and Voluntary Treatment for U.S.-Bound Immigrants in Vietnam.

What is the purpose of this study?

This purpose of this study is to help us understand if offering latent TB infection (LTBI) testing and treatment is feasible during the U.S. visa applicant medical exam process. We are interested in hearing your opinions as staff who were involved in Phase 1 of this study. The information you provide will help us address any challenges if the panel sites continue offer LTBI testing and treatment.

Who is conducting this study?

- The U.S. Centers for Disease Control and Prevention
- National Lung Hospital - Vietnam National TB Programme
- Cho Ray Hospital Visa Medical Department (CRH VMD)
- University of California at San Francisco

What will happen if you take part in the study?

Taking part in this study is voluntary. If you agree to be in this study, you will take part in a focus group with four to five other CRH VMD staff. We will ask the group about their opinions on offering LTBI testing and treatment to visa applicants.

We will audio record the focus group to have an accurate record of what was discussed. Only the study team will have access to the recordings. The study team will transcribe the recordings within six months. The recordings will be destroyed after that. Any names recorded will be deleted from the transcripts. If needed, the transcripts will be translated from Vietnamese to English before data analysis.

What are the benefits of participating in the focus group?

The focus group gives you the chance to let us know your opinions about adding LTBI testing and treatment to the medical exam. Providing this information to us could be a future benefit to you, other CRH VMD staff, and the visa applicants as we determine if we should implement LTBI testing and treatment at the panel sites.

What are the risks of participating in the focus group?

There are no anticipated risks to taking part in the focus group. However, some people may feel uncomfortable providing their opinions in a group. If you feel uncomfortable during the focus group, you can stop at any time. While the study team will keep all information discussed in the focus group private, we cannot guarantee that all

of the other participants will not repeat the information outside of the focus group. We will ask that others participating in the focus group to not talk with anyone outside the group about what was talked about in the group, but we cannot guarantee that they will do so

a) Other Information

We will not keep a link between the study data and your identity. When the results of this study are published or presented, we will not use your name. The discussion will take up to two hours. You do not have to answer every question. At any point during the focus group you may refuse to answer any questions or stop participation.

Who can you contact if you have questions or concerns?

Primary contacts	Office Number	After-Hours Number

For questions about your rights as a research subject, contact the Ethical Committee in Biological Medical Research, Ministry of Health that reviews research on human subjects. They will answer questions about your rights as a research subject and take any comments or complaints. You can contact Dr. Nguyen Ngo Quang by calling 0985858558, or by email to quangbyt@yahoo.com

b) Participant statement

SIGN THIS FORM ONLY IF THE STATEMENTS LISTED BELOW ARE TRUE

- You have read the above information.
- You have discussed the information with a member of the study team.
- Your questions have been answered to your satisfaction.
- You have voluntarily decided to take part in this research study.
- You know that after choosing to be in this study, you may stop at any time.

Printed Name of Participant	Signature of Participant	Date	

Printed Name and Title of Person Obtaining Consent	Signature of Person Obtaining Consent	Date	

Appendix R: Focus Group Discussion Guide

Preventing TB Overseas Pilot Study (PTOPS): Latent Tuberculosis Infection Testing and Voluntary Treatment for U.S.-Bound Immigrants in Vietnam
Phase 2

Focus Group Discussion Guide for Cho Ray Hospital Visa Medical Department Staff

Thank you for agreeing to participate in this discussion. My name is _____
I am working on behalf of the US Centers for Disease Control and Prevention, the National Lung Hospital, Cho Ray Hospital Visa Medical Department, and the University of California at San Francisco. The purpose of the focus group discussion is to learn more about your thoughts and experiences with offering latent TB infection (LTBI) testing and treatment to U.S. visa applicants.

We expect the discussion will take about one to two hours. You will receive refreshments for participating in today's discussion.

We will use the information we learn from you today to better understand issues and challenges around testing and treating visa applicants for LTBI. We will also be using your feedback to inform if we should continue to offer visa applicants LTBI testing and treatment at this site and other panel physician sites around the world. If we do expand the offering of LTBI testing and treatment to other panel sites, the information you provide will help us successfully implement the new approach.

I will ask some questions to begin the discussion, and you are free to contribute as you feel comfortable. There is no right or wrong answer to these questions. We are here to learn from you and we are interested in everyone's opinions based on your experiences or the experiences of others you know.

