COST-EFFECTIVENESS OF POST-OFFER AND PRE-PLACEMENT TUBERCULOSIS SCREENING, TESTING, AND TREATMENT OF HEALTH CARE PERSONNEL IN THE UNITED STATES

by

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(Under the Direction of Zhuo “Adam” Chen)

ABSTRACT

Health care personnel (HCP) are at increased risk for tuberculosis (TB) due to occupational exposure. To prevent the transmission of *Mycobacterium tuberculosis* in health care settings, the United States (US) Centers for Disease Control and Prevention (CDC) recommends that occupational health programs conduct post-offer and pre-placement (i.e., baseline) TB screening for new HCP, where personnel with a positive initial result receiving a confirmatory test. However, the economic value of baseline screening based on the CDC recommendations, along with the use of a confirmatory testing strategy, has not been evaluated in US HCP. This study aims to identify the most optimal post-offer and pre-placement (POPP) TB screening scenario for US HCP.

We conducted two studies to achieve our study aim. First, we systematically reviewed the published literature on LTBI prevalence, conversion, and reversion for US HCP compared with HCP from other high-income, low TB-incidence countries. Second, we conducted a cost-effectiveness analysis to compare health outcomes, costs, effectiveness, and the incremental cost-effectiveness ratios for five POPP screening and treatment scenarios: no screening, two-step

tuberculin skin test (TST) + 9-month isoniazid (9H); two-step TST + 3-month isoniazid-rifapentine (3HP); QuantiFERON-TB Gold In-tube (QFT) + 3HP; and confirm positive QFT with QFT + 3HP (QFT/QFT + 3HP).

The pooled random-effects estimate from the systematic review indicate that 3.8% (95% CI: 2.4, 5.8) of US HCP have LTBI compared to 24% (95% CI: 16.3, 33.9) of HCP in other high-income, low TB-incidence countries. Additionally, 50.3% (95% CI: 38.6, 62.0) of US HCP received a false-positive (i.e., reversion) result during serial screening, with 2.1% (95% CI: 1.1, 3.9) converting from a negative to a positive result. The cost-effectiveness analysis showed that QFT + 3HP yielded the lowest cost to avert a TB case or death. Moreover, QFT + 3HP is the most cost-effective scenario for US-born and non–US-born HCP, at an incremental cost-effectiveness ratio of $14,559 and $14,822 per quality-adjusted life year gained, respectively.

Based on these findings, US occupational health programs should consider implementing QFT + 3HP as the standard baseline screening scenario for all HCP.

INDEX WORDS: Cost-effectiveness analysis, costs, latent tuberculosis infection, healthcare personnel, health worker, occupational health, economic evaluation, United States

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DEDICATION

I dedicate this dissertation work to the women who inspire, support, and uplift me daily: my wife, Haddi; daughter, Emeli; and mother, Awa.

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CHAPTER 1

INTRODUCTION

Public Health Significance

Tuberculosis (TB) disease is a public health problem and a leading cause of infectious disease mortality worldwide. Globally, it is estimated that approximately 10 million persons developed TB in 2017, of which 1.6 million died from the disease (MacNeil, Glaziou, Sismanidis, Maloney, & Floyd, 2019). Although TB incidence and death rates are declining globally, the disease impacts some geographic areas more than others disproportionally. According to the World Health Organization (WHO), countries in Asia and Africa were responsible for 86% of all TB cases in 2018, with eight countries accounting for two-thirds of all reported cases: India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa (World Health Organization, 2019).

In 2018, the United States (US) reported one of the lowest TB incidence case rates globally, at 2.8 cases per 100,000 persons (Talwar et al., 2019). Although US TB cases rates declined by 58% during 1998–2018, the rate of decline has slowed in recent years, at an annual average of 1.6% during 2014–2018, compared to 6.5% during 2009–2013 (Centers for Disease Control and Prevention, 2019b). In 2018, persons born outside of the United States accounted for two-thirds US TB cases, with an incidence rate greater than 14-times that of US-born persons (Talwar et al., 2019). The vast majority of non–US-born persons who develop TB are diagnosed within ten years of arriving in the United States. Such data suggest that reactivation of previously acquired infection of *Mycobacterium tuberculosis*—the causative agent of TB disease in

humans—among immigrants is the primary driver of US TB cases (Yuen, Kammerer, Marks, Navin, & France, 2016). The reactivation of previously acquired *M. tuberculosis* infection is primarily explained by high TB prevalence in a person's country of birth and cumulative duration of exposure to TB disease over several years (Pareek, Greenaway, Noori, Munoz, & Zenner, 2016).

For the US to achieve TB elimination (incidence <1 case per 1 million persons) in the 21st century, targeted testing and treatment of high-risk populations likely to be infected with *M. tuberculosis* is critical (P. A. LoBue & Mermin, 2017). These high-risk populations include persons who were born or resided in high TB-incidence countries, health care personnel (HCP), and those on immunosuppressive treatment. It is estimated that approximately 9–14 million persons in the United States are infected with *M. tuberculosis* (Haddad et al., 2018; Miramontes et al., 2015), of which an estimated 300,000–400,000 are treated annually (Sterling et al., 2006).

Persons infected with *M. tuberculosis* but do not have TB disease because the bacteria are inactive are classified as having latent TB infection (LTBI). Because persons with LTBI are at risk for progression to TB disease, the US government's TB elimination strategy has been broadened to include an LTBI prevention cascade focused on identifying at-risk populations, testing, and treatment with a short-course regimen (P. A. LoBue & Mermin, 2017). However, there is no gold-standard test to detect LTBI, but two testing modalities are currently recommended for the detection of *M. tuberculosis* infection: Mantoux tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) (Lewinsohn et al., 2017).

TST is administered by injecting a purified protein derivative (PPD) solution containing various tuberculous and non-tuberculous mycobacteria antigens—into the inner surface of a patient's forearm (Starke, 2020). The patient then returns 48–72 hours after administration to

have a clinician assess whether a reaction (i.e., induration) occurred. An induration of ≥5 millimeters (mm) is considered positive for persons with HIV infection or other immunocompromised conditions (Centers for Disease Control and Prevention, 2011). Persons classified as high-risk (e.g., a recent immigrant from high TB-incidence countries, contact of a TB patient, HCP) are considered positive if the induration is ≥10 mm; an induration >15 mm is considered positive for any person (Centers for Disease Control and Prevention, 2011). Antigens present in PPD are known to cross-react with those in the bacille Calmette-Guérin (BCG) vaccine strains. As a result, persons previously vaccinated with BCG have a higher likelihood of a positive TST test result when compared to non-vaccinated persons (Wang, Turner, Elwood, Schulzer, & FitzGerald, 2002); thus, suggesting that BCG-vaccinated persons tested using PPD may produce a false-positive test result.

A phenomenon that occurs among persons serially tested with TST is the "boosting" of a person's immune system. A boosted reaction occurs when a person with past TB exposure does not generate an adequate immune response to produce an initial positive test result (Farah et al., 2017). However, when the person is subsequently retested within a one-year period (assuming no TB exposure), a positive test result is generated (Farah et al., 2017). The subsequent positive test is because the initial skin test stimulates the body's immune system to recognize and react to tuberculin.

Although TST is the most known and widely used test globally, IGRAs have been reported to offers many operational advantages over TST, including: 1) removal of the subjectivity and variability involved with placing and interpreting test results (Mancuso, Bernardo, & Mazurek, 2013); 2) better sensitivity in persons that received the BCG vaccine (Joshi, Monson, Joshi, & Woods, 2014); 3) no booster phenomenon on serial tests (Farah et al.,

2017); and 4) the need for a return visit to have test results read (i.e., only one visit is required) (Joshi et al., 2014).

IGRA tests use fresh blood samples to measure the amount of interferon-gamma released by lymphocytes after reacting with specific *M. tuberculosis* antigens, such as early secreted antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10)— (Andersen, Munk, Pollock, & Doherty, 2000). IGRA test results are usually available within 24 hours. Currently, there are three types of commercially available IGRA tests in the United States: QuantiFERON-TB Gold In-Tube (QFT-GIT; Cellestis Limited, Carnegie, Victoria, Australia), QFT Gold Plus (QFT-Plus; Qiagen, Germantown, MD), and T-SPOT.*TB* (T-Spot; Oxford Immunotec, Inc., Malborough, MA). QFT test results are measured based on interferon-gamma concentration in the blood, while T-Spot results are based on the number of interferon-gamma producing cells. For QFT, a value of ≥0.35 IU/ml is considered positive for *M. tuberculosis* infection (Qiagen, 2016), whereas for T-Spot, spot count ≥8 is considered positive, with spot counts of 5, 6, or 7 being considered borderline and requiring retesting with new specimen. Spot counts ≤4 are considered negative (Quest Diagnostics, 2019).

Asymptomatic persons with a positive TST test result who choose to forgo treatment have a 5-10% chance of progressing to TB disease in their lifetime (American Thoracic Society, 2000). In those testing positive by IGRA, the predictive value for TB disease progression increases slightly to 12.9% (Diel, Loddenkemper, Niemann, Meywald-Walter, & Nienhaus, 2011). Persons with weakened immunity due to a medical condition (e.g., HIV, diabetes, end-stage renal disease) or on immunosuppressive treatment (e.g., tumor necrosis factor-α inhibitors) have an increased risk of progression to TB disease (Ferrara et al., 2012). Treatment regimens for LTBI are highly efficacious in preventing TB disease. Traditionally, 6–12 months of isoniazid

monotherapy has been used, but its effectiveness is limited due to low treatment completion rates owning to longer duration and concerns about hepatotoxicity (P. Lobue & Menzies, 2010; Nolan, Goldberg, & Buskin, 1999). However, in recent years, shorter preventive regimens, including 3-month isoniazid-rifapentine (3HP), 4-month rifampin (4R), and 3- or 4-month isoniazid-rifampin (3HR), have been approved and recommended in the US as preferred alternatives to isoniazid monotherapy (Sterling et al., 2020).

LTBI Screening and Testing in US Health Care Personnel

During 2010-2016, Healthcare personnel (HCP) accounted for 4% of all TB cases in the US (Mongkolrattanothai, Lambert, & Winston, 2019). However, HCP are at greater risk of TB exposure than the general population, simply because of the nature of their work (Geiseler, Nelson, Crispen, & Moses, 1986; Menzies, Joshi, & Pai, 2007; Sepkowitz, 1994). For HCP that perform intermediate-risk activities (i.e., general patient care), the annual risk of exposure to a patient with TB disease is 1.3% (G. A. Mullie, K. Schwartzman, A. Zwerling, & D. S. N'Diaye, 2017; Salpeter & Salpeter, 2004). After exposure to an infected patient, the probability of *M. tuberculosis* infection for HCP increases to 22.9% (Muzzi et al., 2014). The annual risk of progression from LTBI to TB disease among HCP is estimated to be similar to the general population and ranges from 0.07%-0.1% (Salpeter & Salpeter, 2004); thus, the vast majority of HCP infected with *M. tuberculosis* will remain asymptomatic and are classified as having LTBI. HCP with *M. tuberculosis* infection who are unidentified or choose to forgo treatment pose some risk for nosocomial TB transmission to immunocompromised patients and staff should they progress to TB disease. As a result, administrative, environmental, and respiratory-protection controls are necessary to limit TB transmission in the healthcare setting.

In 1994 and 2005, the US Centers for Disease Control and Prevention (CDC) released guidelines for preventing *M. tuberculosis* transmission in healthcare settings in the US (Centers for Disease Control and Prevention, 1994; Jensen, Lambert, Iademarco, & Ridzon, 2005). These guidelines provided recommendations on administrative, environmental, and respiratory-protection controls that healthcare organizations could implement to prevent TB transmission in the healthcare setting. As an administrative control, CDC recommended that healthcare organizations create a screening and testing program for HCP who are at risk for TB disease or those who might be exposed to *M. tuberculosis* based on occupational risks. Since the release of these guidelines, healthcare organizations throughout the US have overwhelmingly implemented the screening and testing recommendations, which have contributed to an overall 54% decline in TB disease cases in the US in the last 20 years—from 19,751 cases in 1997 to 9,024 cases in 2018 (Centers for Disease Control and Prevention, 2019b).

However, since 2013, there have been increased discussions among public health and occupational health professionals regarding updating guidelines for serial screening and testing of HCP. Such discussions were based on 1) a national shortage of PPD for TST testing (Centers for Disease Control and Prevention, 2013); 2) evidence indicating a decline in TB incidence among HCP in the US (Dobler et al., 2018); 3) recognized and documented challenges with the TST and IGRA tests (Joshi et al., 2014); 4) a shift to focus on identifying and treating persons with LTBI (P. A. LoBue & Mermin, 2017); 5) concerns about over-testing of HCP in low-incidence settings; and 6) the cost-effectiveness of serial TB testing (G. A. Mullie et al., 2017).

As a result of these concerns, CDC and the National Tuberculosis Controllers Association (NTCA) convened a working group to assess the need to update the 2005 recommendation on TB screening and testing of HCP. The working group included a

multidisciplinary team of TB experts from occupational medicine, state and local public health departments, academia, and CDC (Sosa et al., 2019). The working group conducted a systematic review and meta-analysis of studies assessing TB in HCP from high-income and low TB-incidence countries. Based on findings from the review, the working group concluded that the recommendations on screening and testing needed to be updated based on the limited number of US HCP converting to a positive test result during serial testing, along with the overall changes in TB epidemiology in the United States over the past 15 years. Using findings from the systematic review and expert opinion, the working group published updated recommendations on TB screening, testing, and treatment of US HCP (Sosa et al., 2019).

The updated CDC and NTCA recommendations suggest a baseline TB risk assessment, symptom evaluation, and a TB test at hire (i.e., post-offer and pre-placement) for HCP. However, CDC no longer recommends serial testing for HCP unless there is known exposure or ongoing transmission in the healthcare facility. Moreover, treatment is highly encouraged, but not required, for HCP with a positive test result and no evidence of TB disease.

Problem Statement

Although CDC's updated recommendations are expected to reduce over-testing and increase treatment among HCP infected with *M. tuberculosis*, it does not provide healthcare administrators and decision-makers with information on the most cost-effective baseline testing and treatment scenarios to implement based on nativity status. Currently, no evidence exists that examines the economic value of baseline screening of HCP based on the updated CDC testing and treatment recommendations.

Purpose of the Study and Underlying Conceptual Framework

The purpose of this study is to improve TB control in the United States by using economic evaluation methodologies to inform policymakers and healthcare administrators. Specifically, this study's primary objective is to identify the most cost-effective testing and treatment scenario for US HCP at hire.

This study is based on the Prevention Effectiveness (PE) Model (Teutsch, 1992). The PE Model provides a framework for developing and implementing disease prevention strategies (Teutsch, 1992). PE assesses the impact of public health policies, interventions, and strategies on health outcomes by evaluating their effectiveness, quality, and costs. Figure 1.1 describes the PE framework (Teutsch, 1992). The figure displays how health interventions and strategies evolve from basic and applied research to community demonstrations and widespread dissemination and implementation. The PE domain is assessed from the development stage through the implementation stage using various quantitative methods and qualitative assessments, including decision and economic analyses.

Decision models are used in PE studies when effectiveness evidence is “indirect or uncertain” and can often make the decision process explicit and clarify the criteria used to inform decision making (Haddix, Teutsch, & Corso, 2003, pp. 4-5). Basic decision analysis uses a decision-tree model to compare alternative strategies and scenarios and include probabilities of health outcomes, preferences, or costs (Haddix et al., 2003, p. 4). More advanced models, such as mathematical or microsimulation models, can also be used to understand better the impact of progressing from one disease state to another or replicating disease processes. When available, randomized control trials or systematic reviews and meta-analyses are used to inform decision models (Haddix et al., 2003, pp. 40-41).

Economic models are used to understand the costs and consequences of the available choices when allocating resources. Notable economic analyses used in PE studies include cost-benefit, cost-effectiveness, cost-utility, and budget impact analyses. A cost-benefit analysis (BCA) compares intervention-related costs, benefits (health and non-health), and harms in monetary units (Haddix et al., 2003, pp. 127-153). Decision-makers often use BCA to compare two programs with very different outcomes; measures used to report BCA are benefit-cost ratio, net benefit, or net present value.

Cost-effectiveness analysis (CEA) involves the comparison between intervention costs (investment) and outcomes in their standard health units (Haddix et al., 2003, pp. 156-159). The results of a CEA are compared with other programs or interventions competing for similar resources. CEA is often reported as an average, marginal, or incremental ratio. Cost-utility analysis (CUA) is a specific kind of CEA where the incremental cost of a program or intervention costs are compared to the incremental health improvement benefits measured in terms of utility, often in quality-adjusted life years (QALYs) (Neumann et al., 2018; Rai & Goyal, 2018). CUA can be used to compare two different interventions or programs whose outcomes are different but can be encompassed in a utility framework.

In recent years, budget impact analyses (BIA) are being conducted alongside CEAs to inform decision making. BIAs are used to examine the change in healthcare organizations' expenditure when new interventions or policies are adopted and implemented (Sullivan et al., 2014). BIAs can also inform budget and resource planning, as well as forecasting. Outcomes are typically reported as total costs and savings.

In this study, a CEA will be used to identify the most optimal baseline TB testing and treatment scenarios for occupational health testing programs.

Specific Aims

Two interrelated studies will be undertaken to address the overarching goal of improving TB control in healthcare settings and reduce TB incidence among US HCP. A systematic review and meta-analysis will be conducted to obtain epidemiological characteristics of US HCP and HCP from other low TB-incidence countries in the first study. The epidemiological characteristics for US HCP will be included as input parameters for the second study. The second study is a CEA that will use a decision-analytic and Markov model to examine various baseline testing and treatment scenarios for US- and non–US-born HCP. These scenarios include:

1) No screening or testing
2) baseline test with two-step TST + treatment with self-administered 9H;
3) baseline test with two-step TST + treatment with self-administered 3HP;
4) baseline test with IGRA + treatment with self-administered 3HP; and
5) baseline test with IGRA with a positive result confirmed with a second IGRA + treatment with self-administered 3HP.

The scenarios will be modeled over 20 years from the healthcare system perspective, with costs and effectiveness discounted at an annual rate of 3%.

Part I: Systematic review and meta-analysis

The specific aim of the systematic review and meta-analysis is to:

1. estimate LTBI prevalence, conversion, and reversion rates among US and non-US HCP

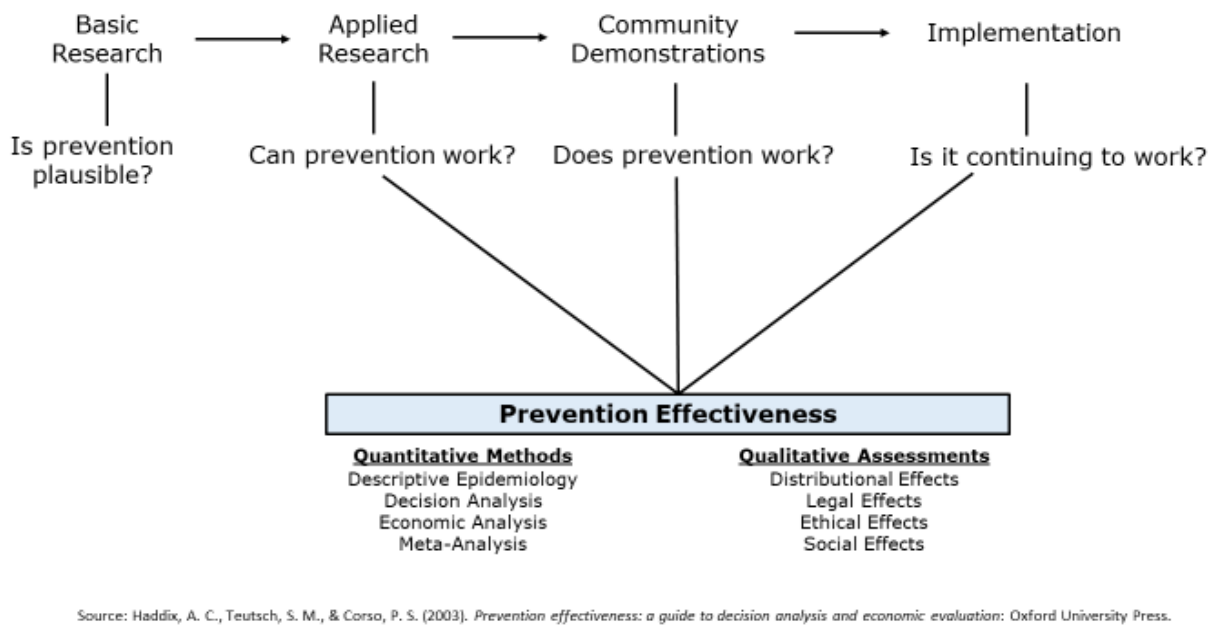
Part II: Cost-effectiveness analysis

The specific aims for the CEA are to:

1. estimate the costs, QALYs, TB cases and deaths averted, cost per TB case avert, and cost per TB death averted for the aforementioned baseline testing and treatment scenarios for US-born and non–US-born HCP from the health system perspective; and
2. evaluate the incremental cost-effectiveness ratios for the aforementioned baseline testing and treatment scenarios for US-born and non–US-born HCP from the health system and societal perspectives.

Summary

In summary, this dissertation will evaluate the most up-to-date evidence available in the peer-review literature and estimate the epidemiological characteristics of HCP from the United States and other low-TB incidence countries. Furthermore, these epidemiological characteristics will be included as input parameters in a CEA of baseline LTBI testing and treatment scenarios for US-born and non-US-born HCP. The CEA is expected to inform decision-makers for US occupational health programs regarding baseline TB screening by identifying the most optimal LTBI testing and treatment scenario for their organization to implement based on demographics, including nativity.



Source: Haddix, A. C., Teutsch, S. M., & Corso, P. S. (2003). *Prevention effectiveness: a guide to decision analysis and economic evaluation*: Oxford University Press.

Figure 1.1. Prevention Effectiveness Conceptual Framework

CHAPTER 2

LITERATURE REVIEW OF LTBI SCREENING, TESTING, AND TREATMENT

Introduction

This chapter provides a critical review, analysis, and summary of literature published on studies that evaluate LTBI screening, testing, and treatment of HCP in the US. The objectives of the literature review were to:

1. describe the LTBI prevalence, treatment initiation, and treatment completion rates among US HCP and HCP-related factors associated with treatment initiation and completion;
2. describe the effectiveness and limitations of TST and IGRAs for baseline and serial testing among HCP; and
3. describe and critique economic evaluation studies focused on screening, testing, and treatment strategies for US HCP.

Methods

Narrow search strategies were used to locate studies focused on LTBI screening, testing, and treatment for US HCP (Table 2.1). The searches included English-language articles indexed in the electronic database MEDLINE and published during January 1, 2001–March 15, 2020. Specifically, to locate economic evaluation studies focused on testing of HCP, the medical subject headings included “latent tuberculosis” AND “cost analyses” AND “interferon-gamma release assay” OR “tuberculin skin test”; similarly, the search for articles focused on LTBI treatment included “latent tuberculosis” AND “cost analyses” AND “treatment.” Articles

focused on HCP from low TB-incidence countries (<20 cases per 100,000 persons) were included if LTBI screening and testing strategies were evaluated using a cost analysis, cost-benefit analysis, or cost-effectiveness analysis. Commentaries, editorials, conference abstracts, pediatric and adolescent-focused, and non-English language articles were excluded.

Results

In total, 44 studies met the inclusion criteria and were included in this literature review. Of these, 19 studies described either LTBI prevalence, treatment initiation and completion, or TST and IGRA test performance; 18 studies were economic evaluations of LTBI treatment strategies; and 11 studies were economic evaluations focused on LTBI screening, testing, and treatment among HCP. Select studies are discussed in the succeeding sections.

LTBI prevalence and treatment initiation and completion in US HCP

Presently, CDC does not require states to collect surveillance data for persons diagnosed with LTBI. As a result, the prevalence of LTBI among US HCP is unknown. A systematic review conducted by CDC estimates that during baseline testing, 3% and 5% of HCP test positive for *M. tuberculosis* infection by TST and IGRA, respectively (Sosa et al., 2019). Of the nearly 64,000 HCP included in the systematic review, none were found to have TB disease. However, surveillance data from CDC indicate that during 2010–2016, there were 2,460 TB cases among HCP in the United States, which represented 4% of all TB cases during that period (Mongkolrattanothai et al., 2019). Moreover, Mongkolrattanothai et al. report that nearly 3 in 4 HCP diagnosed with TB were born outside of the US (Mongkolrattanothai et al., 2019).

Although the treatment of LTBI can mitigate the risk of progression to TB disease, HCP offered LTBI treatment have historically had low rates of treatment initiation and completion. A retrospective study that included over 40,000 US HCP working at a large medical center, 52% of

HCP tested positive by TST rejected treatment for LTBI; of those accepting treatment, 72% completed treatment (Dobler et al., 2018). In a smaller study that included 470 HCP with LTBI, approximately 40% of HcP who tested positive at hire accepted treatment; of those, 29.1% completed treatment (Swift et al., 2019). According to Swift et al., being a physician, researcher, and of older age were associated with less treatment acceptance, while being from a high TB-incidence country was associated with a lesser likelihood of completing treatment (Swift et al., 2019).

Effectiveness of TST and IGRA testing in US HCP

With the absence of a gold standard test for the diagnosis of LTBI, TST was the only test available to detect *Mtb* infection prior to QuantiFERON (QFT) receiving approval from the US Food and Drug Administration (FDA) for use in the US in 2001. QFT lasted on the market until 2005 when the FDA approved its successor, QFT-Gold (QFT-G, Cellestis Limited, Carnegie, Victoria, Australia), which was used to aid in diagnosing both LTBI and TB disease (Mazurek et al., 2005). Soon after FDA approval, CDC published guidance that recommended the use of QFT-G in all situations where TST is used, including sequential testing programs for HCP (Mazurek et al., 2005). CDC's rationale for the new recommendation was based on the belief that QFT-G provided greater specificity than TST. Moreover, studies that directly compared TST to QFT-G found that the sensitivity for both tests were statistically similar (Mazurek et al., 2005). Subsequent IGRA tests, including QFT-Gold In-tube (QFT GIT, Cellestis Limited, Carnegie, Victoria, Australia) and T-SPOT, were approved by the FDA for commercial use in the US in 2007 and 2008, respectively (Mazurek et al., 2010). As a result, in 2010, CDC updated its guidelines to recommend the use of TST, QFT-G, QFT-GIT, and T-SPOT for the detection of

Mtb infection, with a caveat suggesting caution when IGRA is used for serial testing (Mazurek et al., 2010).

In that same year, 2010, the first large study focused on the effectiveness of QFT-GIT in US HCP was published (Gandra et al., 2010b). The Gandra et al. study was a retrospective chart review of approximately 6,500 HCP from a large academic hospital tested using QFT-GIT as part of an annual screening program from January 1, 2008–December 31, 2008. Of the 6,530 HCW tested with QFT-GIT, 287 had a positive result. However, when 164 of the 287 with a positive test result were retested using both TST and QFT-GIT, there was significant disagreement between the two tests; nearly 49% of those previously positive by QFT-GIT reverted to a negative test result. These false-positive test results raised concerns about the effectiveness of QFT-GIT as a sole screening test for HCP in low TB-prevalence settings.

Subsequent to the Gandra et al. study, three studies were published in 2012 that focused on the effectiveness of using IGRAs to serially screen HCP (Fong et al., 2012b; Joshi, Monson, & Woods, 2012; Thanassi et al., 2012). The Fong et al. study suggested that using a single cuff-off point for QFT-GIT led to overdiagnosis of *M. tuberculosis* infection. Meanwhile, Thanassi et al. suggested retesting low-risk HCP with a test result between 0.35–1.11 IU/mL due to a high probability of the initial test being false-positive. Similarly, Joshi et al. found a high positivity rate but suggested a retesting zone 0.35-2.0 IU/mL for serial testing of HCP. Another study published in 2014 examined the reproducibility of QFT-GIT for repeat testing in a large group HCP tested within 60 days and found that test results that were initially positive could not be reproduced, thus suggesting that QFT-GIT produces a high rate of false-positive results (Slater, Welland, Pai, Parsonnet, & Banaei, 2013).

In the most extensive longitudinal study to compare the performance characteristics of QFT-GIT and T-SPOT to TST for serial testing (every six months) among US HCP, Dorman et al. report a baseline positivity proportion of 5.2%, 4.9%, and 6.0% for TST, QFT-GIT, and T-SPOT, respectively (Dorman et al., 2014). Over 18 months, the proportion of HCP who converted during serial testing was significantly higher using an IGRA test (2.3%) than TST (0.9%)—based on a conservative cutoff of 0.70 IU/mL—likely suggesting most conversions were false positives. In 2017, the FDA approved the latest IGRA test, QFT Gold Plus (QFT-Plus; Qiagen, Germantown, MD). Studies directly comparing QFT-Plus to QFT-GIT have found a high degree of agreement when used in HCP (Moon et al., 2017; Theel et al., 2018); however, more research studies using QFT-Plus in HCP are needed, especially as it relates to serial testing.

Economic evaluations of LTBI treatment strategies

The NTCA and CDC published updated guidelines for the treatment of LTBI in the US in February 2020 (Sterling et al., 2020). Preferred treatment regimens include 3-month isoniazid-rifapentine (3HP), 4-month rifampin (4R), and 3- or 4-month isoniazid-rifampin (3HR); alternative regimens include 6- and 9-month isoniazid monotherapy (6H, 9H). Although several high-quality economic evaluations on the cost-effectiveness of various LTBI treatment strategies have been published since 2001, only one examined strategies—from a health system perspective—that included the treatment regimens recommended by the NTCA and CDC (Doan et al., 2019). Doan et al. used a Markov model that included a non-HCP population of 38-year-olds and followed them for 20 years. The study evaluated the regimens mentioned earlier compared with no preventive treatment. Based on a willingness-to-pay threshold of $50,000, Doan et al. found 3HP administered by directly observed therapy (DOT) to be the most cost-effective regimen, at a cost of $28,000 per QALY gain—but, all regimens were found to reduce

costs and increase QALY relative to no preventive treatment (Doan et al., 2019). Findings from the Doan et al. study were based on input parameters from published literature.

Another CEA published in 2013 used a simulation model based on input parameters primarily from clinical trial and public health department data and simulated the cost-effectiveness of 3HP compared to 9H over 20 years (Shepardson et al., 2013). From a health system perspective, the authors found 3HP to be cost-effective relative to 9H at a cost of $4,565 per QALY gained. From a societal perspective, the cost for 3HP relative to 9H was $911 per QALY gained (Shepardson et al., 2013).

Economic evaluations of LTBI screening and testing for HCP from low TB-incidence countries

In total, there were 12 published economic evaluations focused on screening, testing, and treatment of HCP (Choudhary et al., 2006; de Perio, Tsevat, Roselle, Kralovic, & Eckman, 2009; Fox et al., 2009; Giri et al., 2014b; Kowada, 2011; L. Lambert et al., 2003; Linertová, Alvarez-León, García-Pérez, & Serrano-Aguilar, 2010; Mukai et al., 2017; Guillaume A. Mullie, Kevin Schwartzman, Alice Zwerling, & Dieynaba S. N'Diaye, 2017; Png, Yoong, Ong, Fisher, & Bagdasarian, 2019; Salpeter & Salpeter, 2004). Of these, one study was excluded because it was focused on HCP residing in a medium TB-incidence country, Singapore (Png et al., 2019). The summary evidence table of included studies is presented in Table 2.2.

During January 2001–December 2010, there were six economic evaluations from low TB-incidence countries identified by the search strategy used for this literature review. Of these, four were from the United States, one from Israel, and one from Spain. During this period, most economic evaluations focused on HCP were cost analyses that evaluated the costs associated with both TST and QFT for baseline or annual screenings using hospital data. However, the

Salpeter et al. study, published in 2004, was a momentous TB economic evaluation during this era, primarily because it was the first CEA to demonstrate that serial TST screening and treatment was cost-effective and cost-savings when compared with no screening for HCP working in low, moderate, and high-risk settings (Salpeter & Salpeter, 2004).

Although QFT was approved for use in the United States in 2001, it was not until 2009 when the first CEA that compared the use of TST and QFT in screening HCP was published (de Perio et al., 2009). De Perio and colleagues used a Markov state-transition decision-analytic model to compare TST and two IGRAs, QFT-G and QFT-GIT, to detect LTBI among a hypothetical cohort of 35-year old HCP. Over a lifetime, de Perio et al. found that both QFT-G and QFT-GIT were more cost-effective and less costly than TST—at an incremental cost-effectiveness ratio (ICER) of $14,092 per QALY when QFT-G was compared to QFT-GIT among non-BCG vaccinated HCP. However, the de Perio et al. study might not be generalizable to the US HCP population, as hourly wages and lost income were calculated using costs data from the US Department of Veterans Affairs. Moreover, the de Perio et al. study did not evaluate the societal perspective, likely missing additional costs and benefits associated with LTBI screening for HCP.

From January 2011–March 2020, the search strategy identified four economic evaluations from low TB-incidence countries that focused on the screening, testing, and treatment of *M. tuberculosis* infection among HCP. Two of the studies were conducted in Japan, one in the United Kingdom and one in North America (i.e., US and Canada). Two of the four studies were cost analyses (Giri et al., 2014b; Mukai et al., 2017). Giri and colleagues found that using QFT-GIT for a new employee testing program cost less than two-step TST over three years, €85,561 compared to €136,916, respectively. The Mukai et al. study compared the total cost of baseline

testing and retesting of HCP that initially tested positive or indeterminate using QFT-GIT or T-SPOT, and found that the total cost of testing 140 HCP was slightly higher for QFT-GIT than T-SPOT, $7,712 and $6,525, respectively.

Two cost-effectiveness analyses focused on HCP in low TB-incidence countries were also published during January 2011–March 2020 (Kowada, 2011; G. A. Mullie et al., 2017). Kowada et al. modeled three screening strategies from the societal perspective: no screening, QFT testing, and chest radiography examination. Using a lifetime analytic horizon for a cohort of 40-year old HCP, the study found that QFT was most cost-effective when compared with no screening and chest radiography (Kowada, 2011). However, these findings are of limited use for detecting LTBI in HCP, as two of the three strategies included in the study would be most useful to detect active TB disease.

Contrarily, a study focused on screening and testing guidelines for HCP in Canada and the United States compared three screening strategies using both TST and QFT testing (G. A. Mullie et al., 2017): annual testing, targeted testing for high-risk HCP, and post-exposure testing only. Using a cohort of 35-year-old HCP with negative baseline results, the authors simulated a decision model for 20 years and estimated costs, morbidity, QALYs, and mortality. Annual TST testing resulted in a higher incremental cost per additional TB case prevented when compared to post-exposure QFT testing, $1.7 million and $197,000, respectively. Moreover, the authors noted that “in all cases, QFT was more expensive than TST, with no or limited added value” (G. A. Mullie et al., 2017).

Summary of Gaps in Economic Literature

In summary, most economic evaluations focused on HCP screening and testing were cost analyses. Over the past 20 years, four cost-effectiveness analyses have been conducted that

evaluate HCP from low TB-incidence countries—especially the United States. There is significant heterogeneity in study design, screening strategies, and clinical outcomes reported in the published studies. Additionally, few studies included treatment of HCP who test positive for *M. tuberculosis* infection in their models.

Although the Mullie et al. study is the most comprehensive CEA study focused on HCP screening published to date, it—along with other published studies—did not comprehensively assess the cost-effectiveness of HCP screening and testing at hire (i.e., post-offer and pre-placement) combined with the need for a second confirmatory test with LTBI treatment offered, from a payer and societal perspective. Such an analysis would help occupational health programs identify workers who would benefit most from sequential testing and LTBI treatment.

Table 2.1 Search strategy for literature review of economic evaluations

Database	Strategy	Run date	Records
MEDLINE 2001-present	*Effectiveness of LTBI Screening in HCP:* *((health personnel [MeSH Terms]) AND (infection, latent tuberculosis [MeSH Terms])) AND (United States [MeSH Terms])*	03/15/2020	19
	Economic Evaluation of LTBI Treatment strategies: ((((latent tuberculosis [MeSH Terms]) AND (analyses, cost [MeSH Terms])) AND (treatment [MeSH Terms])		18
	Economic Evaluation of LTBI Screening and Testing in HCP: (("tuberculosis"[MeSH Terms] AND "costs and cost analysis"[MeSH Terms]) AND ("interferon-gamma"[MeSH Terms] OR "tuberculin test"[MeSH Terms]))		128

Table 2.2. Summary evidence table of economic evaluations focused on HCP screening, testing, and treatment published in low TB-incidence countries

Author (year)	Location	Study design	Testing strategies	Analytic Horizon	Outcome measure	Costing data source (base year)	Results and summary
Lambert (2003)	US	CA	TST	N/A	TST testing implementation and maintenance costs and program cost per HCP	Hospital and HD data (1998)	Annual costs of implementation and maintenance for hospital ranged from $66,564-$332,728 and $92,886-$291,248 for health departments. Program cost for hospitals ranged from $41-$362 per HCP, whereas the costs for health departments ranged from $176-$247 per HCP.
Salpeter (2004)	US	CEA	TST	12 years	TB cases, death, life expectancy, costs	Literature (2002)	One-year screening of HCP is cost-effective at a net cost of $30,000 per life-year saved when compared to no screening for low-risk HCP; $24, 400 per medium risk HCP, and $14,200 for high risk HCP.
Choudhary (2006)	US	CA	TST	N/A	TST testing program costs	Hospital data (not reported)	Annual two-step TST testing added $9,565 to the employee testing program.
de Perio (2009)	US	CEA	TST, QFT-G, QFT-GIT	Lifetime	Incremental cost/QALY	Literature, IGRA manufacturers, Veterans Affairs (2007)	IGRAs were most cost-effective than TST with ah ICER of 14,092/QALY for QFT-G when compared to QFT-GIT in non-BCG vaccinated HCP. The ICER in BCG-vaccinated HCP was $103,047/QALY when QFT-G was compared to QFT-GIT.
Fox (2009)	Israel	CA	TST, QFT	N/A	# of HCP testing positive and treated, total cost of testing	Tariff reported by Israeli MoH (not reported)	Screening with QFT compared to TST lead to fewer cases, lower costs, and increased treatment adherence. Cost was lowest when QFT was used as a confirmatory test after

							a positive TST (€4155). QFT vs TST only comparison resulted in costs totaling €7280 and €8217, respectively.
Linertova (2010)	Spain	CA	TST, QFT	N/A	Cost per HCP screened; cost per cohort; cost per positive case	Hospital data (2007)	QFT testing cost per HCP was €42.50, TST cost €39.50. Findings are dependent on hourly wages of participants and time spent on testing.
Kowada (2011)	Japan	CEA	No screening, CXR, QFT	Lifetime	Cost per QALY	Literature (2009)	QFT was more cost effective when compared to no screening (QFT: cost $262.84, QALY 22.87; no screening: cost: $448.38, QALY 22.85).
Giri (2014)	UK	CA	TST, QFT-GIT	N/A	Cost savings per year	Clinic data (not reported)	Use of IGRA only over a 3-year period would have cost €85,561 compared to €136,916 for two-step TST, thus saving the program €51,355 (€17,118 per year).
Mukai (2017)	Japan	CA	QFT-GIT, T-SPOT for annual screening, targeted screening or post-exposure screening	N/A	Total cost--initial test and retest for those testing positive or indeterminate	Hospital data (not reported)	Total costs, including retesting, were $78,711.86 and $6,525,42 for QFT-GIT, and T-SPOT test, respectively.
Mullie (2017)	US and Canada	CEA	TST, QFT	20 years	total cost, QALYs, new cases, TB deaths, deaths due to AE to treatment of active TB, deaths die to AE to treatment of LTBI, true positives, false positives	Literature (2015)	Post-exposure screening with TST was least costly. When the targeted test strategy was compared with annual screening strategy for TST, the cost per additional TB case prevented was $1,717,539 compared to $426,678. QFT prevented more cases only for post-exposure screening only.

CHAPTER 3

TUBERCULOSIS SCREENING AND TESTING OF HEALTH CARE PERSONNEL IN HIGH-INCOME, LOW TB-INCIDENCE COUNTRIES: A SYSTEMATIC REVIEW AND META-ANALYSIS[1]

[1] Njie GJ, Sekandi JN, Beeler Asay GR, Chen Z. To be submitted to the *International Archives of Occupational and Environmental Health*

Abstract

Introduction: Health care personnel (HCP) are at higher risk of exposure to tuberculosis (TB) than the general population. Health care organizations typically screen personnel for TB infection upon hire (i.e., baseline) and on a serial (e.g., annual) basis to mitigate the risk of TB outbreaks in the health care setting. This systematic review aims to assess the prevalence of TB infection among HCP in the United States (US) and other high-income, low TB-incidence countries and estimate their rate of conversion and reversion during serial testing.