This session will be recorded and [_____] will be taking notes. However, we will destroy the tapes as soon as we have made complete notes of this meeting, and will not use your real names in preparing the notes. We will not use your names in preparing any reports and will disguise your comments so that no one can identify who made specific remarks. After the report is written, we will destroy all notes from this meeting.

Ground rules about conduct of the discussion group:

Participation in the discussion is voluntary, so if you don't want to answer a particular question you don't have to, and you are free to leave at any time. But please remember that we are trying to gather many different opinions and experiences through these discussions and it is important that you share your thoughts if you have something to say. Your thoughts on challenges of this approach are just as important as those on its benefits. Remember we want to hear different points of view so feel free to disagree with others if you wish, but please be respectful of everyone in the group. All participants should do their part to ensure today's discussion remains confidential.

Because we don't want to miss anything, it is important that only one person talks at a time and that you share what you have to say with the group and not the person next to you. Feel free to ask questions of me or [_____] at any time if the questions are unclear.

[Remind participants that the discussion will be recorded]

Q1: Please describe your role and duties for the medical examination process for visa applicants?

- What was your role, if any, in offering latent TB infection testing and treatment as part of this study?

[Go around room and ask each participant to provide information for Q1]

Q2: How do you think offering LTBI testing and treatment to visa applicants went? *Was it a success, was it a failure, why do you feel that way?*

Q3: What do you think some of the benefits would be if LTBI testing and treatment were added to the medical examination process?

Q4: What were some of the challenges you and other staff faced with adding LTBI testing and treatment to the medical examination process?

-*Were there workflow issues for the staff?*

-Did it slow the regular medical examination process down?

- Were there certain parts of the medical examination flow that needed additional help (registration, phlebotomy, lab, pharmacy, or DOT?)

Q5: How do you think the visa applicants felt about LTBI testing and treatment?

- *What do you think were the reasons that some people declined the LTBI test?*
- *For those that were LTBI positive, why do you think some participants declined treatment?*
    - *What could have been done to encourage those who declined to accept treatment?*
    - *Do you think the informed consent was a barrier?*
- *For those participants who took LTBI treatment, how do you think there experience was?*
    - *Did you face any challenges getting the participants to continue taking their medication?*
    - *What did you do to convince participants to complete treatment?*
    - *What could have been done to make it a better experience for the participants?*

Q6: If Cho Ray Hospital Visa Medical Department were to continue to offer LTBI testing and treatment what would need to happen to ensure that it is a success?

-additional resources (human, financial, additional supplies?)

- what kind of (type and content) training would staff need to feel comfortable offering LTBI testing and treatment?

- educational resources for patients and staff?

- any other ideas?

Q7: Is there anything else you would like us to know about LTBI testing and treatment that we haven't already discussed?

Appendix S. Staff Confidentiality Agreement

Recognizing the sensitive nature of, and my access to, information collected as part of the project entitled, "**Preventing TB Overseas Pilot Study (PTOPS): Latent Tuberculosis Infection Testing and Voluntary Treatment for U.S.-Bound Immigrants in Vietnam** ":

- I agree that I will not use, disseminate, disclose or in any way circulate or broadcast any confidential information relating to this project except as necessary to conduct my work on the project.
- I agree that I will keep all computer passwords confidential and will not provide access to any confidential information to any unauthorized person.
- I agree to comply with all applicable laws and regulations regarding the confidentiality of individually identifiable health care information.
- I agree to notify my supervisor immediately should I become aware of or suspect a breach of confidentiality or a situation that could potentially result in a breach, whether this is on my part or on the part of another person.

Date:-

_____

Name (printed):

_____

Signature:

_____

Appendix T. Form 7: Adverse Events Form

Place Barcode Here

PTOPS

Form 7: Adverse Event Form

Study ID: ☐☐☐☐

Complete this form when a participant has a reportable adverse event (AE) (Grade 3 or higher or a Serious Adverse Event) that occurs while taking rifapentine and isoniazid (3HP) treatment and up to 14 days after the final study dose.

For additional instructions, refer to the PTOPS Manual of Operating Procedures.

Record all dates in the following format: DD-MMM-YYYY ***(e.g., 01-JAN-2017)***.