Methods: Using the search strategy from an existing systematic review (January 2006–November 2017) that assessed baseline and serial testing for HCP, an update search (December 2017–November 2020) of the literature was conducted, evaluated, and appraised by two independent reviewers using the *Community Guide* methodology. Analysis of the data was completed in November 2020.

Results: The analysis included 37 unique studies from the United States and other high-income, low TB-incidence settings. The estimated pooled prevalence of TB infection among US HCP was 3.8% (95% CI, 2.4–5.8). When evaluated during serial testing, 2.1% (95% CI, 1.1–3.9%) of US HCP converted from a negative baseline result to a positive result, while 50.3% (95% CI 38.6–62.0) reverted from a positive baseline result to a negative result. Studies set outside of the US reported a higher baseline prevalence for TB infection, ranging from 8.7%–31.7%. Moreover, non-US studies reported higher conversion but lower reversion rates than US studies. Significant heterogeneity was identified among the included studies based on location and test type.

Conclusions: The prevalence of TB infection among HCP in the United States is lower than in other high-income, low TB-incidence countries. Serial TB testing among HCP should be reconsidered in settings with low TB prevalence due to a higher rate of reversion.

Keywords: healthcare workers, screening test, latent tuberculosis

Introduction

Tuberculosis (TB) is one of the leading causes of morbidity and mortality globally. In 2019, approximately 10 million TB cases were reported to the World Health Organization, of which 1.4 million persons died of the disease (World Health Organization, 2020). Compared to the general population, health care personnel (HCP) are at increased risk of exposure to *Mycobacterium tuberculosis*—the causative agent for TB disease in humans—because of the higher likelihood to interact with an infectious patient (Baussano et al., 2011; Menzies et al., 2007). Moreover, inadequate infection-control practices increase the risk of TB transmission in health care settings (Jensen et al., 2005). In 2019, the reported case rate among HCP in low- and middle-income countries ranged from 9.5 to 1,972 cases per 100,000 persons (World Health Organization, 2020); the high case rates among HCP is likely attributable to the inability of health care organizations to implement administrative, environmental, and personal-respiratory control recommendations.

In contrast to low- and middle-income countries, TB cases rates among HCP in the United States (US) have been declining since early to mid-1990s, when there were increased reports of nosocomial transmission of TB in hospitals (Beck-Sagué et al., 1992; Pearson et al., 1992; Sepkowitz, 1994). During 1995–2007, the annual TB incidence rate for HCP was 4.2 per 100,000 persons compared to 2.5 cases per 100,000 persons during 2010–2016 (L. A. Lambert, Pratt, Armstrong, & Haddad, 2012; Mongkolrattanothai et al., 2019). The decline in TB cases in HCP can largely be attributed to the adoption and implementation of infection-prevention control strategies published in guidelines released by US Centers for Disease Control and Prevention (CDC) in 1994 and 2005 (Centers for Disease Control and Prevention, 1994; Jensen et al., 2005).

In the United States, TB case rates are higher among foreign-born HCP than US-born HCP. When annual TB case rates during 2010–2016 were stratified by nativity status, foreign-born HCP had a rate nearly 14 times higher than US-born HCP (Mongkolrattanothai et al., 2019). The high TB rates among foreign-born persons are likely the result of reactivation TB due to untreated *M. tuberculosis* infection acquired before immigrating to the United States. Administrative controls from the 2005 CDC guidelines recommend that occupational health programs screen newly hired HCP for *M. tuberculosis* infection before placement and on a serial basis. However, scant data are available regarding LTBI prevalence for US HCP and the proportion that converts or reverts during serial screening. This review aims to estimate the prevalence of TB infection among HCP from high-income, low TB-incidence countries and assess whether serial testing is an effective strategy in identifying *M. tuberculosis* infection in US health care settings.

Methods

Conceptual approach and analytic framework

In this review, persons working in a health care setting who are paid or unpaid staff are considered HCP. The conceptual approach to evaluate LTBI and TB prevalence and the effectiveness of serial screening and testing is depicted in the analytic framework in Figure 3.1. Briefly, screening and testing HCP for *M. tuberculosis* infection is anticipated to increase the number of HCP evaluated for TB symptoms and provide enhanced TB risk factor assessment for HCP with previous negative results. Screening HCP should lead to increased testing and detection of LTBI and TB disease and increased treatment of persons with TB infection. Moreover, screening for TB disease is expected to reduce transmission of TB in occupational

and non-occupational settings. This would ultimately reduce the incidence of TB disease among HCP and reduce TB-related morbidity and mortality overall.

Search for Evidence

The search for evidence involved updating the search strategy developed for an unpublished systematic review that informed the recently published CDC and National Tuberculosis Controllers Association (CDC-NTCA) screening, testing, and treatment for HCP guidelines (Sosa et al., 2019). The initial search sought English-language articles focused on screening and testing of HCP that were published during January 2006–November 2017. To ensure the inclusion of the most up-to-date evidence available for this review, the initial search strategy was updated to locate studies published from November 2017 to November 2020.

Using systematic review methodology developed for *The Community Preventive Services Task Force* and *Community Guide* (Briss et al., 2000; Zaza et al., 2000), electronic databases including MEDLINE, Scopus, and Embase were searched for evidence. The search terms used included: “tuberculosis” AND “health personnel” OR “occupational diseases” OR “healthcare worker” OR “health care worker” OR “healthcare personnel” OR “health care personnel” OR “health worker” OR “health care worker.”

Study selection

Studies were included in this if they (1) focused was on tuberculosis screening and/or testing among paid or unpaid HCP; (2) were conducted in the United States and other high-income (The World Bank, 2020), low TB-incidence country (World Health Organization, 2014); (3) reported outcomes including LTBI prevalence, conversion, reversion, TB transmission rate, or active TB disease cases; and (4) employed a study design was a randomized controlled trial (RCT), quasi-experimental, cohort studies, cross-sectional surveys, and other designs with

concurrent comparison groups. Non-English language articles, case reports, editorials, commentaries, descriptive articles on nosocomial outbreaks were excluded.

Data abstraction and quality assessment

Data from included studies were abstracted by two independent reviewers using a data abstraction form adapted from *The Community Guide* (https://www.thecommunityguide.org/sites/default/files/assets/abstractionform.pdf). Any disagreements related to data extraction elements were resolved by consensus between the two reviewers. The following information was extracted from each included study if available: study and population characteristics, screening and testing details, type of test used, BCG vaccination history, occupation type, sample size, number of HCP testing positive at baseline, number of HCP who tested positive (i.e., conversion) after baseline test, number of HCP who tested negative (i.e., reversion) after baseline test, TB transmission rate in a health setting, and number of HCP who developed active TB disease.

Included studies were independently assessed for threats to internal and external validity by the same two reviewers using *The Community Guide* quality assessment form (Zaza et al., 2000). Limitations were assigned based on factors such as the description of the study population and testing procedures; sampling frame; valid and reliable outcome measurements; loss to follow up; reporting of statistical and analytic methods; and interpretation of results and limitations. Studies included in the review were characterized as having good (≤1 limitation), fair (2-4 limitations), or poor (≥5 limitations) quality of execution.

Data synthesis and analysis

The study and HCP characteristics of the included body of evidence are presented using descriptive statistics. Meta-analyses were conducted to assess the primary outcomes of interest,

including the proportion of HCP with *M. tuberculosis* infection at baseline, conversion after baseline testing, and reversion after baseline testing. Secondary outcomes such as TB cases and TB transmission rates are described descriptively. A random-effects model was used to estimate the pooled effect estimate because of heterogeneity among study location and setting. An inverse variance method with logit transformation was used to estimate weighted proportions (Schwarzer, Chemaitelly, Abu-Raddad, & Rücker, 2019). Statistical heterogeneity across the studies was assessed using Higgins' I-squared (I^2) statistic (Higgins & Thompson, 2002). I^2 values range from 0% to 100%. For this review, an I^2 value ≥50% was considered to be indicative of substantial heterogeneity. Potential publication bias was assessed through visual inspection of funnel plots. Outcomes are presented by study location and grouped by the type of test used. Statistical analyses were conducted in November 2020 using the "meta" package in R, version 4.0.3 (R Core Team, 2020).

Results

Search results and quality assessment

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009) flow diagram displaying the selection of articles for both the original and update literature searches are provided in Figure 3.2. The original search identified 1,147 articles from the electronic databases searched, of which 84 full-text articles were relevant and screened for inclusion. Upon full-text screening, 37 articles from the original search met the inclusion criteria. One study was excluded from the analysis due to poor quality of execution (Giri et al., 2014a); thus, 36 studies from the original search were included in the analysis (Barsegian, Mathias, Wrighton-Smith, Grosse-Wilde, & Lindemann, 2008; Baussano et al., 2007; Casas et al., 2009; Choudhary et al., 2006; Cummings et al., 2009; Dobler et al., 2018;

Dorman et al., 2014; Durando et al., 2015; Farah et al., 2017; Fong et al., 2012a; Freeman et al., 2012; Frenzel, Thomas, & Hanna, 2006; Gandra et al., 2010a; Gillenwater, Sapp, Pearce, & Siberry, 2006; Girardi et al., 2009; Joshi et al., 2014; Joshi et al., 2012; King et al., 2015; Lamberti et al., 2016; Larcher et al., 2012; Miranda, Yen-Lieberman, Terpeluk, Tomford, & Gordon, 2009; Moucaut et al., 2013; Nienhaus, Schablon, Bacle, Siano, & Diel, 2008; Olivieri et al., 2016; Pollock et al., 2008; Ringshausen et al., 2010; Ringshausen et al., 2011; Schablon, Harling, Diel, & Nienhaus, 2010; Schablon, Nienhaus, Ringshausen, Preisser, & Peters, 2014; Sherman et al., 2011; Slater et al., 2013; Soborg et al., 2007; Tripodi et al., 2009; Vinton et al., 2009; Weddle, Hamilton, Potthoff, Rivera, & Jackson, 2014).

The update search identified 78 titles and abstracts for screening; of those, 63 were not relevant to this review. Therefore, 15 full-text articles were review for inclusion, and only one met the inclusion criteria and was included in the analysis (Casas et al., 2020). In total, 37 articles met the criteria for inclusion and were included in the analysis.

Overall, the included body of evidence was of good quality, with nearly 60% (22/37) of included studies assigned ≤1 limitation. Fourteen studies (38%) were of fair quality, and one study was excluded from the analysis due to poor quality of execution. The most common limitation assigned to included studies in the review was for poor reporting of data analytic methods, followed by poor description of the sampling frame and screening and testing procedures. Few studies were assigned a limitation for factors related to outcome measurement and interpretation of results.

Study and HCP characteristics

The characteristics of the included studies are reported in Table 3.1. Of the 37 included studies, 18 (48.6%) were conducted in Europe (Barsegian et al., 2008; Baussano et al., 2007;

Casas et al., 2020; Casas et al., 2009; Durando et al., 2015; Girardi et al., 2009; Lamberti et al., 2016; Larcher et al., 2012; Moucaut et al., 2013; Nienhaus et al., 2008; Nienhaus, Schablon, Preisser, Ringshausen, & Diel, 2014; Olivieri et al., 2016; Ringshausen et al., 2010; Ringshausen et al., 2011; Schablon et al., 2010; Schablon et al., 2014; Soborg et al., 2007; Tripodi et al., 2009), 16 (43.2%) in the United States (Choudhary et al., 2006; Cummings et al., 2009; Dobler et al., 2018; Dorman et al., 2014; Farah et al., 2017; Fong et al., 2012a; Frenzel et al., 2006; Gandra et al., 2010a; Gillenwater et al., 2006; Joshi et al., 2014; Joshi et al., 2012; King et al., 2015; Miranda et al., 2009; Pollock et al., 2008; Slater et al., 2013; Weddle et al., 2014), and one (2.7%) in Australia (Vinton et al., 2009), Israel (Sherman et al., 2011), and New Zealand (Freeman et al., 2012), respectively. The vast majority (95%) of studies were conducted in a hospital setting, with the remaining studies conducted in other settings (e.g., clinic). No included study used an RCT design; included studies used a retrospective cohort (n=15), cross-sectional survey (n=14), or prospective cohort design (n=8).

HCP in the included studies comprised of working-age adults (median = 38.5 years old; interquartile interval [IQI] = 36.2–42.0), with the vast majority of HCP being female (76.1%). A median of 45.5% (IQI = 15.6–76.0) of HCP received the bacille Calmette-Guerin (BCG) vaccine. Of the US-based studies, 10.6% (IQI = 3.3–36.7) of HCP were born outside of the United States.

Baseline testing

Figure 3.3 displays the forest plot for 14 US studies reporting *M. tuberculosis infection* at baseline (Cummings et al., 2009; Dobler et al., 2018; Dorman et al., 2014; Fong et al., 2012a; Frenzel et al., 2006; Gandra et al., 2010a; Gillenwater et al., 2006; Joshi et al., 2014; Joshi et al., 2012; King et al., 2015; Miranda et al., 2009; Pollock et al., 2008; Weddle et al., 2014). Among

104,380 US HCP from these 14 studies, the estimated pooled prevalence of *M. tuberculosis* infection was 3.8% (95% CI, 2.4–5.8). However, when stratified by the type of test used, HCP tested with tuberculin skin test (TST) reported a lower prevalence than those tested with QuantiFERON-TB (QFT) or T-SPOT. Among 55,183 HCP tested with TST at baseline, from six studies reporting, an estimated 2.3% (95% CI, 1.0–5.2) of HCP tested positive, while 3.7% (95% CI, 1.4–9.3; 2 studies; 22,048 HCP) and 5.3% (95% CI, 3.4–8.2; 9 studies; 27,149 HCP) tested positive at baseline when T-SPOT and QFT were used, respectively.

Compared to US HCP, the prevalence of *M. tuberculosis* infection was higher among HCP from other high-income, low TB-incidence countries (Table 3.2). Between 15 studies from Europe that reported baseline testing using TST (Barsegian et al., 2008; Baussano et al., 2007; Casas et al., 2020; Casas et al., 2009; Durando et al., 2015; Girardi et al., 2009; Giri et al., 2014a; Lamberti et al., 2016; Larcher et al., 2012; Moucaut et al., 2013; Nienhaus et al., 2008; Olivieri et al., 2016; Ringshausen et al., 2011; Schablon et al., 2010; Slater et al., 2013; Soborg et al., 2007), the estimated pooled prevalence of *M. tuberculosis* infection among 12,286 HCP was 24.0% (95% CI 16.3–33.9). When QFT was used to test 14,468 HCP at baseline in 15 studies (Casas et al., 2020; Casas et al., 2009; Durando et al., 2015; Girardi et al., 2009; Giri et al., 2014a; Lamberti et al., 2016; Larcher et al., 2012; Moucaut et al., 2013; Nienhaus et al., 2008; Olivieri et al., 2016; Schablon et al., 2010; Soborg et al., 2007), the estimated pooled prevalence declined to 8.7% (95% CI, 6.2–12.1), with T-SPOT reporting an estimated pooled prevalence of 14.8% (5.6–33.5) among 262 HCP tested from 3 studies (Barsegian et al., 2008; Casas et al., 2009; Girardi et al., 2009). Baseline prevalence was also reported by studies set in Israel (Sherman et al., 2011), Australia (Vinton et al., 2009), and New Zealand (Freeman et al., 2012), with testing using TST ranging from 26.6% to 31.7%. Two studies from Australia and New

Zealand reported an estimated pooled prevalence of 7.5% (95% CI, 5.8–9.6), when testing was conducted using QFT among 806 HCP. Significant statistical heterogeneity was reported for US and non-US studies that reported baseline testing.

Conversion and reversion after baseline testing

In 11 studies that tested US HCP on a serial (i.e., annual) basis (Choudhary et al., 2006; Dobler et al., 2018; Dorman et al., 2014; Farah et al., 2017; Fong et al., 2012a; Gandra et al., 2010a; Gillenwater et al., 2006; Joshi et al., 2014; King et al., 2015; Pollock et al., 2008; Slater et al., 2013), an estimated 2.1% (95% CI, 1.1–3.9%) converted from a negative baseline result to a positive result (Figure 3.4). US HCP tested with TST reported an estimated pooled conversion rate of 0.7% (95% CI, 0.4–1.2), with QFT and T-SPOT reporting slightly higher rates at 3.6% (95% CI, 2.7–5.0) and 4.5% (95% CI, 0.7–24.9), respectively. Of those US HCP who tested positive at baseline and were retested during serial testing, approximately half (50.3%; 95% CI, 38.6–62.0) reverted to a negative test result (Figure 3.5). Reversion rates were highest for HCP tested using TST (62.5%; 95% CI, 41.4–79.7), followed by QFT (50.3%; 95% CI, 38.1, 62.5) and T-SPOT (38.0%; 95% CI, 7.2–82.9).

Few studies from Europe reported outcomes for conversion and reversion. From the six studies that reported conversion (Baussano et al., 2007; Casas et al., 2020; Moucaut et al., 2013; Ringshausen et al., 2010; Ringshausen et al., 2011; Schablon et al., 2014), 4.9% (95% CI, 2.4–10) of HCP converted from a negative baseline result to a positive result during serial testing. Conversion rates were highest among HCP tested using TST (5.0%; 95% CI, 2.3–10.2), followed by QFT (3.5%; 95% CI, 1.8–6.8) and T-SPOT (1.4%; 95% CI, 0.1–18.7) (Table 3.2). No studies from Europe reported reversion when TST was used. However, six studies using QFT reported a pooled reversion rate of 19.9% (95% CI, 9.7–36.5) among HCP serially tested (Casas et al.,

2020; Moucaut et al., 2013; Nienhaus et al., 2014; Ringshausen et al., 2010; Ringshausen et al., 2011; Schablon et al., 2014), and one study (Ringshausen et al., 2011), which used T-SPOT, reported a lower reversion rate of 8.6% (95% CI, 2.8–23.4). Significant I^2 statistics were reported between studies that report outcomes for test conversion and reversion and set in the United States and Europe. Studies from Israel, Australia, and New Zealand did not report outcomes for conversion and reversion.

Secondary outcomes and publication bias

No studies reported outcomes for TB transmission or progression to active TB disease during serial screening. Visual inspection of the funnel plot for studies reporting baseline testing outcomes indicates no publication bias among US and non-US studies. However, potential publication bias was indicated for studies set in Europe that reported conversion and reversion outcomes.

Discussion

This systematic review evaluated the published evidence on TB screening and testing among HCP in the United States and other high-income, low TB-incidence countries during January 2006–November 2020. The review found that US HCP reported a lower prevalence of *M. tuberculosis* infection at baseline than non-US HCP. Among HCP testing positive at baseline, a high proportion reverted to a negative test result during annual screening, irrespective of location. Few US HCP converted from a negative baseline result to a positive result during annual screening. However, non-US HCP reported slightly elevated conversion rates, with those tested with TST reporting the highest conversion rates. No included studies reported outcomes for TB transmission. Moreover, no US HCP developed TB disease in the included studies.

This review's findings are consistent with a recent systematic review that evaluated the use of interferon-gamma release assay (IGRA) among HCP in low TB-incidence countries (Peters, Kozak, Nienhaus, & Schablon, 2020). The Peters et al. review found that 4.5% of HCP from North America test positive for *M. tuberculosis* infection at baseline when tested using IGRA (Peters et al., 2020). Similarly, this review estimated a baseline prevalence of 4% when US HCP were tested with T-SPOT and 5% when QFT is used. However, the Peters et al. review reported a higher prevalence for HCP in Europe than those found in this review. Peters et al. found 16.4% of HCP in Europe infected with *M. tuberculosis* when tested using an IGRA (Peters et al., 2020). In this review, 8.7% and 14.8% of HCP in Europe tested positive at baseline when QFT or T-SPOT are used, respectively. The difference in prevalence estimates is likely because the two reviews used different inclusion criteria. The Peters et al. review included studies in Europe with TB prevalence with less than 40 TB cases per 100,000 persons, whereas our review only included studies from high-income economies with less than 20 TB cases per 100,000 persons.

In another review published in 2012 (Zwerling et al., 2012), the prevalence of LTBI among HCP from low TB-incidence countries was lower when HCP were tested with an IGRA compared to TST. This finding is consistent with what this review found for studies set outside of the United States. However, in our review, US HCP tested with TST reported a lower baseline positivity rate than those tested with QFT. The lower TST positivity rate is likely because the BCG vaccine is no longer used in the US, limiting the potential for cross-reactivity and leading to a false-positive baseline test. Moreover, serial testing outcomes (i.e., conversion and reversion) from the Zwerling et al. review are consistent with those found in this review, with

high reversion rates among those previously testing positive at baseline and lower conversion rates among those who were negative at baseline.

The findings from this review indicate that TST, QFT, and T-SPOT are appropriate for baseline testing of US HCP, as the estimated pooled prevalence between the three tests was relatively similar. However, the small proportion of US HCP converting from a negative to a positive test result during annual screening may indicate limited utility in conducting annual testing among HCP in low TB-prevalence settings. Additionally, the low number of positive LTBI identified during annual testing and the increased likelihood of unnecessary LTBI treatment calls into question the economic value of serial screening in the US. The relatively high BCG-vaccinated HCP rates in Europe likely explain why nearly 1 in 4 HCP tested with TST in this review had a positive result at baseline. Therefore, using an IGRA for baseline testing for HCP in Europe and other high-income, low TB-incidence countries could reduce the false-positivity rate and identify personnel for appropriate LTBI treatment.

This review had several limitations. First, the narrow, English-only search strategy used for this review could have resulted in some high-quality studies published in other languages being missed. We chose to limit our review to English-only articles due to the lack of resources needed to translated articles from other languages to English. Second, there was significant unexplained statistical heterogeneity among the included studies for each outcome assessed, thus indicating caution in interpreting this review's findings. Lastly, our review did not identify any study that provided follow-up outcomes for TB transmission in US health care settings, thus indicating a research gap that needs to be addressed in future studies.

Conclusions

The body of evidence included in this review identified low TB infection prevalence among US HCP when tested using TST or IGRA. Moreover, few US HCP personnel with a negative baseline test result converted during annual screening. These findings further support recent guidance from CDC and NTCA, eliminating the need for annual testing of US HCP working in health care settings without ongoing TB transmission (Sosa et al., 2019). Higher baseline positivity rates from studies conducted in Europe might suggest a need to switch from TST to IGRA for baseline testing due to higher BCG vaccination among foreign-born HCP. Additionally, serial TB screening might still be needed in other high-income, low TB-incidence countries due to higher background TB rates than the United States.

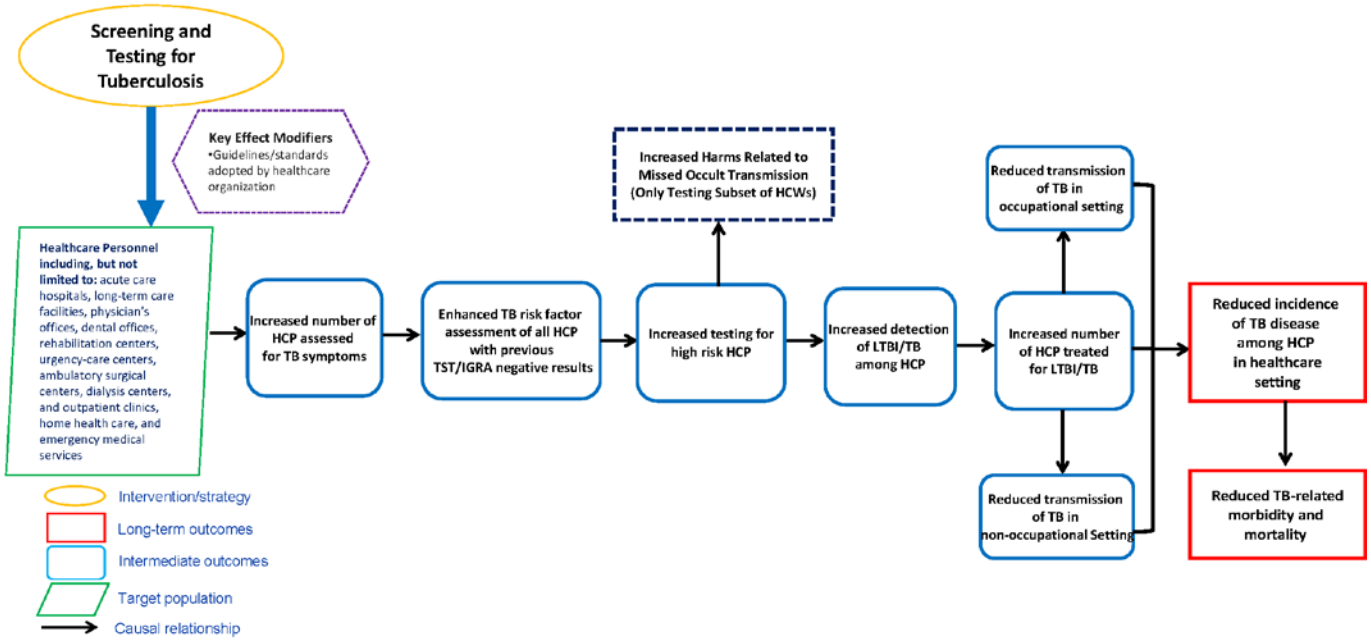


Figure 3.1. Analytic framework for screening and testing healthcare personnel for latent tuberculosis infection.

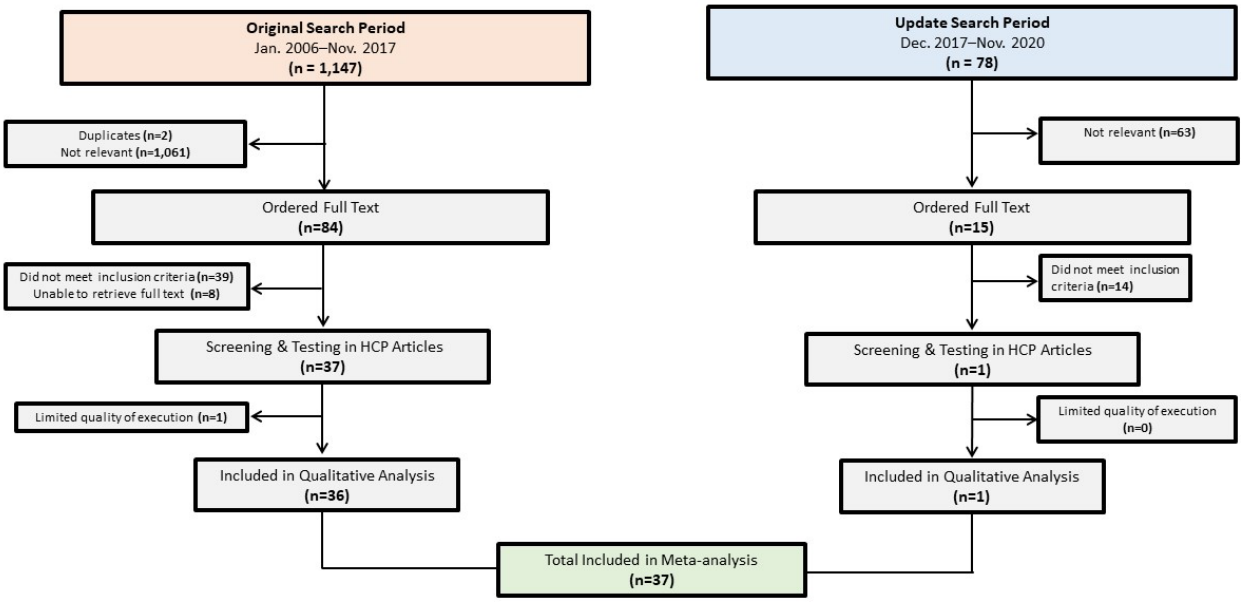


Figure 3.2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for original and update searches.

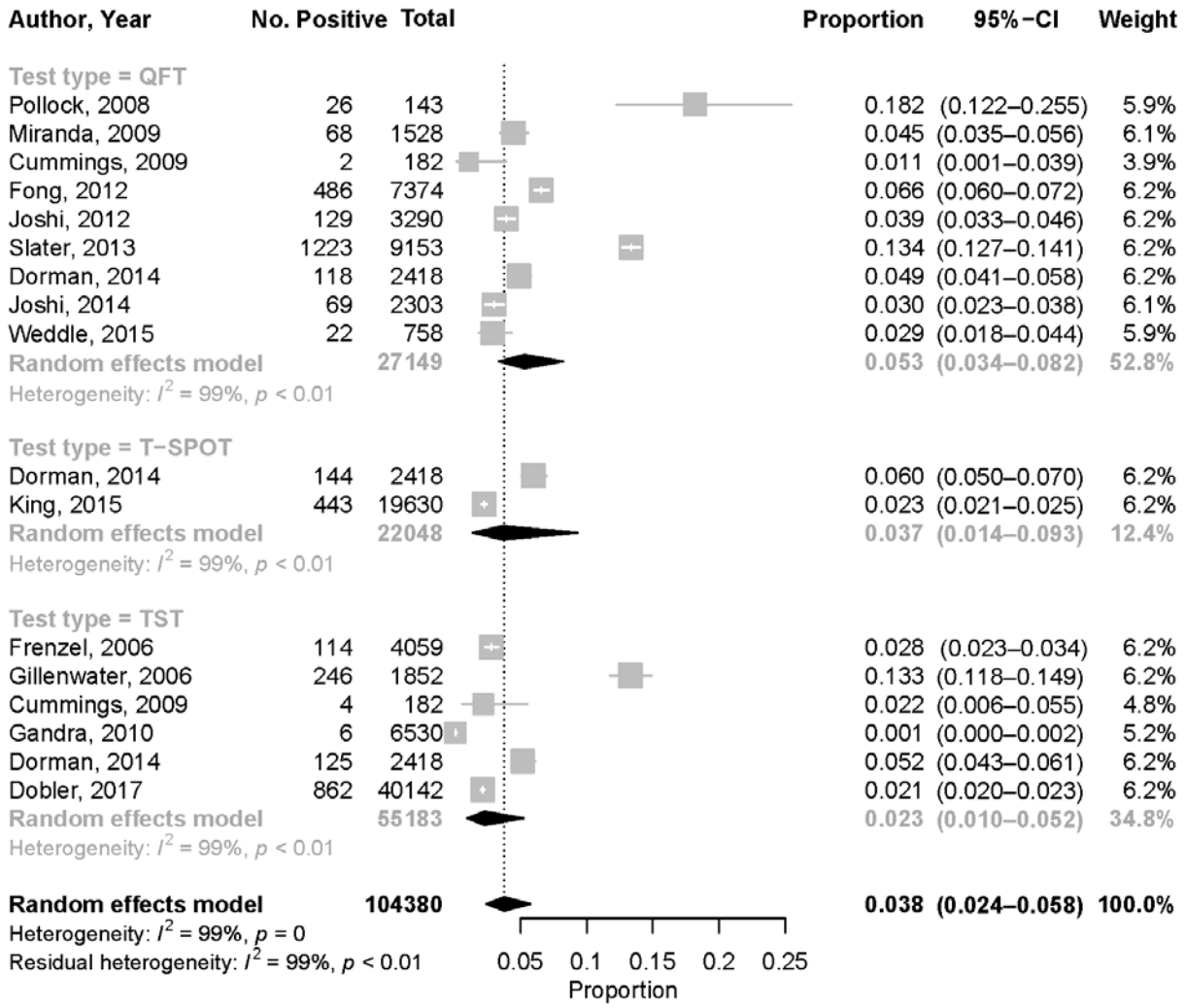


Figure 3.3. Proportion of *M. tuberculosis* infection among US health care personnel during POPP (i.e., baseline) testing (n=14 studies)

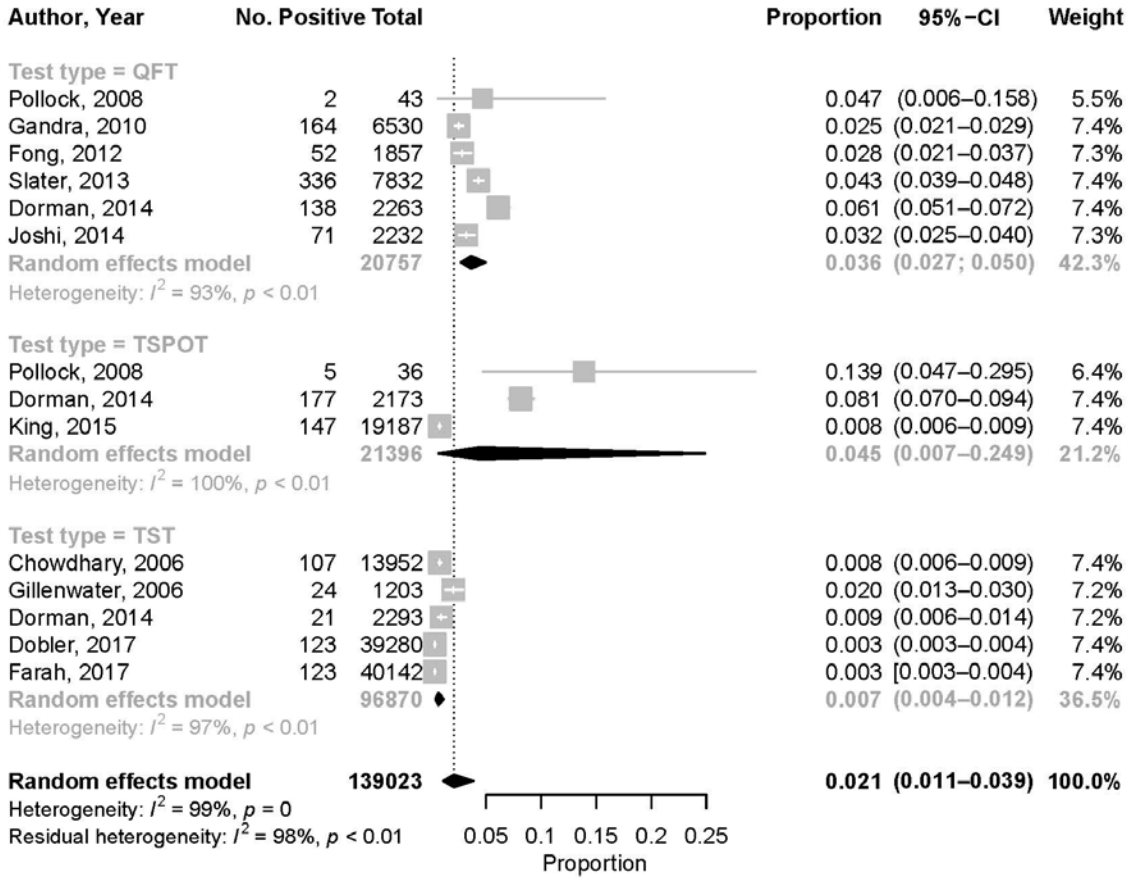


Figure 3.4. Proportion of US HCP who tested negative for *M. tuberculosis* infection at baseline and converted to a positive result during serial screening (n=9 studies).

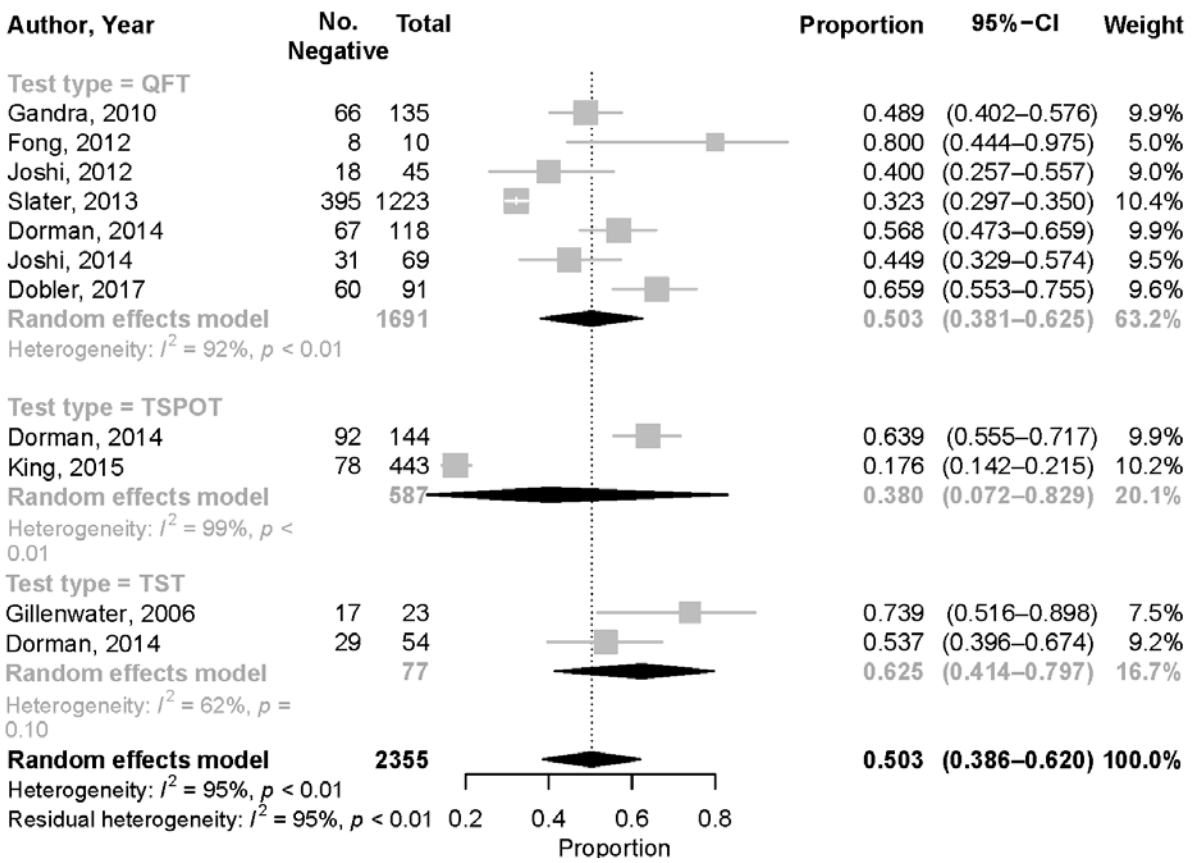


Figure 3.5. Proportion of US HCP who tested positive for *M. tuberculosis* infection at baseline and reverted to a negative result during serial screening (n=9 studies).

Table 3.1. Study characteristics of included body of evidence

Characteristic		No. of studies reporting (%)
Location	Europe	18 (48.6)
	United States	16 (43.2)
	Australia/New Zealand	2 (5.4)
	Israel	1 (2.7)
Study design	Randomized controlled trial	0 (0)
	Retrospective cohort	15 (40.5)
	Prospective cohort	8 (21.6)
	Cross-sectional survey	14 (37.8)
Type of test used at baseline	TST	12 (32.4)
	IGRA	11 (29.7)
	TST + IGRA	14 (37.8)
Setting	Hospital	35 (94.6)
	Other	2 (5.4)
Study focus	Testing only	16 (43.2)
	Screening and testing	21 (56.8)

Abbreviations: IGRA, interferon-gamma release assay; TST, tuberculin skin test

Table 3.2. Outcomes for non-US studies by location and test type

Location	Type of test	Outcome measure	No. of studies reporting	Sample size	Pooled effect estimate (95% CI)
Europe	TST	Baseline testing	15	12,286	24.0% (16.3–33.9)
	QFT	Baseline testing	15	14,468	8.7% (6.2–12.1)
	T-SPOT	Baseline testing	3	262	14.8% (5.6–33.5)
	TST + QFT	Baseline testing	1	491	23.8% (20.3–27.8)
	TST	Conversion	2	2,437	5.0% (2.3–10.2)
	QFT	Conversion	5	1,292	3.5% (1.8–6.8)
	T-SPOT	Conversion	1	35	1.4% (0.1–18.7)
	QFT	Reversion	6	472	19.9 (9.7–36.5)
	T-SPOT	Reversion	1	35	8.6 (2.8–23.4)
Israel	TST	Baseline testing	1	2,292	31.7% (29.8–33.7)
	TST	Conversion	1	450	20.7% (17.2–24.7)
Australia/New Zealand	TST	Baseline testing	2	689	26.6% (16.5–40.0)
	QFT	Baseline testing	2	806	7.5% (5.8–9.6)

Abbreviations: QFT, QuantiFERON-TB Gold In-tube; T-SPOT, T-SPOT.*TB*; TST, tuberculin skin test

CHAPTER 4

COST-EFFECTIVENESS OF POST-OFFER AND PRE-PLACEMENT TUBERCULOSIS SCREENING, TESTING, AND TREATMENT OF US HEALTH CARE PERSONNEL[2]

[2] Njie GJ, Beeler Asay GR, Sekandi JN, and Chen Z. To be submitted to the *Journal of Public Health Practice and Management*

Abstract

Introduction: Current guidelines in the United States (US) recommend that newly hired health care personnel (HCP) receive baseline tuberculosis (TB) screening, testing, and treatment. We sought to compare the cost-effectiveness of post-offer and pre-placement (POPP) TB screening scenarios for US-born and non–US-born HCP from the health system perspective.