A. Adverse Event Description

1. Report date: ☐☐-☐☐☐-☐☐☐☐
2. Onset date: ☐☐-☐☐☐-☐☐☐☐
   (If pregnancy, report estimated conception date = last menstrual period date + 14 days)
3. What type of reportable event was it **(check only one)**?
   - ☐ Pregnancy **(For pregnancy, complete an AF Form when the outcome of pregnancy is known)**
   - ☐ Liver injury/disorder **Record all laboratory results in section ___**
   - ☐ Systemic drug reaction
   - ☐ Suspected drug interaction **(including methadone)**
   - ☐ Acute cardiovascular event
   - ☐ AIDS-defining illness, other than TB **(Refer to page 4 for a list of WHO Clinical Stage 4 Conditions)**
   - ☐ None of these **(Continue to A4)**
4. Was a diagnosis assigned? ☐ Yes ☐ No **(Skip to A4b)**
   a. If "yes", specify each diagnosis:
   _____
   b. If "no", specify each symptom:
   _____
5. Was this event a worsening of pre-existing symptoms or medical condition to a grade 3 or higher?
   ☐ Yes ☐ No
6. Was this a serious adverse event (SAE) **(A SAE requires that CDC PI and UCSF PI be notified within 48 hours)**
   ☐ Yes ☐ No **(Skip to B1)**
   a. If "yes", indicate type of SAE **(select all that apply)**:
      - ☐ Death
      - ☐ Any life-threatening experience
      - ☐ Any inpatient hospitalization **(>24 hours)** or prolongation of any hospitalization
      - ☐ Persistently or significantly disabling event **(as determined by the principal investigator)**
      - ☐ Congenital anomaly or birth defect
      - ☐ Other medically important event **(an event that may jeopardize the participant's health or may require medical or surgical intervention (treatment) to prevent one of the other SAEs listed above)**

Place Barcode Here

PTOPS
Form 7: Adverse Event Form

Study ID: ☐☐☐☐

B. Management of Adverse Event

1. List signs and Symptoms

_____
_____
_____
_____

2. Were any non-study medications taken within 7 days prior to the AE?
☐ Yes ☐ No ☐ Unknown **(If "Yes", List drug name and dosage)**

_____
_____
_____
_____
_____

3. Are results for any of the following procedures available for this AE?
(If "Yes" to any of the following, report results below)

a. Laboratory evaluations ☐ Yes ☐ No **(LB Form)**
b. Clinical evaluations **(E.g., chest x-ray)** ☐ Yes ☐ No **(CE Form)**
c. Sputum or other specimen collected for AFB workup ☐ Yes ☐ No **(MB Form)**

List the name of the test, date the test was done and the results of each test or procedure done:

_____
_____
_____
_____
_____
_____
_____

4. Treatment start date: ☐☐-☐☐☐-☐☐☐☐

5. After how many drug doses did the AE occur? ☐☐☐

6. Date last 3HP dose was taken? ☐☐-☐☐☐-☐☐☐☐

7. Clinician action taken with regard to study treatment **(check only one)**:
   - ☐ Dose not changed
   - ☐ Dose reduced
   - ☐ Drug interrupted **(i.e., drug held)**
   - ☐ Drug withdrawn **(i.e., permanently discontinued)**
   - ☐ Not applicable **(i.e., not taking study treatment)**

Place Barcode Here

PTOPS
Form 7: Adverse Event Form

Study ID: ☐☐☐☐

C. Conclusion

a. In the opinion of the investigator, what is the attribution to study treatment in causing this AE?
(Refer to attribution scale on page 6. Check only one.)

- ☐ Definite
- ☐ Probable
- ☐ Possible
- ☐ Unlikely
- ☐ Not related
- ☐ Unclassifiable

b. In the opinion of the investigator, is this an anticipated or unanticipated AE?
(Refer to page 6 for definitions. Check only one.)

- ☐ Anticipated
- ☐ Unanticipated

c. Indicate the maximum toxicity grade of event by the time of this report.
(Refer to the Common Terminology Criteria in PTOPS Manual of Procedures. Check only one.)

- ☐ Grade 1
- ☐ Grade 2
- ☐ Grade 3
- ☐ Grade 4
- ☐ Grade 5

Place Barcode Here

PTOPS
Form 7: Adverse Event Form

Study ID: ☐☐☐☐

D. Comments

Answer the questions listed below and provide a summary of the AE:

1. How long, in hours, after the dose immediately before the AE did the signs and symptoms start?

2. Did the participant present with signs and symptoms similar to those reported in this AE report, but of lower toxicity grade, prior to this AE?