Methods: A Markov state-transition decision-analytic model was constructed to compare health outcomes, costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio for five POPP screening scenarios: no screening, two-step tuberculin skin test (TST) + 9-month isoniazid (9H), two-step TST + 3-month isoniazid-rifapentine (3HP), QuantiFERON-TB Gold In-tube (QFT) + 3HP, and QFT/QFT + 3HP. Outcomes were estimated over 20 years, with future costs and QALYs discounted at 3% per year.

Results: For US-born HCP, the QFT + 3HP scenario yielded the largest number of TB cases averted over 20 years at 36 cases per 10,000 HCP; two-step TST + 3HP yielded the largest number of TB cases averted for non-US-born HCP at 39. From the HS perspective, QFT + 3HP is cost-effective for US-born HCP at an ICER of $14,559 per QALY gained relative to no screening. For non-US-born HCP, QFT + 3HP is also cost-effective at an ICER of $14,822 per QALY gained relative to no screening. All other scenarios were dominated by QFT + 3HP for both cohorts. The model was most sensitive to LTBI treatment initiation rate followed by the prevalence of LTBI in HCP.

Conclusions: QFT + 3HP is cost-effective as a POPP TB screening scenario for both US-born and non-US-born HCP. US occupational health programs might want to reconsider using two-step TST + 9H as a POPP screening scenario, as it was the least effective scenario in our model.

Keywords: Health care personnel; Cost-effectiveness; Economic evaluation; Latent tuberculosis infection; United States; Baseline testing; Tuberculosis screening

Introduction

Historically, health care personnel (HCP) have been at increased risk of *Mycobacterium tuberculosis* infection due to occupational exposure (Haagsma, Tariq, Heederik, & Havelaar, 2012). However, recent surveillance data indicate the annual rate of TB in HCP in the United States (US) has declined by 47% when compared with cases reported during 1995–2007 (i.e., 2.5 vs. 4.7 cases per 100,000 persons) (L. A. Lambert et al., 2012; Mongkolrattanothai et al., 2019). The decline in TB cases among US HCP might be partly explained by the widespread adoption and implementation of US Centers for Disease Control and Prevention (CDC) guidelines for preventing *Mycobacterium tuberculosis* transmission in US health care settings (Centers for Disease Control and Prevention, 1994; Jensen et al., 2005).

The 2005 CDC guidelines include recommendations for occupational health programs to implement administrative, environmental, and respiratory-protection controls to prevent *M. tuberculosis* transmission. In 2019, the CDC and National Tuberculosis Controllers Association (NTCA) published recommendations that updated an administrative control from the 2005 guidelines, which focused on TB screening and testing of new hires—specifically, post-offer and pre-placement (POPP) TB (i.e., baseline) screening for US HCP (Sosa et al., 2019). POPP TB screening now includes a symptom evaluation and test for newly hired HCP without documented prior TB disease or latent TB infection (LTBI), in addition to an individual TB risk assessment. Implementing a POPP TB screening program for new hires is expected to help health care organizations: 1) identify persons with active TB disease; 2) identify persons with LTBI and offer the appropriate treatment; and 3) interpret future TB test results for staff exposed to a TB patient (Thanassi et al., 2020).

Although the updated guidance recommends a TB test for newly hired HCP as part of POPP screening, it does not explicitly state which test to use (i.e., a tuberculin skin test [TST] or interferon-gamma release assay [IGRA]). Instead, the updated HCP guidance relies on the 2017 TB diagnostic guideline from the American Thoracic Society (ATS), Infectious Diseases Society of America (IDSA), and CDC, which prefer using IGRA instead of TST to identify *M. tuberculosis* infection in most situations for persons at low or intermediate risk of TB progression (Lewinsohn et al., 2017). Moreover, the ATS/IDSA/CDC guidelines recommend a second confirmatory test for persons with an initial positive result—where either an IGRA or TST could be used for the second test. IGRAs, such as QuantiFERON-TB Gold In-tube (QFT) and T-SPOT.*TB,* offer several advantages over TST for POPP TB screening. These advantages include the need for only a single visit to conduct the test, greater specificity in persons that received the Bacillus Calmette-Guérin (BCG) vaccine, and a short turn-around time to receive test results (Mazurek et al., 2005).

An economic evaluation, published in 2009, compared the use of IGRAs to TST with treatment using 9-month isoniazid (9H) for US HCP, and it found IGRAs to be more effective and less costly than TST (de Perio et al., 2009). Since the publication of this cost-effectiveness analysis (CEA), new guidance for the treatment of LTBI has been published by CDC and NTCA, with short-course regimens such as 3-month isoniazid-rifapentine (3HP) being preferred over traditional isoniazid regimens, such as 9H (Sterling et al., 2020). Still, the economic value of using a sequential, confirmatory IGRA testing strategy, combined with a short-course treatment regimen, as part of POPP TB screening for US HCP is unclear. The purpose of this study is to compare the relative cost-effectiveness of POPP TB screening scenarios—including sequential, confirmatory testing—for newly hired US HCP from the health system perspective.

Methods

Study Design Overview

Using TreeAge Pro Healthcare 2020 (TreeAge Software Inc., Williamstown, MA, USA), we developed a decision tree and Markov cohort model to estimate the health outcomes, costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER) for five POPP screening scenarios in a hypothetical cohort of 10,000 newly hired 35-year-old US HCP. The model included four transition states representing the possible clinical events for HCP tested: no infection, LTBI, TB, and death. Model input data were derived from the published literature and publicly-available data from the US Department of Veterans Affairs (VA) (US Department of Veterans Affairs, 2020). The base-case analysis was conducted using the health system. The health system perspective included direct program costs related to conducting POPP TB screening, including material and labor costs.

Costs and outcomes were projected over a 12-month cycle, with a 20-year analytic horizon. Costs are reported in 2018 US dollars using the health care component of the Personal Consumption Expenditure Price Index from the US Bureau of Economic Analysis (Bureau of Economic Analysis, 2020). All future costs and health outcomes were discounted at an annual rate of 3%. The results from this analysis are intended to inform US policymakers and administrators of occupational health and wellness programs. Moreover, the findings may also be of use to public health researchers and state and local TB programs. This study was reviewed by the University of Georgia and determined to be excluded from ethics approval (IRB ID: 00002230).

Model Description

The model includes both a decision tree and Markov state-transition model to capture the long-term, natural history of TB reactivation. A detailed diagram of the decision trees for the included testing strategies is included in the accompanying appendix for this report. The decision tree focused on four testing strategies: no testing, two-step TST alone, QFT alone, and a confirmatory strategy, where an initial QFT positive result is confirmed with another QFT. Moreover, we used half-cycle corrections to account for transitions that might occur mid-year.

Decision Tree. Briefly, each testing strategy begins with a branch that captures the prevalence of LTBI in US HCP, followed by the probability of having the first TST read. HCP testing positive after the first TST will receive chest radiography (CXR) and additional workup to confirm TB disease, with those diagnosed with TB transferred to the Markov model. For HCP that initially test negative when TST is used, a second test is placed, and those testing negative again are transferred to the Markov model. HCP whose TST test result is not read are lost to follow-up and transferred to the Markov model. For HCP tested using QFT, those testing positive but have a normal CXR, or those testing negative, are transferred to the Markov model. In general, HCP were "handed off" to one of three health states for the Markov model: previous TB disease, no LTBI, no LTBI treatment, and LTBI treatment (Figure 4.1).

Markov Model. HCP entering the model with previous TB disease might remain in the same state, die from TB, or transition to "cured" after receiving anti-TB treatment; we assumed no TB remission among those with previous TB disease. HCP in the cured state can remain healthy, relapse to TB disease, or die from other causes based on the age-specific background mortality rate in the United States (Arias, 2019). The "no LTBI treatment" subgroup includes HCP with LTBI lost to follow-up or those who failed to initiate or complete LTBI treatment. These HCP entered the Markov model either with no infection or with LTBI. HCP who entered

the Markov model with no infection were at risk of converting to TB disease based on annual occupational risk for an intermediate-risk health care facility; those with LTBI were at risk for TB progression based on annual TB reactivation risk.

Two LTBI treatment regimens were modeled: self-administered 9H and 3HP. HCP who initiate LTBI treatment using either regimen could complete treatment without complication and transition to the no infection submodel. HCP who experienced complications are categorized into two groups: mild hepatotoxicity or fatal hepatotoxicity. HCP with mild hepatotoxicity are assumed not to complete treatment and progress to TB disease. HCP with TB either recovered once anti-TB treatment was completed, died from TB, or died from other causes.

Testing and Treatment Scenarios

No screening. Upon hire, HCP are not screened and tested for *M. tuberculosis* infection nor are they offered LTBI treatment.

Two-step TST with 9H treatment (two-step TST + 9H). Upon hire, HCP receive a baseline individual TB risk assessment, which is useful for interpreting test results. Two-step TST testing is conducted. If the initial test result is positive (i.e., induration ≥5 mm for high-risk persons and ≥10 mm for low-risk persons), the personnel is considered infected with *M. tuberculosis* and evaluated for TB disease using a TB symptom evaluation and CXR. HCP with an abnormal CXR and symptoms consistent with TB are diagnosed with previous TB disease. If the initial test result is negative, the HCP is administered a second test 1 to 3 weeks after the initial TST rest is read. HCP who test positive after the second test are considered infected with *M. tuberculosis* and evaluated for LTBI treatment; those testing negative likely do not have TB infection, and no further evaluation is necessary. HCP who do not return to have their test results

read are lost to follow-up. HCP diagnosed with TB infection are offered self-administered 9H for LTBI treatment once TB disease is excluded.

Two-step testing + 3HP treatment (two-step TST + 3HP). Upon hire, testing is conducted as described in the paragraph for the two-step TST + 9H scenario; however, HCP diagnosed with LTBI are offered treatment using self-administered 3HP.

QFT testing + 3HP treatment (QFT + 3HP). Upon hire, HCP receive an individual risk assessment, and a blood sample is collected for the QFT test. HCP with a positive QFT test result are evaluated for TB disease using a TB symptom evaluation form and CXR. HCP with an abnormal CXR and symptom consistent with TB are diagnosed with previous TB disease. HCP with unremarkable CXR findings are considered to be infected with *M. tuberculosis* and offered self-administered 3HP treatment. Persons with a negative test result are considered healthy and are not offered LTBI treatment.

Sequential confirmatory QFT testing: confirm QFT positive result with another QFT (QFT/QFT + 3HP). Upon hire, HCP receive an individual risk assessment and QFT test. If the QFT test result is negative, then no further action is required, and the HCP is considered not to be infected with *M. tuberculosis*. However, if the QFT test is positive, then another blood sample is required for a second QFT test. If both QFT tests are positive, then the HCP is evaluated for TB disease using a TB symptom evaluation form and CXR; HCP with an abnormal CXR with symptoms consistent with TB are diagnosed with previous TB disease. HCP with an unremarkable CXR are diagnosed with LTBI and offered self-administered 3HP treatment.

Sequential confirmatory TST testing: confirm QFT positive result with TST (QFT/TST + 3HP). Upon hire, HCP receive an individual risk assessment and QFT test. If the QFT test result is negative, then no further action is required. However, if the QFT test is

positive, a TST is placed and read within three days to confirm the initial QFT test result. HCP with both a positive QFT and TST are evaluated for TB disease using a TB symptom evaluation form and CXR; HCP with an abnormal CXR with symptoms consistent with TB are diagnosed with previous TB disease. HCP with an unremarkable CXR are diagnosed with LTBI and offered self-administered 3HP treatment.

Key variables and model assumptions

Base-case parameter values were selected from the published literature and are presented in Table 4.1. Considering LTBI is currently not a reportable condition to the CDC, surveillance data regarding its prevalence among US HCP are unavailable. Therefore, we conducted a systematic review and meta-analysis to estimate epidemiological parameters such as LTBI prevalence for US HCP (see chapter 3). Based on the meta-analysis, the pooled estimated prevalence of US HCP infected with *M. tuberculosis* was 3.8% (95% CI, 2.4–5.8%). In the absence of a gold standard test for LTBI, sensitivity and specificity for TST and QFT were obtained from a study that conducted a Bayesian latent class analysis to estimate diagnostic test accuracy for a large US cohort based on selected characteristics, including nativity status (Stout et al., 2018). The annual risk of TB reactivation used for US-born and non-US-born HCP was 82 and 98 per 100,000 persons, respectively (Shea, Kammerer, Winston, Navin, & Horsburgh, 2014). Moreover, we estimated that US HCP initiate LTBI treatment at a probability of 42% (Arguello Perez, Seo, Schneider, Eisenstein, & Brown, 2017; Dobler et al., 2018; Swift et al., 2019). Our model assumes newly hired HCP were healthy and without comorbidities such as diabetes and HIV/AIDS. It also assumes that QFT tests were always adequate and produced determinant test results. Our model did not explicitly consider BCG-vaccination among non-US

born HCP since this information would have been considered for test characteristic reported in the latent class analysis published by Stout and colleagues (Stout et al., 2018).

Cost inputs from the health system are presented in Table 4.2. As recommended by the Second Panel on Cost-effectiveness in Health and Medicine (Sanders et al., 2016), the costs of LTBI treatment medications were derived from the VA Federal Supply Schedule (US Department of Veterans Affairs, 2020). We assumed that health care organizations would absorb costs traditionally incurred by patients; these include the costs associated with HCP obtaining LTBI treatment and any visit to the occupational health clinic during work hours. For simplicity, we also assumed that HCP who initiate LTBI treatment and experienced toxicity did not complete treatment and developed TB disease. Moreover, these HCP incurred medication costs for two months with one follow-up clinic visit cost after baseline if they were prescribed 3HP and two follow-up clinic visits cost if prescribed 9H.

Using the standard gamble approach to elicit health state utilities, HCP lost 0.03 and 0.15 QALYs per annum to treat LTBI and active TB disease, respectively (Bauer et al., 2015; G. A. Mullie et al., 2017). HCP who experienced toxicity during treatment lost 0.25 QALYs (Holland, Sanders, Hamilton, & Stout, 2009; McLernon, Dillon, & Donnan, 2008; Shepardson et al., 2013), while those with previous TB disease were attributed a per annum decrement of 0.06 QALYs (Doan et al., 2019). We assumed HCP with LTBI who do not initiate treatment lost no QALYs per annum.

Outcomes and analyses

The outcomes estimated for each scenario included the number of TB cases and death averted, cost per TB cases and death averted, mean costs, mean QALYs, and ICERs, defined as the additional cost per QALY gain relative to the next most expensive strategy. We performed

one-way deterministic sensitivity analyses using a tornado diagram to assess parameter uncertainty. Parameter values varied for the one-way sensitivity analysis included LTBI prevalence, test characteristics and costs, LTBI treatment initiation, and treatment completion costs. We also performed 10,000-iteration probabilistic sensitivity analyses (PSA) using second-order Monte Carlo simulation. Probability values were sampled using a beta distribution, with test characteristics were sampled from a triangular distribution using minimum, likeliest, and maximum values; costs values were sampled using a gamma distribution.

Results

Base-case analysis: health system perspective

Table 4.3 displays the number of TB cases and deaths averted per 100,000 HCP and their associated costs. For US-born HCP, the QFT + 3HP scenarios yielded the highest number of TB cases averted at 36 per 10,000 HCP. The cost to avert a TB case using the QFT + 3HP scenario is $43,926. For TB deaths averted, both the QFT + 3HP and 2-step TST + 9H prevent the most TB deaths at 2 per 10,000 HCP, respectively, at a cost of $996,562 and $1,072,470 per death averted. For non-US-born HCP, two-step TST + 3HP yielded the highest number of TB cases averted at 39 per 10,000 HCP and a cost of $75,666 to avert a single TB case. For TB deaths averted, QFT + 3HP and two-step TST + 9H prevent two deaths, respectively, costing $935,059 and $1,339,278.

Summary cost-effectiveness results for US-born and non-US born HCP from the health system perspective are presented in Table 4.4. For US-born HCP, the no screening scenario reports the lowest cost at $105 per HCP screened, and QFT + 3HP and two-step TST + 3HP report the largest effectiveness at 14.872 QALYs. Of the undominated scenarios, QFT + 3HP is the most cost-effective scenario, at an ICER of $14,559 per QALY gained, relative to no

screening. The confirm positive scenario, QFT/QFT + 3HP, is extendedly dominated by QFT + 3HP at an ICER of $24,742 per QALY gained.

The results for non-US-born HCP are consistent with findings for US-born HCP. The QFT + 3HP scenario is the most optimal scenario at a cost of $159 per HCP screened, QALY of 14.782, and ICER of $14,822 per QALY gained.

Sensitivity analysis

Deterministic one-way and probabilistic sensitivity analyses were performed to evaluate uncertainty in the base-case analysis. Selected parameter probabilities were varied by values reported in the literature, while the upper and lower values for costs and LTBI treatment initiation were varied by 50%.

Figure 4.2 report the tornado diagrams for effectiveness for US-born and non-US born HCP. From the health system, the rate that US- and non-US-born HCP initiate LTBI treatment is the most influential variable on effectiveness. At low rates of treatment initiation, QFT + 3HP is the most effective scenario, but as the initiation rate rises above 50%, the effectiveness of two-step TST + 3HP increases for both US-born and non-US- born HCP.

The cost-effectiveness acceptability curves (CEAC) from the PSA are presented for in Figure 4.3 for US- and non-US-born HCP. For US-born, the QFT + 3HP scenario has a probability of cost-effectiveness of 67.3% at a WTP threshold of $100,000 per QALY gained for US-born HCP, while the two-step TST + 3HP scenario has a probability of cost-effectiveness of 32.7% at a threshold of $100,000 per QALY gained. For non-US-born HCP, QFT + 3HP is optimal at a probability of 99% at a threshold of 100,000 per QALY.

Discussion

Our analysis sought to compare the health outcomes, cost, effectiveness, and ICER, and POPP screening scenarios for US- and non-US-born HCP from the health system and societal perspectives. The findings suggest that QFT + 3HP is the most cost-effective POPP screening scenario for US HCP, relative to no screening, from the health system perspective for both US- and non-US-born HCP over 20 years. The confirm positive scenario, QFT + QFT + 3HP, is extendedly dominated by QFT + 3HP from the health system perspective for all US HCP.

Our model is most sensitive to uncertainty for LTBI treatment initiation rate; this is expected because as treatment initiation rates increase, effectiveness also increases; moreover, an increase in treatment initiation rates increases LTBI treatment cost. Secondarily, LTBI prevalence was also an influential variable, for higher LTBI prevalence increases testing costs and reduces effectiveness when test specificity is low, likely resulting in unnecessary LTBI treatment due to a false-positive test result. The increased probability of two-step TST + 3HP being cost-effective in the PSA, relative to QFT + 3HP, is due to the relatively high TST specificity used in our model for US-born HCP. A high TST specificity results in lower incremental cost, which is a primary driver in the ICER calculation since both scenarios have equal QALYs.

Our findings are consistent with other studies that found a QFT testing strategy to be cost-effective for HCP in low-incidence countries (de Perio et al., 2009; Kowada, Takasaki, & Kobayashi, 2015). To the best of our knowledge, our study is the first to focus on US HCP that included a short-course treatment regimen, 3HP, in the scenarios and considered a confirmatory testing strategy, QFT+ QFT. Although our study primarily focused on testing strategies recommended for US HCP, we conducted additional analyses that included other scenarios that

might be used in non-HCP populations, including one-step TST + 3HP, TST/QFT + 3HP, QFT/TST + 3HP + two-step TST/QFT + 3HP . While our analysis found the additional scenarios to be cost-effective, the TST/QFT + 3HP scenario offered the lowest ICER per QALY gained for all HCP (see appendix).

However, the TST/QFT+ 3HP scenario is impractical for US HCP because two-step TST is required since a TST test could stimulate an immune response that might have waned after being previously infected (i.e., boosted reaction). The boosted reaction could subsequently be misinterpreted as a recent infection when personnel are retested after TB exposure in a health care setting (Thanassi et al., 2020).

A strength of our study includes using self-administered 3HP as an LTBI treatment regimen in our scenarios. Previous CEAs focused on HCP included 6- or 9-month isoniazid as the treatment regimen; however, the latest CDC LTBI treatment guidelines prefer short-course regimens, such as 3HP, over traditional isoniazid regimens because of higher completion rates (Sterling et al., 2020). Moreover, the epidemiological characteristics included in our study are based on a meta-analysis that updates findings for the systematic review used to update the CDC and NTCA screening, testing, and treatment recommendations for US HCP (Sosa et al., 2019).

Our study had several limitations. First, our model did not account for comorbidities such as diabetes and HIV, as these conditions are known to weaken the immune system and increase TB reactivation risk. Second, our model did not explicitly consider BCG-vaccination among non-US born HCP since this information would have been considered for test characteristic reported in the latent class analysis published by Stout and colleagues (Stout et al., 2018). Third, drug prices reported in our analysis were obtained from the VA Federal Supply Schedule, which supports the VA and other federal government agencies' drug procurement needs; therefore, our

model's drug prices may not be representative of the pricing available to the private sector. Lastly, we did not assess the impact extended travel (i.e., ≥30 days) to a TB-endemic country might have on our results. Future studies should evaluate the impact of comorbidities and the effectiveness of the individual TB risk assessment used as part of POPP TB screening.

Conclusions

Based on the assumptions included in our base-case analysis, the QFT + 3HP scenario is cost-effective for US- and non-US-born HCP from the health system perspective. This finding supports the ATS/IDSA/CDC TB diagnostic guidelines, which prefers using QFT for groups with low to intermediate risk of TB progression (Lewinsohn et al., 2017). Although a confirmatory testing strategy might be used in practice to retest HCP with a low risk of TB infection, we did not find the confirm-positive scenario to be cost-effective for POPP screening, for it has a lower cost per HCP screened but higher cost per QALY gained than QFT + 3HP (i.e., extended dominance). Occupational health programs in the US might want to consider replacing two-step TST with QFT for baseline testing. Moreover, HCP diagnosed with LTBI should be offered and encouraged to complete treatment using 3HP.

Table 4.1. Base-case model parameter values and ranges used for sensitivity analyses for US-born cohort (non-US–born cohort, if different)

Parameter	Base-case value	Range	Source(s)
Epidemiological characteristics			
LTBI prevalence among HCP	0.04	0–0.06	Calculated from meta-analysis
Prob. HCP converts after baseline	0.02	0.01–0.04	Calculated from meta-analysis
Prob. of LTBI reactivation	Time-dependent	–	(Shea et al., 2014)
Background mortality rate	Age-dependent	–	(Arias, 2019)
Test characteristics			
TST sensitivity	0.73 (0.81)	0.62–0.84 (0.73–0.91)	(Stout et al., 2018)
TST specificity	0.92 (0.70)	0.90–0.94 (0.68–72)	(Stout et al., 2018)
QFT sensitivity	0.78 (0.79)	0.65–0.91 (0.70–0.90)	(Stout et al., 2018)
QFT specificity	0.98 (0.99)	0.96–0.99 (0.96–1)	(Stout et al., 2018)
Prob. first TST is read	0.88	0.78–1	(de Perio et al., 2009)
Prob. second TST is placed	0.45	0.30–0.60	(de Perio et al., 2009)
Sensitivity of second TST	0.9	0.80–1	(de Perio et al., 2009)
Specificity of second TST	0.95	0.90–1	(de Perio et al., 2009)
Prob. of returning for second TST read	0.9	0.80–1	(de Perio et al., 2009)
LTBI treatment			
Prob. of HCP initiating LTBI treatment	0.42	0.38–0.45	(Arguello Perez et al., 2017; Dobler et al., 2018; Philip A. LoBue & Catanzaro, 1998; Swift et al., 2019)
Prob. of developing hepatitis, 9H	0.018	0.01–0.12	(Kunst & Khan, 2010)
Prob. of developing hepatitis, 3HP	0.08	0.06–0.10	(Njie et al., 2018)
Prob. of death due to hepatitis, 9H	0	0–0.00001	(Kunst & Khan, 2010)
Prob. of death due to hepatitis, 3HP	0.007	0.005–0.008	(Njie et al., 2018)
Prob. of completing 9H treatment	0.46	0.44–0.48	(Arguello Perez et al., 2017; Horsburgh et al., 2010; Swift et al., 2019)

Prob. of completing 3HP treatment	0.87	0.75–0.95	(Arguello Perez et al., 2017)
TB disease treatment			
Prob. of successful treatment ≤ 1 year	0.90	Fixed	(Centers for Disease Control and Prevention, 2020)
Prob. of recurrent TB	0.05	0.042–0.057	(Kim, Moonan, Yelk Woodruff, Kammerer, & Haddad, 2013)
Prob. of death during TB treatment	0.07	Fixed	(Centers for Disease Control and Prevention, 2020)
Quality of life adjustments: QALYs lost per year			
LTBI, no treatment	0	Assumed	
LTBI treatment	0.03	0–0.05	(Bauer et al., 2015; G. A. Mullie et al., 2017)
Drug-induced hepatotoxicity	0.25	0–0.40	(Holland et al., 2009; McLernon et al., 2008; Shepardson et al., 2013)
Previous TB disease	0.06	0–0.13	(Doan et al., 2019)
Active TB disease treatment	0.15	0.10–0.30	(Bauer et al., 2015; G. A. Mullie et al., 2017)

Abbreviations: 3HP, 3-month isoniazid-rifapentine regimen; 9H, 9-month isoniazid regimen; CXR, chest radiography; HCP, health care personnel; LTBI, latent tuberculosis infection; Prob., probability; TB, tuberculosis; TST, tuberculin skin test; QALYs, quality-adjusted years; QFT, QuantiFERON-TB Gold In-tube test

Table 4.2. Cost inputs from the health system perspective

Variable	Cost	Range	Source
Baseline risk assessment and symptom screen	$5	3–8	(Wrighton-Smith, Sneed, Humphrey, Tao, & Bernacki, 2012)
Two-step TST (placement and reading)	$92	46–138	Wrighton-Smith(Wrighton-Smith et al., 2012)
Two-step TST (placement and reading for non-returners)	$98	49–147	(Wrighton-Smith et al., 2012)
TST, one-step (placement and reading)	$12	6–18	(Wrighton-Smith et al., 2012)
TST, non-return (completion of 1st step only)	$18	9–27	(Wrighton-Smith et al., 2012)
QuantiFERON TB Gold In-tube	$46	23–69	(de Perio et al., 2009)
Cost of CXR (2-view) and interpretation	$57	29–86	(Centers for Medicare and Medicaid Services, 2019; Wrighton-Smith et al., 2012)
Complete 3HP treatment	$410	205–615	(Shepardson et al., 2013; US Department of Veterans Affairs, 2020)
Incomplete 3HP treatment	$315	158–743	(Shepardson et al., 2013; US Department of Veterans Affairs, 2020)
Complete 9H treatment	$489	245–734	(Shepardson et al., 2013; US Department of Veterans Affairs, 2020)

Incomplete 9H treatment	$229	115–344	(Shepardson et al., 2013; US Department of Veterans Affairs, 2020)
Mild hepatitis due to LTBI treatment	$244	122–366	(Linas, Wong, Freedberg, & Horsburgh, 2011; Shepardson et al., 2013; Tasillo et al., 2017)
Severe hepatitis with fatality	$8,713	4,357–13,070	(Linas et al., 2011)
Active TB diagnosis	$286	143–429	(G. A. Mullie et al., 2017)
Outpatient TB treatment	$3,307	1,654–4,961	(Brown et al., 1995; Shepardson et al., 2013; Tasillo et al., 2017)
Inpatient TB treatment	$28,583	14,292–42,875	(de Perio et al., 2009; Owusu-Edusei, Marks, Miramontes, Stockbridge, & Winston, 2017; Salpeter & Salpeter, 2004; Shepardson et al., 2013)

Abbreviations: 3HP, 3-month isoniazid-rifapentine regimen; 9H, 9-month isoniazid regimen; CXR, chest radiography; HCP, health care personnel; Prob., probability; TB, tuberculosis; TST, tuberculin skin test

Table 4.3. Results of TB cases and deaths averted and their associated costs from the health system perspectives

Cohort	Scenario	TB cases averted per 10,000 HCP	TB deaths averted per 10,000 HCP	Cost per TB case averted	Cost per TB death averted
US-born	No screening	–	–	–	–
	QFT + QFT + 3HP	28	1	$55,534	$1,208,923
	QFT + 3HP	36	2	$43,926	$996,562
	2-step TST + 9H	25	2	$74,416	$1,072,470
	2-step TST + 3HP	35	1	$54,801	$1,584,667
Non-US born	No screening	–	–	–	–
	QFT + QFT + 3HP	29	1	$53,388	$1,121,143
	QFT + 3HP	37	2	$42,846	$935,059
	2-step TST + 9H	13	2	$181,256	$1,339,278
	2-step TST + 3HP	39	1	$75,666	$4,172,429

Abbreviations: 3HP, 3-month isoniazid-rifapentine; 9H, 9-month isoniazid; HCP, health care personnel; TB, tuberculosis; QFT, QuantiFERON-TB Gold In-tube

Table 4.4. Base-case results for US-born and non-US–born HCP from the health system perspective, relative to no screening

Cohort	Scenario	Cost	Incr. Cost	QALYs	Incr. QALYs	ICER ($/QALY) vs. no screening
US-born	No screening	$105	–	14.868	–	–
	QFT/QFT + 3HP	$158	$53	14.870	0.0021	Dominated
	QFT + 3HP	$160	$55	14.872	0.0038	$14,559
	2-step TST + 9H	$182	$78	14.867	-0.0005	Dominated
	2-step TST + 3HP	$190	$86	14.872	0.0037	Dominated
Non-US born	No screening	$104	–	14.868	–	–
	QFT/QFT + 3HP	$157	$53	14.870	0.0022	Dominated
	QFT + 3HP	$159	$54	14.872	0.0037	$14,822
	2-step TST + 9H	$241	$137	14.865	-0.0028	Dominated
	2-step TST + 3HP	$292	$188	14.870	0.0023	Dominated

Abbreviations: 3HP, 3-month isoniazid-rifapentine; 9H, 9-month isoniazid; Eff., effectiveness; HCP, health care personnel; Incr., incremental; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; QFT, QuantiFERON-TB Gold In-tube

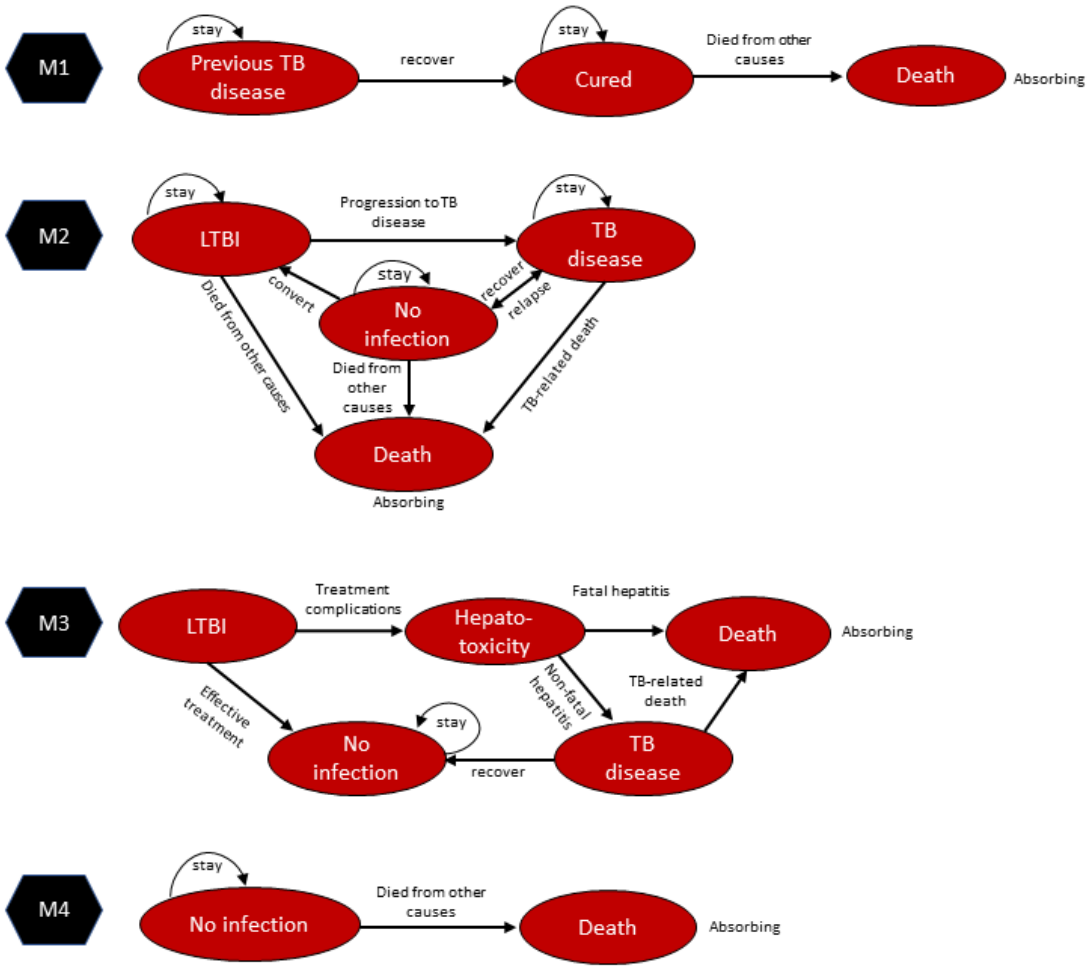
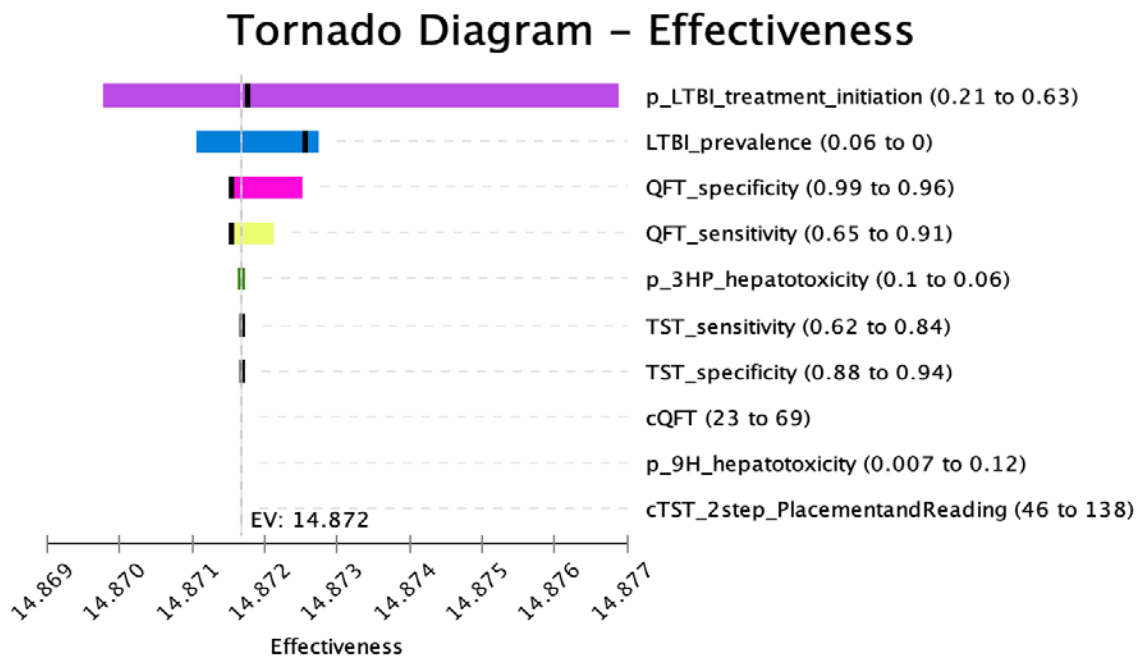


Figure 4.1. Simplified state-transition diagram of Markov model subtrees for previous TB disease (M1), LTBI, no treatment (M2), LTBI with treatment (M3), No LTBI, no treatment (M4)

(A)



(B)

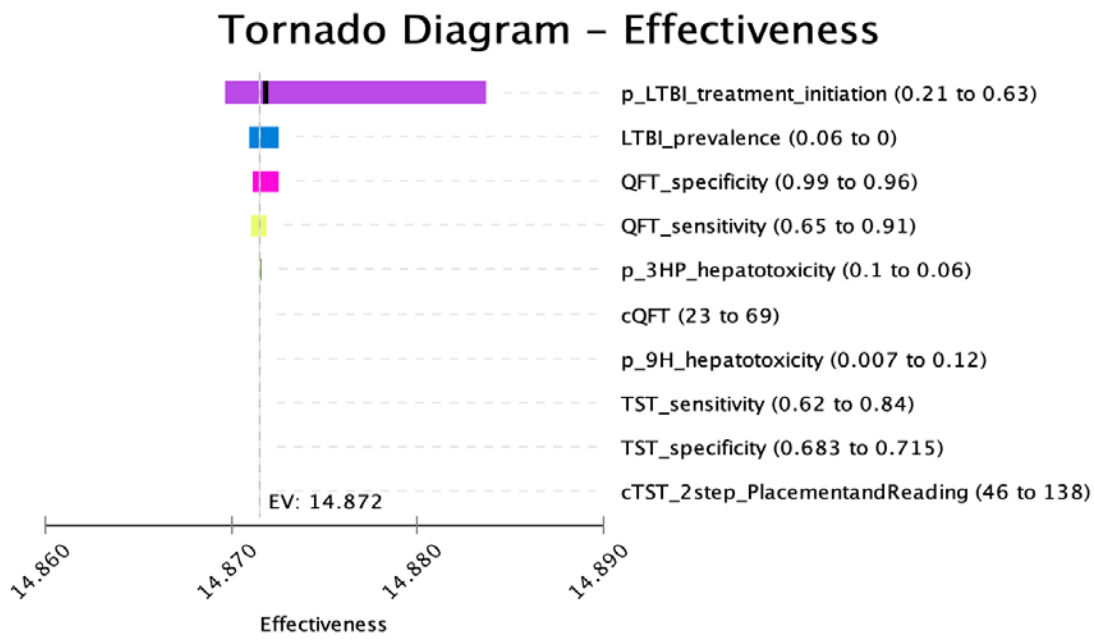
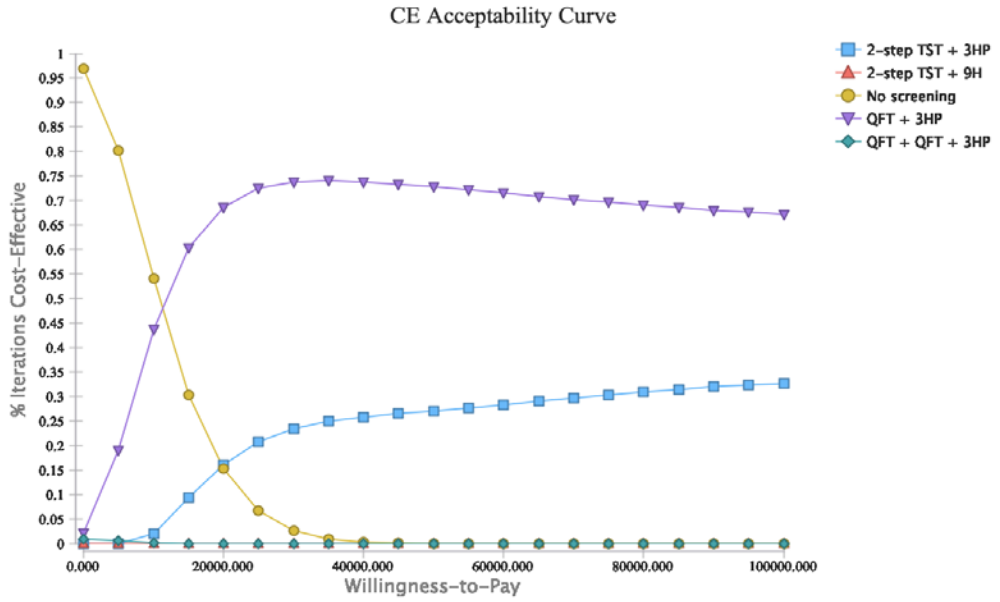


Figure 4.2. Tornado diagram of the discounted expected QALYs per HCP over 20 years for (A) US-born HCP and (B) non-US-born HCP

(A)



(B)

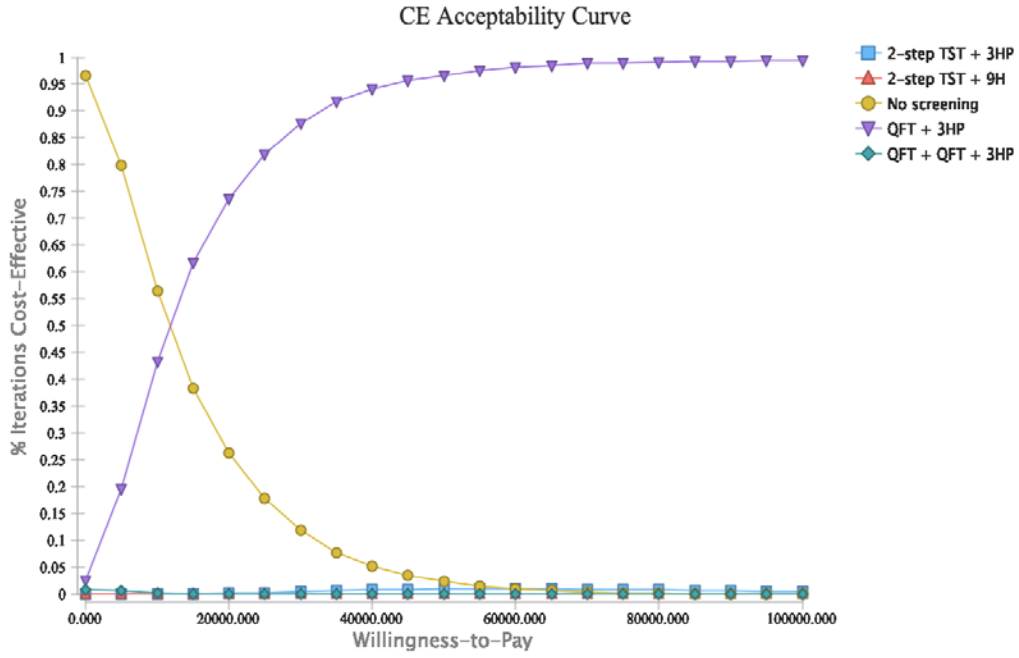


Figure 4.3 Cost-effectiveness acceptability curves from the probabilistic sensitivity analyses for (A) US-born HCP (b) non-US-born HCP

CHAPTER 5

CONCLUSION

Overview

This chapter will summarize the two studies included in this dissertation and conclusions drawn based on findings from those studies. Moreover, it will discuss the implications for public health policy and practice, limitations of this study, and future research considerations. Lastly, the chapter concludes with a broad summary.