3. Was participant seen by an MD, urgent care or ER staff **(including Cho Ray study staff)**?

4. Was alcohol associated with the AE?

5. If applicable, list the medications that were prescribed to treat the AE, including doses and frequency:

6. If applicable, describe any changes shown in the current chest x-ray in comparison to the most recent previously reported chest x-ray:

7. If applicable, describe any additional action **(not reported elsewhere)** taken in response to the AE **(e.g., repeat test, follow-up)**:

8. If applicable, list other factors related to the AE:

9. If applicable, specify how long after the onset date the AE resolved **(hours, days, weeks)**:

10. If applicable, specify whether the participant permanently discontinued study treatment because of medical advice or participant decision:

Place Barcode Here

PTOPS

Form 7: Adverse Event Form

Study ID: ☐☐☐☐

E. Summary of AE

Use the SOAP **(Subjective, Objective, Analysis, and Plan)** format for a brief clinical description. Include the context for clinician action taken in regard to changes in study medication, if applicable.
If more than one AE occurred on the same day, note here and report event on a separate AE form.

F. Form Completion

PRINT name of Principal Investigator or Co-PI: _____

Signature of Principal Investigator or Co-PI: _____

PRINT name of person completing form: _____

Signature of person completing form: _____

Place Barcode Here

PTOPS

Form 7: Adverse Event Form

Date Adverse Event Form completed: ☐☐-☐☐☐-☐☐☐☐

WHO Stage 4 Clinical Conditions (07-Aug-2006)

American trypanosomiasis, reactivation (meningoencephalitis or myocarditis)
Atypical disseminated leishmaniasis
Candidiasis of bronchi, trachea or lungs
Candidiasis, esophageal
Cardiomyopathy, symptomatic, HIV-associated
Cervical cancer, invasive
Cryptococcosis, extrapulmonary, including meningitis
Cryptosporidiosis, chronic intestinal, with diarrhea (>1 months duration)
Cytomegalovirus infection (retinitis or infection of other organs)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV-related
Herpes simplex infection, chronic (orolabial, genital or anorectal site for > 1 month or visceral herpes at any site
Histoplasmosis, disseminated or extrapulmonary
HIV wasting syndrome
Isosporiasis, chronic intestinal (>1 months duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary of brain
Lymphoma (cerebral or B-cell non-Hodgkin)
Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Mycosis, disseminated
Nephropathy, symptomatic, HIV-associated
Pneumocystis pneumonia
Pneumonia, bacterial, recurrent, severe
Progressive multifocal leukoencephalopathy
Salmonella bacteremia, recurrent, nontyphoidal
Toxoplasmosis of brain or CNS

Scale for Attribution of Adverse Events

Category	Definition
Definite	Events occurring within a timely manner after administration of the study drug(s) that are known sequelae to the administration of the study drug(s), and follow a previously documented pattern of reaction but for which no other explanation is known. This category applies to those AEs that the investigator believes are incontrovertibly related to the study drug(s).
Probable	Any event occurring in a timely manner after administration of the study drug(s), that follows a known pattern of reaction to the study drug(s), and for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are believed with a high degree of certainty to be related to the study drug(s).
Possible	Any event occurring in a timely manner after administration of the study drug(s) that does not follow a known pattern of reaction and for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unlikely to be related but cannot be ruled out with certainty.
Unlikely	In general, this category can be considered applicable to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unrelated to administration of the study drug(s).
Not related	Any AE for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the study drug(s) and the AE does not follow any previously documented pattern. This category applies to those AEs that, after careful medical consideration, are clearly and incontrovertibly due to causes other than the study drug(s).
Unclassifiable	There is insufficient information about the AE to allow for an assessment of causality.

Anticipated and Unanticipated Adverse Events (AE)

Category	Definition
Anticipated	AE which meets any one (or both) of the following: 1. Consistent with listing in the current study protocol narrative and/or consent form and/or pharmaceutical package insert for the study treatment(s), in terms of the nature, intensity, and frequency. 2. Based on clinical judgment by the principal investigator/primary treating physician, the adverse event was expected to occur based on the study participant's underlying medical condition and/or concomitant disorder, disease process, or non-study treatment.
Unanticipated	AE which meets BOTH of the following: 1. NOT consistent with listing in the current study protocol narrative and/or consent form and/or pharmaceutical package insert for the study treatment(s), in terms of the nature, intensity, and frequency. AND 2. Based on clinical judgment by the principal investigator/primary treating physician, the adverse event was NOT expected to occur based on the study participant's underlying medical condition and/or concomitant disorder, disease process, or non-study treatment.