Background

Tuberculosis (TB) is a leading cause of morbidity and mortality globally. Health care personnel (HCP) are at increased risk for TB due to occupational exposure. In the United States (US), the Centers for Disease Control and Prevention (CDC) has published several guidelines over the past two decades that include administrative, environmental, and personal-respiratory controls to prevent the transmission of *Mycobacterium tuberculosis* in health care settings. In the latest guidelines, published in 2019, the CDC recommends that all newly hired HCP receive TB screening using an individual TB risk assessment along with testing for *M. tuberculosis* infection at baseline (i.e., post-offer and pre-placement [POPP]) (Sosa et al., 2019). Moreover, the guidelines also recommend a second, confirmatory test for HCP with a positive initial test result, with treatment strongly encouraged for personnel diagnosed with latent TB infection (LTBI). However, POPP screening's economic value using sequential confirmatory testing has not been evaluated in US HCP.

This research's primary objective is to identify the most optimal POPP screening, testing, and treatment scenario for US HCP. The first study systematically reviewed the published literature to estimate LTBI prevalence and test conversion and revision rates during serial screening for HCP in the US and other high-income, low-TB incidence countries. The second study compared the costs, effectiveness, incremental cost-effectiveness ratio (ICER), and net monetary benefits (NMB) of POPP screening—including sequential, confirmatory testing—and treatment scenarios for US-and non–US-born HCP, using the epidemiological parameters from the first study. The findings from this research are intended to inform US healthcare administrators and policymakers for occupational health programs.

Study Aims and Key Findings

Study 1: Systematic review and meta-analysis

The meta-analysis was designed to estimate the epidemiological characteristics of US and non-US HCP. Findings from the meta-analysis were used to inform a cost-effectiveness analysis (CEA) by asking the following research questions:

1. What is the prevalence of LTBI among HCP in the United States and other high-income, low TB-incidence countries?
2. What proportion of US and non-US HCP convert from a positive test result to a negative test result during serial screening?
3. What proportion of US and non-US HCP revert to a negative test result during serial screening after testing positive at baseline?

The findings from the research questions outlined above are as follows:

From 14 studies reporting the prevalence of M. tuberculosis infection in US HCP, we estimate that 3.8% (95% CI, 2.4–5.8) of HCP in the US have LTBI. LTBI prevalence in US HCP

varied by the type of test used, with TST reporting a lower prevalence than interferon-gamma release assay (IGRA). Contrarily, we estimate an LTBI prevalence of 24.0% (95% CI 16.3–33.9) for HCP from other high-income, low TB-incidence countries, from 15 studies reporting. When tested on a serial basis, an estimated 2.1% (95% CI 1.1–3.9) of US HCP converted from a negative baseline test to positive; whereas, 4.9% (95% 2.4–10) of HCP from other high-income, low TB-incidence countries convert during serial testing. Of those US HCP who tested positive at baseline and were retested during serial testing, 50.3% (95% CI, 38.6–62.0) reverted to a negative test result. Reversion rates were highest for HCP tested using TST compared to interferon-gamma release assays (IGRAs). For non-US studies, reversion rates ranged 8.6%–19.9 depending on the type of test used.

Based on these findings, we concluded that LTBI prevalence is lower in the US compared to other high-income, low TB-incidence countries. Furthermore, US HCP revert from a positive baseline test result to a negative result at a higher proportion than non-US HCP, especially when tested using IGRAs. Furthermore, the US has a lower proportion of HCP who convert during serial screening than other high-income, low TB-incidence countries, suggesting minimal TB transmission in US healthcare settings.

Study 2: *Economic evaluation of POPP testing and treatment scenarios*

A decision tree and Markov model were constructed to compare the estimated health outcomes, costs, quality-adjusted life years (QALYs), ICER, and NMB for five testing and treatment scenarios over 20 years from the health system perspective, with future costs and effectiveness discounted at an annual rate of 3%. The five scenarios compared were as follows:

1. no screening
2. two-step TST with 9-month isoniazid treatment (TST + 9H);

3. two-step TST with 3-month isoniazid + rifapentine treatment (TST + 3HP);
4. QFT alone with 3HP (QFT + 3HP); and
5. sequential confirmatory testing with QFT used for the initial and a positive result confirmed with another QFT with 3HP treatment (QFT/QFT + 3HP).

The findings from the cost-effectiveness analysis are as follows:

For US-born HCP, the QFT + 3HP scenarios yielded the highest number of TB cases averted at 36 per 10,000 HCP. The cost to avert a TB case using the QFT + 3HP scenario is $43,926. For TB deaths averted, both the QFT + 3HP and 2-step TST + 9H prevent the most TB deaths at 2 per 10,000 HCP, respectively, costing of $996,562 and $1,072,470 per death averted. For non-US-born HCP, two-step TST + 3HP yielded the highest number of TB cases averted at 39 per 10,000 HCP and a cost of $75,666 to avert a single TB case. For TB deaths averted, QFT + 3HP and two-step TST + 9H prevent two deaths, respectively, costing $935,059 and $1,339,278.

Regarding cost-effectiveness, for US-born HCP, the no screening scenario reported the lowest cost at $105 per HCP screened, and QFT + 3HP and two-step TST + 3HP were the most effective scenarios at 14.872 QALYs. Of the undominated scenarios, QFT + 3HP is the most cost-effective, at an ICER of $14,559 per QALY gained, relative to no screening. The results for non-US-born HCP are consistent with findings for US-born HCP. The QFT + 3HP scenario is the most optimal scenario at a mean cost of $159 per HCP screened, QALY of 14.782, and ICER of $14,822 per QALY gained. The model was most sensitive to the proportion of HCP who initiated LTBI treatment, followed by the prevalence of LTBI in the HCP population.

Implications for Public Health Policy and Practice

POPP TB screening is an essential administrative control necessary for preventing TB transmission in health care settings. Our study found that economic outcomes were most sensitive to LTBI treatment initiation rates. In the United States, LTBI treatment initiation rates for HCP are lower than the general public (Arguello Perez et al., 2017; Dobler et al., 2018; Philip A. LoBue & Catanzaro, 1998; Swift et al., 2019); this is because HCP are more likely to believe that the harms associated with LTBI treatment outweigh the risk of progressing to active TB disease (Swift et al., 2019). However, with updated guidelines from the CDC preferring short-course regimens over the traditional isoniazid regimens (Sterling et al., 2020), future LTBI treatment uptake rates among US HCP might increase. Based on the current treatment initiation rates, QFT + 3HP is the most optimal scenario for US health care organizations. However, our study found that as treatment initiation rates improve, the cost-effectiveness of two-step TST + 3HP also improves. Therefore, for occupational health programs that can attain high treatment initiation rates, two-step TST + 3HP could be considered an alternative scenario, based on the decisionmaker's willingness to pay threshold.

Although two-step TST + 3HP might be an option for some occupational health programs, it is operationally and logistically disadvantageous to implement compared to QFT + 3HP, primarily because it requires multiple visits. These additional visits present an opportunity cost for HCP by taking time away from caring for patients. Moreover, it leads to lost productivity, which the health care organization bears since the HCP would be visiting the occupational clinic during working hours. Additionally, considering the recent nationwide shortage of Aplisol–one of two TST antigens approved by the US Food and Drug Administration

for skin testing—using an IGRA test, such as QFT, offers added advantage should the Aplisol shortage persist (Centers for Disease Control and Prevention, 2019a).

Even though this study examined the economic value of POPP TB screening based on nativity status, in practice, it is likely unlawful for occupational health programs to offer screening services solely based on country of birth. Therefore, occupational health programs should assess their workforce demographics to ensure the most appropriate scenario to meet their needs is implemented.

Limitations and Recommendations for Future Research

This study has several limitations. First, because LTBI is not a reportable condition in most jurisdictions in the United States, it is impossible to know the prevalence of LTBI in US HCP. To account for this limitation, we conducted a systematic review of the published literature to estimate LTBI prevalence in US HCP. However, our review was unable to stratify prevalence based on nativity status for US HCP. Second, because there is no gold standard test for LTBI, TST and IGRA's test characteristics are difficult to assess without a reference standard. As a result, this study's test characteristics were obtained from a latent class analysis using non-HCP cohort data from the United States. Third, this study did not account for the impact serial screening might have on testing costs, as the CDC no longer recommends serial screening in settings without ongoing TB transmission. A recent publication also questioned the economic value of screening HCP on a serial basis (G. A. Mullie et al., 2017). Fourth, the use of TSPOT.*TB* for POPP screening was not considered in this study; nevertheless, we anticipate that T-SPOT could be substituted for QFT with minimal impact on each scenario’s cost-effectiveness. Fifth, as the burden of diabetes continues to increase in the United States, it is expected that the disease will increasingly afflict HCP. As such, future studies should consider

the impact of TB-diabetes comorbidity on the cost-effectiveness of POPP screening scenarios. Lastly, no known publicly available data source provides occupational health costs related to TB testing and treatment; therefore, cost inputs in the CEA are based on previously published data and might not be generalizable to all health care settings.

To better understand the impact of LTBI in the United States, the CDC is collaborating with state and local health departments to develop a national LTBI surveillance system. This new surveillance system will capture variables such as the type of screening test used, medical risk factors, and LTBI treatment outcomes. However, it is unclear if the system will capture a person's occupation and extended travel history outside of the United States. Should these data become available in the future, it would be valuable to reproduce this study using surveillance data specific to HCP. Next, to obtain a more comprehensive and accurate understanding of the cost involved in POPP TB screening, it would be useful to conduct a time-in-motion study in geographically diverse health care organizations. Future economic evaluations on this topic should consider scenarios with other recommended LTBI treatment regimens, including 6-month isoniazid, 3-month isoniazid-rifampin, and 4-month rifampin.

Summary

In summary, this study evaluated the cost-effectiveness of various POPP TB screening scenarios for US HCP. Based on the assumptions included in this study, QFT + 3HP is the most optimal screening scenario for all HCP, irrespective of nativity status. Policymakers for occupational health programs should consider switching from two-step TST to QFT testing based on its economic value and operational advantages. It is reasonable for health care organizations with a $100,000 willingness-to-pay threshold to consider the two-step TST + 3HP scenario as a secondary testing option, given a high LTBI treatment initiation rate within its

workforce. In deciding the best scenario for their workforce, decision-makers should also consider the recent shortage of TST antigens, which might interrupt or delay the placement of new hires.

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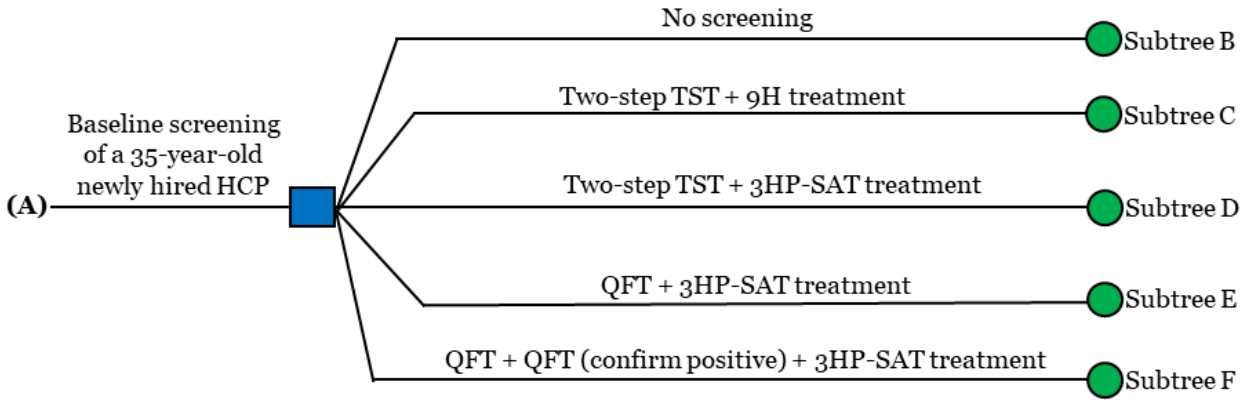
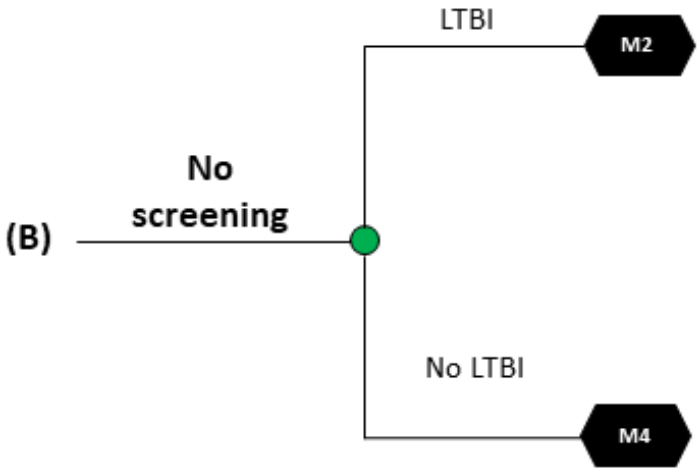
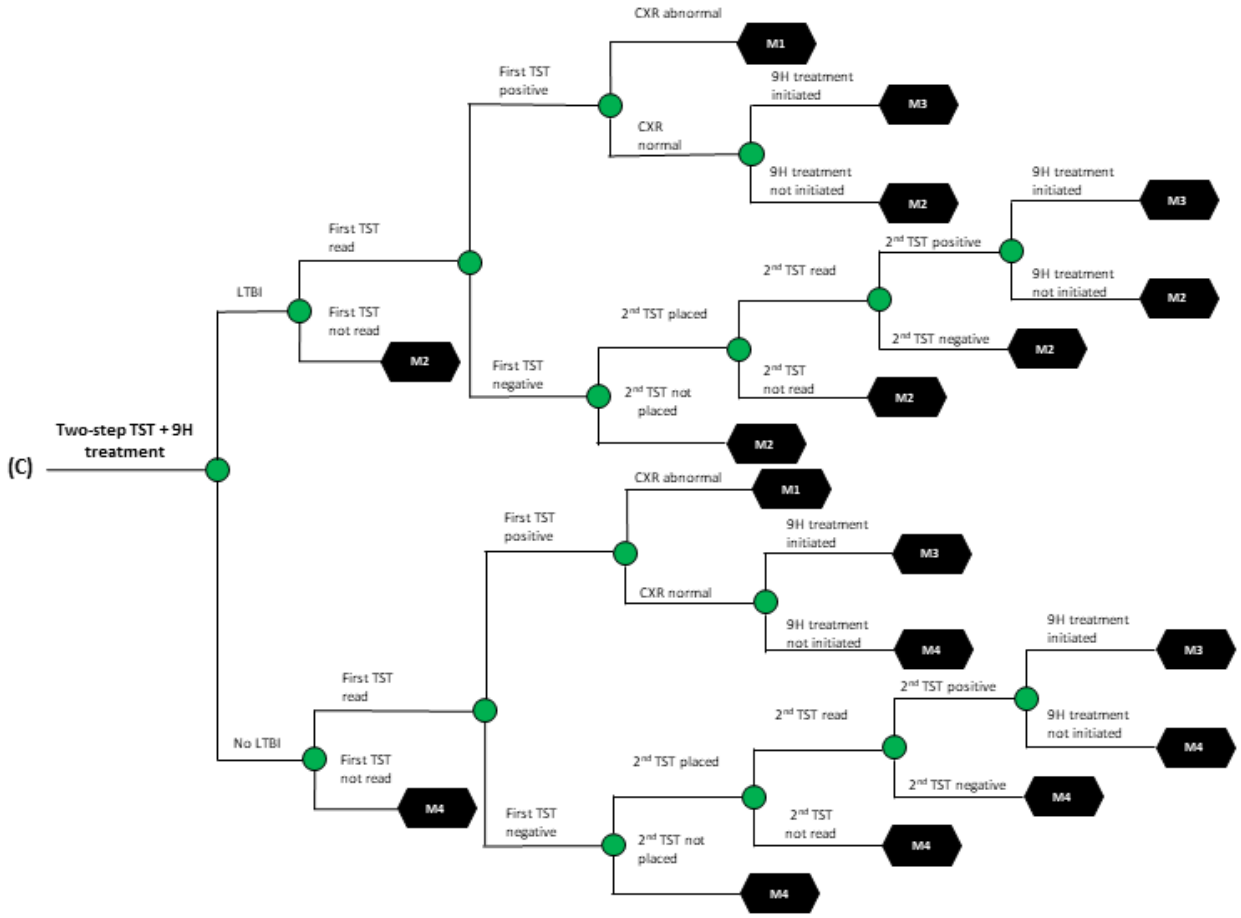
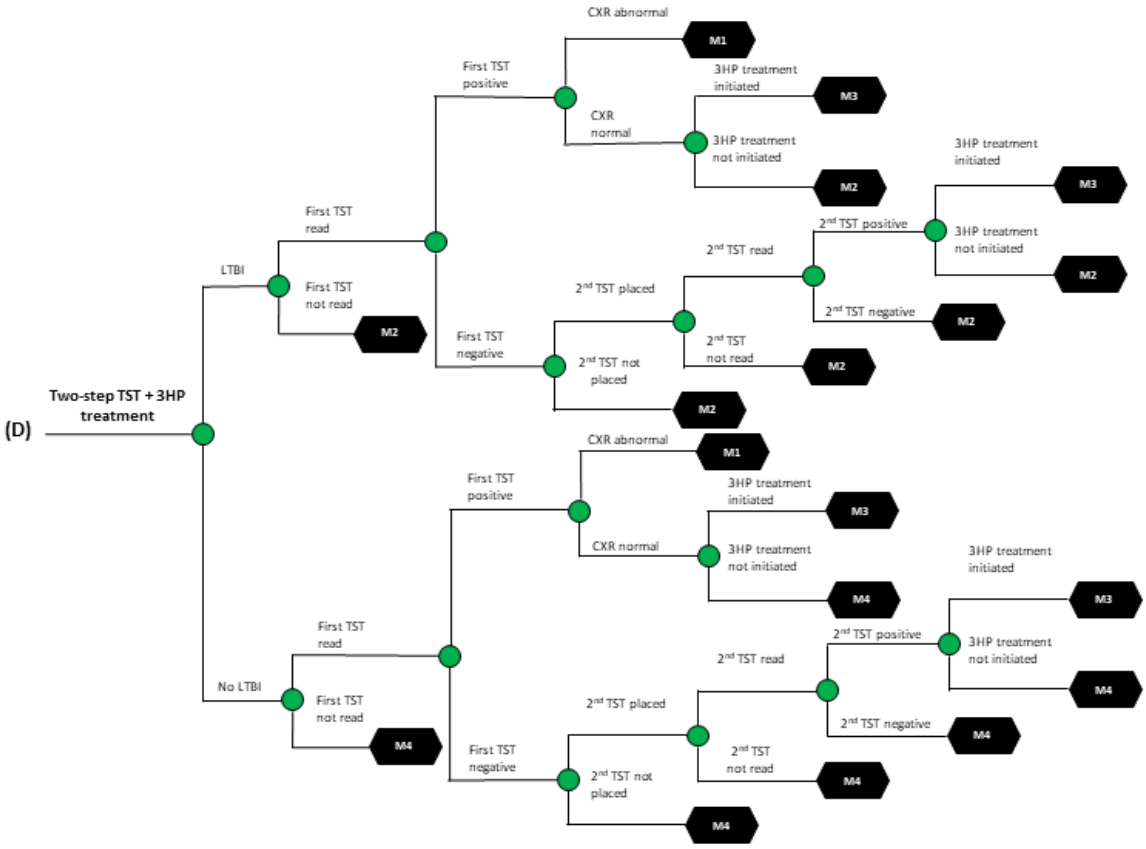
Appendix A: Decision trees