Appendix U. Form 8: Adverse Events Follow-Up Form

Place Barcode Here

PTOPS
Form 8: Adverse Event Follow-up Form

Study ID: ☐☐☐☐

Instructions: Complete this Adverse Event Follow-up (AF) Form within 45 days of the onset date, whether the adverse event (AE) has resolved or not. If the AE has not resolved, continue to update the existing AF Form, whenever there is a change in status, until the AE has resolved or the study has ended. Indicate the date when information is updated or added.
In the event of pregnancy, submit an AF Form when the outcome of pregnancy is known.

For additional instructions, refer to the PTOPS Manual of Operating Procedures.

Record all dates in the following format: DD-MMM-YYYY **(e.g., 01-JAN-2017)**.

A. Adverse Event Description

1. Date of AE follow-up visit: ☐☐-☐☐☐-☐☐☐☐
2. AE as initially reported on the AE Form
   a. Onset date: ☐☐-☐☐☐-☐☐☐☐
   b. Diagnosis:

   _____

   OR

   c. Symptom:

   _____

3. Is the **FINAL** diagnosis different from the initial diagnosis or symptom that was originally reported on the AE Form? **(If a symptom was reported on the AE form but a diagnosis is now assigned, select YES and report the diagnosis)**

   ☐ Yes ☐ No **(Skip to Section B)**

   a. If "yes", specify diagnosis:

_____

_____

_____

Place Barcode Here

PTOPS
Form 8: Adverse Event Follow-up Form

Study ID: ☐☐☐☐

B. Management of AE

1. Status of the AE **(check only one)**:
   - ☐ Resolved
   - ☐ Resolved with sequelae

     If resolved, provide resolution date: ☐☐-☐☐☐-☐☐☐☐
   - ☐ Fatal

     If fatal, provide death date: ☐☐-☐☐☐-☐☐☐☐
     (Obtain death certificate)
   - ☐ Resolving **(i.e., improving)**
   - ☐ Not resolved **(i.e., ongoing or worsening)**
   - ☐ Unknown

   a. Pregnancy outcome: **(If "live birth" or "fetal death", continue to B1b, otherwise, skip to B2)**
      - ☐ Not applicable
      - ☐ Spontaneous abortion
      - ☐ Elective abortion
      - ☐ Live birth
      - ☐ Fetal death
      - ☐ Unknown

   b. If "live birth" or "fetal death", were any congenital anomalies present? ☐ Yes ☐ No
      (If "Yes", complete an additional AE Form)

2. Additional tests done in response to this AE:
   (If "Yes" to any of the following, only report new results that were not previously recorded. (Link this AE follow up form to the AE form by report date to an existing form for results already reported.)

   a. Laboratory evaluations ☐ Yes ☐ No
   b. Clinical evaluations **(E.g., chest x-ray)** ☐ Yes ☐ No
   c. Sputum or other specimen collected for AFB workup ☐ Yes ☐ No

Place Barcode Here

PTOPS
Form 8: Adverse Event Follow-up Form

C. Drug Re-challenge

1. Was all or any part of study treatment held for any period of time?
   ☐ Yes ☐ No
   (If "No", Skip to Section D)

2. Was participant re-challenged with the intention of restarting study treatment?
   (Re-starting treatment with a full drug dose is not considered a re-challenge)
   ☐ Yes ☐ No
   (If "Yes", record doses on form 4 DOT Symptom and Monitoring form)

D. Final Conclusion

1. In the opinion of the investigator, what is the final attribution to study treatment in causing this AE?
   (May differ from what was originally reported on the AE Form. Refer to attribution scale on page 6. Check only one.)
   ☐ Definite
   ☐ Probable
   ☐ Possible
   ☐ Unlikely
   ☐ Not related
   ☐ Unclassifiable

2. Was the AE attributed to one or more study drugs? ☐ Yes ☐ No **(Skip to D3)** ☐ Unknown
   a. If "yes", select the study drug(s) that the AE is attributed to **(select all that apply)**:
      ☐ Isoniazid
      ☐ Rifapentine

3. In the opinion of the investigator, is this an anticipated or unanticipated AE?
   (Refer to page 6 for definitions. Check only one.)
   ☐ Anticipated
   ☐ Unanticipated

4. Indicate the maximum toxicity grade, during the course of the AE.
   (Refer to the Common Terminology Criteria version 4.0.3 in the Manual of Procedures. Check only one.)
   ☐ Grade 1
   ☐ Grade 2
   ☐ Grade 3
   ☐ Grade 4
   ☐ Grade 5

Place Barcode Here

PTOPS
Form 8: Adverse Event Follow-up Form

D. Comments _____

Update your previous answers to the questions listed below and provide a summary of the current status of the AE. Only update the answers that have changed from prior report(s).

1. How long, in hours, after the dose immediately before the AE did the signs and symptoms start?
   _____
2. Did the participant present with signs and symptoms similar to those reported in this AE report, but of lower toxicity grade prior to this AE?
   _____
3. Was participant seen by an MD, urgent care or ER staff **(including study staff)**?
   _____
4. Was alcohol associated with the AE?
   _____
5. If applicable, list the medications that were prescribed to treat the AE, including doses and frequency:
   _____
6. If applicable, describe any changes shown in the current chest x-ray in comparison to the most recent previously reported chest x-ray:
   _____
7. If applicable, describe any additional action **(not reported elsewhere)** taken in response to the AE **(e.g., repeat test, follow-up)**:
   _____
8. If applicable, list other factors related to the AE:
   _____
9. If applicable, specify how long after the onset date the AE resolved **(hours, days, weeks)**:
   _____
10. If applicable, specify whether the participant permanently discontinued study treatment because of medical advice or participant decision:
    _____

Place Barcode Here

PTOPS
Form 8: Adverse Event Follow-up Form

E. Summary of AE

Use the SOAP **(Subjective, Objective, Analysis, and Plan)** format for a brief clinical description. Include the context for clinician action taken in regard to changes in study medication, if applicable.

F. Form Completion

PRINT name of Principal Investigator or Co-PI:

Signature of Principal Investigator or Co-PI:

PRINT name of person completing form:

Signature of person completing form:

Date Adverse Event Form completed: ☐☐-☐☐☐-☐☐☐☐

Scale for Attribution of Adverse Events

Category	Definition
Definite	Events occurring within a timely manner after administration of the study drug(s), that are known sequelae to the administration of the study drug(s), and follow a previously documented pattern of reaction but for which no other explanation is known. This category applies to those AEs that the investigator believes are incontrovertibly related to the study drug(s).
Probable	Any event occurring in a timely manner after administration of the study drug(s), that follows a known pattern of reaction to the study drug(s), and for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are believed with a high degree of certainty to be related to the study drug(s).
Possible	Any event occurring in a timely manner after administration of the study drug(s) that does not follow a known pattern of reaction and for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unlikely to be related but cannot be ruled out with certainty.
Unlikely	In general, this category can be considered applicable to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unrelated to administration of the study drug(s).
Not related	Any AE for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the study drug(s) and the AE does not follow any previously documented pattern. This category applies to those AEs that, after careful medical consideration, are clearly and incontrovertibly due to causes other than the study drug(s).
Unclassifiable	There is insufficient information about the AE to allow for an assessment of causality.

Anticipated and Unanticipated Adverse Events (AE)

Category	Definition
Anticipated	AE which meets any one (or both) of the following: 1. Consistent with listing in the current study protocol narrative and/or consent form and/or pharmaceutical package insert for the study treatment(s), in terms of the nature, intensity, and frequency. 2. Based on clinical judgment by the principal investigator/primary treating physician, the adverse event was expected to occur based on the study participant's underlying medical condition and/or concomitant disorder, disease process, or non-study treatment.
Unanticipated	AE which meets BOTH of the following: 1. NOT consistent with listing in the current study protocol narrative and/or consent form and/or pharmaceutical package insert for the study treatment(s), in terms of the nature, intensity, and frequency. AND 2. Based on clinical judgment by the principal investigator/primary treating physician, the adverse event was NOT expected to occur based on the study participant's underlying medical condition and/or concomitant disorder, disease process, or non-study treatment.