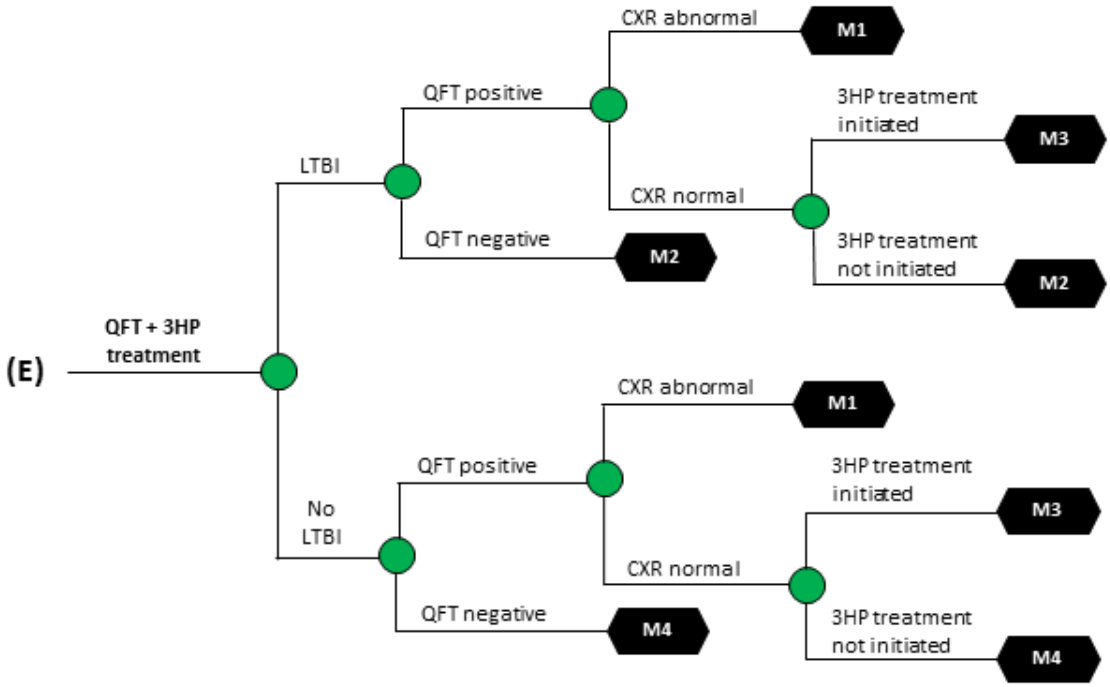
Appendix Figure A-1. Decision tree model for post-offer/pre-placement TB screening for US HCP. Path A is the schematic overview of the testing and treatment scenarios. Subtree B is the scenario for two-step TST testing with 9-month of isoniazid for LTBI treatment. Subtree C is the scenario for two-step TST testing with 3-month isoniazid-rifapentine (3HP) for LTBI treatment. Subtree D is the scenario for testing with QFT and 3HP for LTBI treatment. Subtree E is the scenario for sequential testing to confirm an initial QFT test with a TST test and treat LTBI with 3HP. Subtree F is the scenario for sequential testing to confirm an initial QFT test with another QFT test and treat LTBI with 3HP.

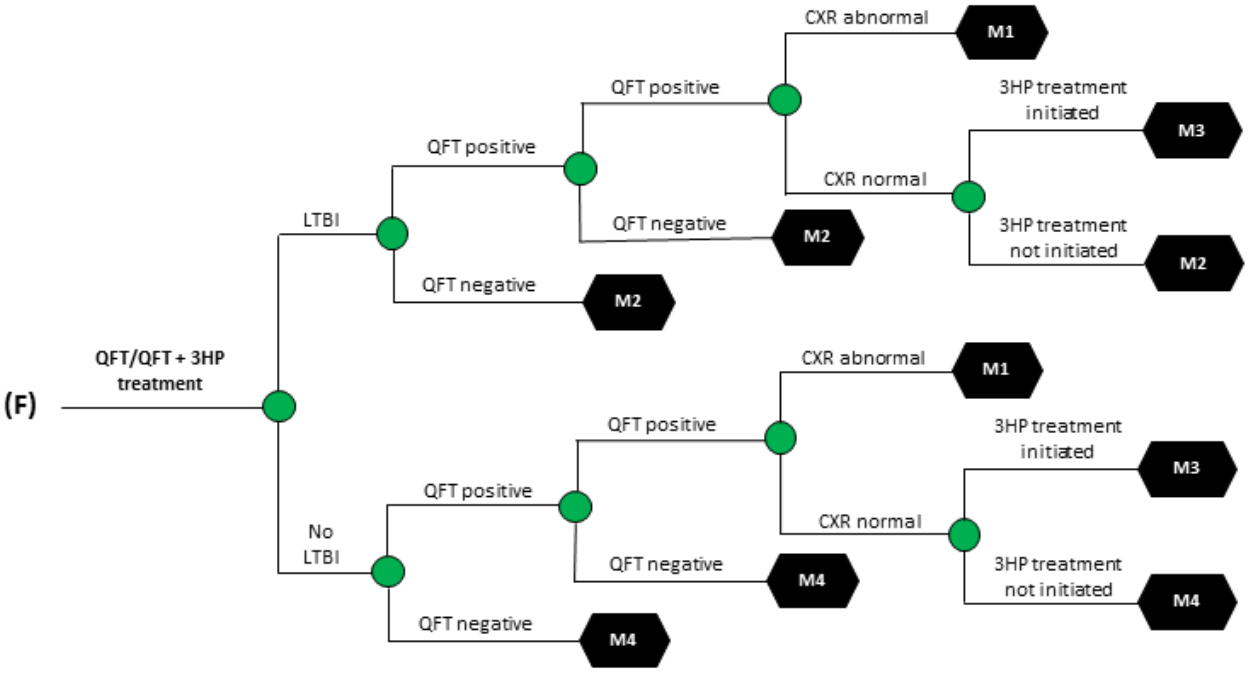



(B)
No screening
LTBI
M2
No LTBI
M4


(C)
Two-step TST + 9H treatment
LTBI
First TST read
First TST not read
M2
First TST positive
CXR abnormal
M1
CXR normal
9H treatment initiated
M3
9H treatment not initiated
M2
First TST negative
2nd TST placed
2nd TST not placed
M2
2nd TST read
2nd TST not read
M2
2nd TST positive
9H treatment initiated
M3
9H treatment not initiated
M2
2nd TST negative
M2
No LTBI
First TST read
First TST not read
M4
First TST positive
CXR abnormal
M1
CXR normal
9H treatment initiated
M3
9H treatment not initiated
M4
First TST negative
2nd TST placed
2nd TST not placed
M4
2nd TST read
2nd TST not read
M4
2nd TST positive
9H treatment initiated
M3
9H treatment not initiated
M4
2nd TST negative
M4


(D)
Two-step TST + 3HP treatment
LTBI
No LTBI
First TST read
First TST not read
First TST positive
First TST negative
CXR abnormal
CXR normal
2nd TST placed
2nd TST not placed
2nd TST read
2nd TST not read
2nd TST positive
2nd TST negative
3HP treatment initiated
3HP treatment not initiated
M1
M2
M3
M4


(E)
QFT + 3HP treatment
LTBI
No LTBI
QFT positive
QFT negative
CXR abnormal
CXR normal
3HP treatment initiated
3HP treatment not initiated
M1
M2
M3
M4


(F)
QFT/QFT + 3HP treatment
LTBI
No LTBI
QFT positive
QFT negative
QFT positive
QFT negative
CXR abnormal
CXR normal
3HP treatment initiated
3HP treatment not initiated
M1
M2
M3
M4

Appendix B: Annual rate of TB reactivation for US-born and non-US born persons

The annual rate of TB reactivation was obtained from a study conducted by Shea and colleagues (Shea et al., 2014). We used an annual rate of 82 per 100,000 person-years for US-born HCP and 98 per 100,000 person-years for HCP born outside of the United States. Rates were converted to probabilities using the following formula:

$$Probability = 1 - exp^{(-rt)}$$

where r = rate, t = time

Appendix Table B-1. Annual probability of TB progression for US-born HCP

Year	Probability Value
0	0
1	0.000819664
2	0.001638656
3	0.002456977
4	0.003274627
5	0.004091606
6	0.004907917
7	0.005723558
8	0.00653853
9	0.007352835
10	0.008166472
11	0.008979442
12	0.009791746
13	0.010603384
14	0.011414356
15	0.012224664
16	0.013034308
17	0.013843288
18	0.014651605
19	0.01545926
20	0.016266252

Appendix Table B-2. Annual probability of TB progression for non-US born HCP

Year	Probability Value
0	0
1	0.00097952
2	0.00195808
3	0.002935682
4	0.003912327
5	0.004888015
6	0.005862747
7	0.006836524
8	0.007809347
9	0.008781218
10	0.009752136
11	0.010722104
12	0.011691121
13	0.01265919
14	0.01362631
15	0.014592482
16	0.015557709
17	0.01652199
18	0.017485326
19	0.018447719
20	0.019409169

Appendix C: Background Mortality Rate in the United States

To obtain the probability of a US HCP dying from events unrelated to TB, we used data published by the National Center for Health Statistics (Arias, 2019), which reports the age-related probability of dying based on 2017 vital statistics data for the total US population. Probability of death data are reported for ages 35-55, which represents the beginning age of our HCP cohort and ending 20 cycles later.

Appendix Table C-1. Probability of death for persons in the United States based on age distribution, 2017

Age (years)	Probability Value
35-36	0.001615
36-37	0.001679
37-38	0.001740
38-39	0.001798
39-40	0.001860
40-41	0.001936
41-42	0.002036
42-43	0.002160
43-44	0.002306
44-45	0.002470
45-46	0.002647
46-47	0.002846
47-48	0.003079
48-49	0.003357
49-50	0.003682
50-51	0.004030
51-52	0.004401
52-53	0.004820
53-54	0.005285
54-55	0.005778
55-56	0.006284

Appendix D: Cost of LTBI treatment

Appendix D-1. Cost calculations for LTBI treatment

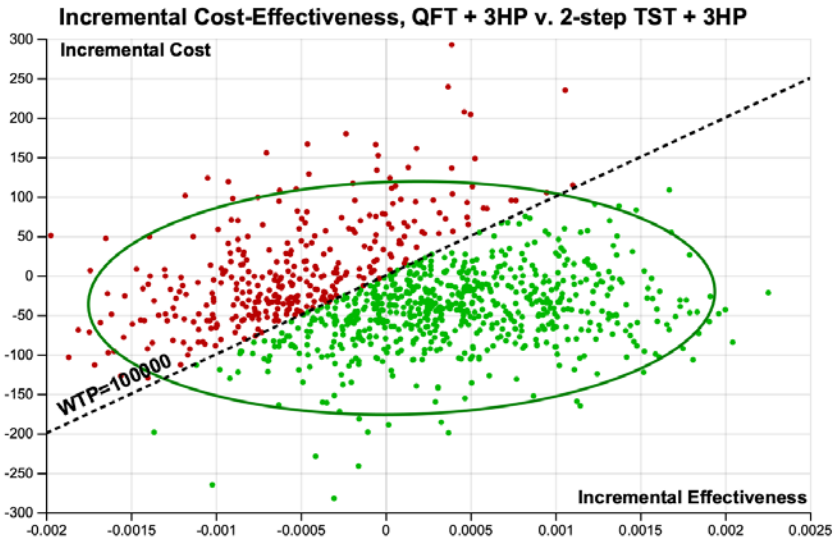
Category	Health System Cost
Complete 3HP treatment	*$ 410*
Medication cost	
900 mg RPT @ $48 per month for 3 months	$ 144
900 mg INH @ $5.1 per month for 3 months	$ 15
Initial visit	$ 187
Follow-up visits ($32 per visit for 2 visits)	$ 64
Incomplete 3HP treatment	*$ 325*
Medication cost	
900 mg RPT @ $48 per month for 2 months	$ 96
900 mg INH @ $5 per month for 2 months	$ 10
Initial visit	$ 187
Follow-up visit ($32 per visit for 1 visits)	$ 32
Complete 9H treatment	*$ 489*
Medication cost	
900 mg INH @ 5.10 per month for 9 months	$ 46
Initial visit	$ 187
Follow-up visits ($32 per visit for 8 visits)	$ 256
Incomplete 9H treatment	*$ 229*
Medication cost	
900 mg INH @ 5.10 per month for 2 months	$10
Initial visit	$187
Follow-up visit ($32 per visit for 1 visits)	$ 32
Mild hepatitis due to LTBI treatment (no hospitalization)	*$ 244*
Severe hepatitis with fatality due to LTBI treatment	*$ 8,713*
Loss productivity due to fatality	

Abbreviations: 3HP, 3-month isoniazid-rifapentine; 9H, 9-month isoniazid, INH, isoniazid, LTBI, latent tuberculosis infection; RPT, rifapentine

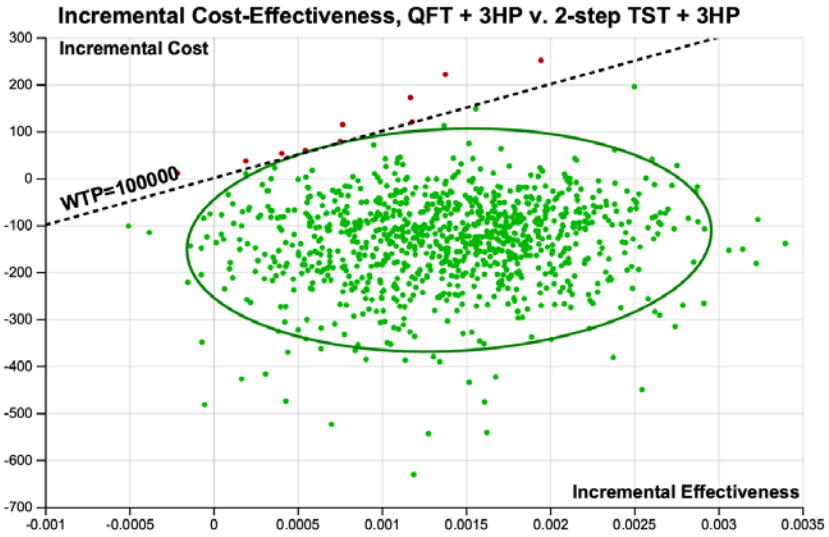
Appendix E: Incremental Cost-effectiveness Scatter Plots

Appendix Figure E-1. Incremental cost-effectiveness scatter plots for (A) US-born and (B) non-US born HCP from the health system perspective

(A)



(B)



Appendix F: Results from the Probabilistic Sensitivity Analysis

Appendix Table F-1. Probabilistic sensitivity analysis results relative to no screening, from health system perspective.

Cohort	Scenario	Cost (95% Crt. Int.)	Incr. Cost	QALYs (95% Crt. Int.)	Incr. QALY	ICER	Reactivation TB, % Total Cohort	TB death, % Total Cohort
USB	No screening	104 (7, 352)		14.868 (14.868, 14.868)			0.012	0.001
	QFT + 3HP	160 (39, 408)	56	14.872 (14.871, 14.872)	0.0038	14,785	0.008	0.000
Non-USB	No screening	104		14.868 (14.868, 14.868)			0.012	0.001
	QFT + 3HP	159	55	14.872 (14.870, 14.872)	0.0037	15,062	0.008	0.000

Abbreviation: Crt. Int, creditable interval

Appendix G: Findings for Additional Scenarios

In addition to the scenario examined in our primary analysis, we evaluated other scenarios that could hypothetically be used in non-HCP populations: one-step TST + 3HP, TST/QFT + 3HP, QFT/TST + 3HP, and two-step TST/QFT + 3HP.

Appendix Table G-1. Results for all scenarios for US-born HCP from the health system perspective

US-born: Health System							
Scenario	**Cost ($)**	**Incr Cost ($)**	**QALYs**	**Incr Eff**	**ICER ($)**	**TB cases averted**	**TB deaths averted**
No screening	105		14.868				
TST/QFT + 3HP	107	2.22	14.870	0.002	1,193	24	1
One-step TST + 3HP	123	18.61	14.874	0.006	3,257	31	1
QFT /TST + 3HP	156	51.27	14.869	0.001	Dominated	14	1
QFT/QFT + 3HP	158	52.85	14.870	0.002	Dominated	29	1
QFT + 3HP	160	55.12	14.872	0.004	Dominated	37	2
2-step TST/QFT + 3HP	177	72.10	14.876	0.008	8,959	35	1
2-step TST + 9H	196	90.78	14.867	-0.001	Dominated	26	2
2-step TST + 3HP	201	96.36	14.872	0.004	Dominated	37	1
Excluding Dominated							
Scenario	**Cost ($)**	**Incr Cost ($)**	**QALYs**	**Incr Eff**	**ICER ($)**	**TB cases averted**	**TB deaths averted**
No screening	105		14.868				
TST/QFT + 3HP	107	2.22	14.870	0.002	1,193	24	1
One-step TST + 3HP	123	16.39	14.874	0.004	4,253	7	0
2-step TST/QFT + 3HP	177	53.49	14.876	0.002	22,916	4	0

Appendix Table G-2. Results for all scenarios for non-US-born HCP from the health system perspective

Non-US-born: Health System							
Scenario	**Cost ($)**	**Incr Cost ($)**	**QALYs**	**Incr Eff**	**ICER ($)**	**TB cases averted**	**TB deaths averted**
No screening	105		14.868				
TST /QFT + 3HP	108	3.00	14.870	0.002	1,323	27	1
QFT/TST + 3HP	156	51.65	14.869	0.001	Dominated	16	1
QFT/QFT + 3HP	157	52.66	14.870	0.002	Dominated	30	1
QFT + 3HP	159	54.29	14.872	0.004	Dominated	38	2
One-step TST + 3HP	170	64.99	14.883	0.015	4,213	35	1
2-step TST/QFT + 3HP	210	105.65	14.885	0.017	6,146	38	1
2-step TST + 9H	253	148.37	14.865	-0.003	Dominated	14	2
2-step TST + 3HP	301	196.56	14.871	0.003	71,701	40	1
Excluding Dominated							
Scenario	**Cost ($)**	**Incr Cost ($)**	**QALYs**	**Incr Eff**	**ICER ($)**	**TB cases averted**	**TB deaths averted**
No screening	105		14.868				
TST + QFT + 3HP	108	3.00	14.870	0.002	1,323	27	1
One-step TST + 3HP	170	61.99	14.883	0.013	4,710	8	1
2-step TST + QFT + 3HP	210	40.66	14.885	0.002	23,049	3	0